

BIBLIOGRAFIA

- Adolphe M, Benoit B. Culture de chondrocytes articulaires humains. Intérêt en pharmacotoxicologie. *Ann. Pharmaceutiques Françaises*. 1994; **52**: 177-183.
- Afoke NYP, Byers PD, Hutton WC. Contact pressures in the human hip joint. *J. Bone Joint Surg.* 1987; **69B**: 536-542.
- Aguiar DJ, Knudson W, Knudson CB. Internalization of the hyaluronan receptor CD44 by chondrocytes. *Exp. Cell Res.* 1999; **252**: 292-302.
- Akiyama T, Ogawara H. Use and specificity of genistein as inhibitor of protein tyrosine kinases. *Methods Enzymol.* 1991; **201**: 362-370.
- Alaaeddine N, Di Battista JA, Pelletier JP, Kiansa K, Cloutier JM, Martel-Pelletier J. Inhibition of tumor necrosis factor alpha-induced prostaglandin E2 production by the antiinflammatory cytokines interleukin-4, interleukin-10, and interleukin-13 in osteoarthritic synovial fibroblasts: distinct targeting in the signaling pathways. *Arthritis Rheum.* 1999; **42**: 710-718.
- Alessi DR, Cuenda A, Cohen P, Dudley DT, Saltiel AR. PD 98059 is a specific inhibitor of the activation of mitogen-activated protein kinase kinase in vitro and in vivo. *J. Biol. Chem.* 1995; **270**: 27489-27494.
- Allen RG, Tresini M. Oxidative stress and gene regulation. *Free Radic. Biol. Med.* 2000; **28**: 463-499.
- Alsalameh S, Firestein GS, Oez S, Kurrie R, Kalden JR, Burmester GR. Regulation of granulocyte macrophage colony stimulating factor production by human articular chondrocytes. Induction by both tumor necrosis factor- α and interleukin 1, downregulation by transforming growth factor β and upregulation by basic fibroblast growth factor. *J. Rheumatol.* 1994; **21**: 993-1002.
- Andrews HJ, Bunning RA, Plumpton TA, Clark IM, Russell RG, Cawston TE. Inhibition of interleukin-1-induced collagenase production in human articular chondrocytes in vitro by recombinant human interferon-gamma. *Arthritis Rheum.* 1990; **33**: 1733-1738.
- Angel P, Imagawa M, Chiu R, Stein B, Imbra RJ, Rahmsdorf HJ, Jonat C, Herrlich P, Karin M. Phorbol ester-inducible genes contain a common *cis* element recognized by a TPA-modulated trans-acting factor. *Cell.* 1987; **49**: 729-739.
- Angel P, Karin M. The role of Jun, Fos and the AP-1 complex in cell-proliferation and transformation. *Biochim. Biophys. Acta.* 1991; **1072**: 129-157.
- Arner EC, Pratta MA. Independent effects of interleukin-1 on proteoglycan breakdown, proteoglycan synthesis and prostaglandin E₂ release from cartilage in organ culture. *Arthritis Rheum.* 1989; **32**: 288-297.
- Arner EC, Tortorella MD. Signal transduction through chondrocyte integrin receptors induces matrix metalloproteinase synthesis and synergizes with interleukin-1. *Arthritis Rheum.* 1995; **38**: 1304-1314.
- Asada S, Fukuda K, Oh M, Hamanishi C, Tanaka S. Effect of hydrogen peroxide on the metabolism of articular chondrocytes. *Inflamm. Res.* 1999; **48**: 399-403.
- Assreny J, Cunha FQ, Liew FY, Moncada S. Feedback inhibition of nitric oxide synthase activity by nitric oxide. *Br. J. Pharmacol.* 1993; **108**: 833-837.

Bibliografia

- Attur MG, Patel RN, Abramson SB, Amin AR. Interleukin-17 up-regulation of nitric oxide production in human osteoarthritis cartilage. *Arthritis Rheum.* 1997; **40**: 1050-1053.
- Attur MG, Dave MN, Clancy RM, Patel IR, Abramson SB, Amin AR. Functional genomic analysis in arthritis-affected cartilage: yin-yang regulation of inflammatory mediators by $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrins. *J. Immunol.* 2000; **164**: 2684-2691.
- Badger AM, Cook MN, Lark MW, Newman-Tarr TM, Swift BA, Nelson AH, Barone FC, Kumar S. SB 203580 inhibits p38 mitogen-activated protein kinase, nitric oxide production, and inducible nitric oxide synthase in bovine cartilage-derived chondrocytes. *J. Immunol.* 1998; **161**: 467-473.
- Bakker AC, van de Loo FA, van Beuningen HM, Sime P, van Lent PL, van der Kraan PM, Richards CD, van den Berg WB. Overexpression of active TGF-beta-1 in the murine knee joint: evidence for synovial-layer-dependent chondro-osteophyte formation. *Osteoarthritis Cartilage.* 2001; **9**: 128-136.
- Bass DA, Parce JW, Dechatelet LR, Szejda P, Seeds MC, Thomas M. Flow cytometric studies of oxidative product formation by neutrophils: a graded response to membrane stimulation. *J. Immunol.* 1983; **130**: 1910-1917.
- Beck KF, Eberhardt W, Walpen S, Apel M, Pfeilschifter J. Potentiation of nitric oxide synthase expression by superoxide in interleukin-1 β -stimulated rat mesangial cells. *FEBS Lett.* 1998; **435**: 35-38.
- Beg AA, Finco TS, Nantermet PV, Baldwin AS. Tumor necrosis factor and interleukin-1 lead to phosphorylation and loss of I κ B- α : a mechanism for NF- κ B activation. *Mol. Cell. Biol.* 1993; **13**: 3301-3310.
- Béraud C, Henzel WJ, Baeuerle PA. Involvement of regulatory and catalytic subunits of phosphoinositide 3-kinase in NF- κ B activation. *Proc. Natl. Acad. Sci. USA.* 1999; **96**: 429-434.
- Berenbaum F, Jacques C, Thomas G, Corvol MT, Béréziat G, Masliah J. Synergistic effect of interleukin-1 beta and tumor necrosis factor alpha on PGE₂ production by articular chondrocytes does not involve PLA₂ stimulation. *Exp. Cell Res.* 1996; **222**: 379-384.
- Bergmann M, Hart L, Lindsay M, Barnes PJ, Newton R. I κ B α degradation and nuclear factor κ B DNA binding are insufficient for interleukin-1 β and tumor necrosis factor- α -induced κ B-dependent transcription. Requirement for an additional activation pathway. *J. Biol. Chem.* 1998; **273**: 6607-6610.
- Bird HA. When are NSAIDs appropriate in Osteoarthritis? *Drugs Aging.* 1998; **12**: 87-95.
- Birkedal-Hansen H. Proteolytic remodeling of extracellular matrix. *Curr. Opin. Cell Biol.* 1995; **7**: 728-735.
- Blais V, Rivest S. Inhibitory action of nitric oxide on circulating tumor necrosis factor-induced NF-kappaB activity and COX-2 transcription in the endothelium of the brain capillaries. *J. Neuropathol. Exp. Neurol.* 2001; **60**: 893-905.
- Blanco FJ, Lotz M. IL-1-induced nitric oxide inhibits chondrocyte proliferation via PGE₂. *Exp. Cell. Res.* 1995; **218**: 319-325.
- Blanco FJ, Geng Y, Lotz M. Differentiation-dependent effects of IL-1 and TGF- β on human articular chondrocyte proliferation are related to inducible nitric oxide synthase expression. *J. Immunol.* 1995a; **154**: 4018-4026.
- Blanco F, Ochs RL, Schawrz H, Lotz M. Chondrocyte apoptosis induced by nitric oxide. *Am. J. Pathol.* 1995b; **146**: 75-85.

Bibliografia

- Blanco FJ, Guitian R, Vázquez-Martul E, de Toro FJ, Galdo F. Osteoarthritis chondrocytes die by apoptosis. A possible pathway for osteoarthritis pathology. *Arthritis Rheum.* 1998; **41**: 284-289.
- Boese M, Busse R, Mulsch A, Schinikerth V. Effect of cyclic GMP-dependent vasodilators on the expression of inducible nitric oxide synthase in vascular smooth muscle cells – role of cyclic AMP. *Br. J. Pharmacol.* 1996; **119**: 707-715.
- Boittin M, Rédini F, Loyau G, Pujol JP. Effect of diacerhein (ART 50) on the matrix synthesis and collagenase secretion by cultured joint chondrocytes in rabbits. *Rev. Rhum. (Ed. Fr.)* 1993; **60**: 68S-76S.
- Boata A, Johnson B, Lee KL, Blaskovich MA, Liu SX, Kagan VE, Hamilton A, Pitt B, Sebti SM, Davies P. Prenyltransferase inhibitors block superoxide production by pulmonary vascular smooth muscle. *Am. J. Physiol.* 2000; **278**: L329-L334.
- Boumediene K, Vivien D, Macro M, Bogdanowicz P, Lebrun E, Pujol J-P. Modulation of rabbit articular chondrocyte (RAC) proliferation by TGF- β isoforms. *Cell Prolif.* 1995; **28**: 221-234.
- Boyle DL, Han Z, Rutter JL, Brinckerhoff CE, Firestein GS. Posttranscriptional regulation of collagenase-1 gene expression in synoviocytes by adenosine receptor stimulation. *Arthritis Rheum.* 1997; **40**: 1772-1779.
- Brandt KD, Smith G, Kang SY, Myers S, O'Connor B, Albrecht M. Effects of diacerhein in an accelerated model of osteoarthritis. *Osteoarthritis Cartilage.* 1997; **5**: 438-449.
- Bredt DS, Schmidt HHHW. The citrulline assay. In Feilisch M, Stampler JS (eds). *Methods in Nitric Oxide Research.* John Wiley & Sons Ltd. Chichester. 1996. 249-255.
- Bren GD, Solan NJ, Miyoshi H, Pennington KN, Pobst LJ, Paya CV. Transcription of the RelB gene is regulated by NF- κ B. *Oncogene.* 2001; **20**: 7722-7733.
- Brennan FM, Gibbons DL, Cope AP, Katsikis P, Maini RN, Feldmann M. TNF inhibitors are produced spontaneously by rheumatoid and osteoarthritic synovial joint cell cultures: evidence of feedback control of TNF action. *Scand. J. Immunol.* 1995; **42**: 158-165.
- Brinckerhoff CE, Matrisian LM. Matrix metalloproteinases: a tail of a frog that became a prince. *Nat. Rev. Mol. Cell Biol.* 2002; **3**: 207-214.
- Bucht A, Larsson P, Weisbrot L, Thorne C, Pisa P, Smedegård EC, Keystone EC, Grönberg A. Expression of interferon-gamma (IFN- γ), IL-10, IL-12 and transforming growth factor-beta (TGF- β) mRNA in synovial fluid cells from patients in the early and late phases of rheumatoid arthritis (RA). *Clin. Exp. Immunol.* 1996; **103**: 357-367.
- Burger D, Chicheportiche R, Giri JG, Dayer J-M. The inhibitory activity of human Interleukin-1 Receptor Antagonist is enhanced by Type II Interleukin-1 Soluble Receptor and hindered by Type I Interleukin-1 Soluble Receptor. *J. Clin. Invest.* 1995; **96**: 38-41.
- Burns K, Cladworthy J, Martin L, Martinon F, Plumpton C, Maschera B, Lewis A, Ray K, Tschopp J, Volpe F. Tollip, a new component of the IL-1RI pathway, links IRAK to the IL-1 receptor. *Nat. Cell Biol.* 2000; **2**: 346-351.
- Burridge K, Fath K, Kelly T, Nuckolls G, Turner C. Focal adhesions: transmembrane junctions between the extracellular matrix and the cytoskeleton. *Annu. Rev. Cell Biol.* 1988; **4**: 487-525.
- Burridge K, Turner CE, Romer LH. Tyrosine phosphorylation of paxillin and pp125^{FAK} accompanies cell adhesion to extracellular matrix: a role in cytoskeleton assembly. *J. Cell Biol.* 1992; **119**: 893-903.
- Burton-Wuster N, Lust G. Molecular and immunologic differences in canine fibronectins from articular cartilage and plasma. *Arch. Biochem. Biophys.* 1989; **269**: 32-45.

Bibliografia

- Buschmann MD, Gluzband YA, Grodzinsky AJ, Hunziker EB. Mechanical compression modulates matrix biosynthesis in chondrocyte/agarose culture. *J. Cell Sci.* 1995; **108**: 1497-1508.
- Calderwood DA, Shattil SJ, Ginsberg MH. Integrins and actin filaments: reciprocal regulation of cell adhesion and signaling. *J. Biol. Chem.* 2000; **275**: 22607-22610.
- Campbell IK, Last K, Novak U. Recombinant human interleukin 1 inhibits plasminogen activator inhibitor-1 (PAI-1) production by human articular cartilage and chondrocytes. *Biochem. Biophys. Res. Commun.* 1991a; **174**: 251-254.
- Campbell IK, Novak U, Cebon J, Layton JE, Hamilton JA. Human articular cartilage and chondrocytes produce hemopoietic colony-stimulating factors in culture in response to IL-1. *J. Immunol.* 1991b; **147**: 1238-1246.
- Campion GV, Lebsack ME, Lookabaugh J, Gordon G, Catalano M, e o "IL-Ra Arthritis Study Group". Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. *Arthritis Rheum.* 1996; **39**: 1092-1101.
- Cao Z, Henzel WJ, Gao X. IRAK: a kinase associated with the Interleukin-1 Receptor. *Science.* 1996a; **271**: 1128-1131.
- Cao Z, Xiong J, Takeuchi M, Kurama T, Goeddel DV. TRAF6 is a signal transducer for interleukin-1. *Nature.* 1996b; **383**: 443-446.
- Catterall JB, Carrere S, Koshy PJ, Degnan BA, Shingleton WD, Brinckerhoff CE, Rutter J, Cawston TE, Rowan AD. Synergistic induction of matrix metalloproteinase 1 by interleukin-1 α and oncostatin M in human chondrocytes involves signal transducer and activator of transcription and activator protein 1 transcription factors via a novel mechanism. *Arthritis Rheum.* 2001; **44**: 2296-2310.
- Cawston TE, Curry VA, Summers CA, Clark IM, Riley GP, Life PF, Spaull JR, Goldring MB, Koshy PJ, Rowan AD, Shingleton WD. The role of oncostatin M in animal and human connective tissue collagen turnover and its localization within the rheumatoid joint. *Arthritis Rheum.* 1998; **41**: 1760-1771.
- Chabaud M, Page G, Miossec P. Enhancing effect of IL-1, IL-17, and TNF- α on macrophage inflammatory protein-3 α production in rheumatoid arthritis: regulation by soluble receptors and Th2 cytokines. *J. Immunol.* 2001; **167**: 6015-6020.
- Chan ED, Winston BW, Uh ST, Wynes MW, Rose DM, Riches DW. Evaluation of the role of mitogen-activated protein kinases in the expression of inducible nitric oxide synthase by IFN- γ and TNF- α in mouse macrophages. *J. Immunol.* 1999; **162**: 415-422.
- Chang L, Karin M. Mammalian M μ L Q1 Q $\frac{4}{4}$ *Nature.* 2001; **410**: 37-40.
- Chantre P, Cappelaere A, Leblan D, Guedon D, Vandermander J, Fournie B. Efficacy and tolerance of Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. *Phytomedicine.* 2000; **7**: 177-183.
- Chen FE, Ghosh G. Regulation of DNA binding by Rel/NF- κ B transcription factors: structural views. *Oncogene.* 1999; **18**: 6845-6852.
- Chen C-C, Wang J-K. p38 but not p44/42 mitogen-activated protein kinase is required for nitric oxide synthase induction mediated by lipopolysaccharide in RAW 264.7 macrophages. *Mol. Pharmacol.* 1999; **55**: 481-488.
- Chen H-C, Appeddu PA, Parsons JT, Hildebrand JD, Schaller MD, Guan J-L. Interaction of focal adhesion kinase with cytoskeletal protein talin. *J. Biol. Chem.* 1995a; **270**: 16995-16999.

Bibliografia

- Chen Z, Hagler J, Palombella VJ, Melandri F, Scherer D, Ballard D, Maniatis T. Signal-induced site-specific phosphorylation targets I κ B α to the ubiquitin-proteasome pathway. *Genes Dev.* 1995b; **9**: 1586-1597.
- Chen C-C, Wang J-K, Chen WC, Lin SB. Protein kinase C ϵ mediates lipopolysaccharide-induced nitric oxide synthase expression in primary astrocytes. *J. Biol. Chem.* 1998; **273**: 19424-19430.
- Chen C-C, Chiu KT, Sun YT, Chen WC. Role of the cyclic AMP-protein kinase A pathway in lipopolysaccharide-induced nitric oxide synthase expression in RAW 264.7 macrophages. Involvement of cyclooxygenase-2. *J. Biol. Chem.* 1999; **274**: 31559-31564.
- Cheon H, Yu SJ, Yoo DH, Chae IJ, Song GG, Sohn J. Increased expression of pro-inflammatory cytokines and metalloproteinase-1 by TGF- β 1 in synovial fibroblasts from rheumatoid arthritis and normal individuals. *Clin. Exp. Immunol.* 2002; **127**: 547-552.
- Chevalier X, Groult N, Labat-Robert J. Biosynthesis and distribution of fibronectin in normal and osteoarthritic cartilage. *Clin. Phys. Biochem.* 1992; **9**: 1-6.
- Chevalier X, Tyler JA. Production of binding proteins and role of the insulin-like growth factor I binding protein 3 in human articular cartilage explants. *Br. J. Rheum.* 1996; **35**: 515-522.
- Cho MK, Suh SH, Kim SG. JunB/AP-1 and NF- κ B-mediated induction of nitric oxide synthase by bovine type I collagen in serum-stimulated murine macrophages. *Nitric Oxide.* 2002; **6**: 319-332.
- Chomczynski P, Sacchi N. Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. *Anal. Biochem.* 1987; **162**: 156-159.
- Chopra R, Anastassiades T. Specificity and synergism of polypeptide growth factors in stimulating the synthesis of proteoglycans and a novel high molecular weight anionic glycoprotein by articular chondrocyte cultures. *J. Rheumatol.* 1998; **25**: 1578-1584.
- Choy EHS. Clinical pharmacology and therapeutic potential of monoclonal antibody treatment in rheumatoid arthritis. *Drugs Aging.* 1998; **12**: 139-148.
- Chu SC, Marks-Konczalik J, Wu H-P, Banks TC, Moss J. Analysis of the cytokine-stimulated human inducible nitric oxide synthase (iNOS) gene: characterization of differences between human and mouse iNOS promoters. *Biochem. Biophys. Res. Commun.* 1998; **248**: 871-878.
- Clancy RM, Rediske J, Tang X, Nijher N, Frenkel S, Philips M, Abramson SB. Outside-in signaling in the chondrocyte. Nitric Oxide disrupts fibronectin-induced assembly of a subplasmalemmal actin/Rho A/Focal adhesion kinase signaling complex. *J. Clin. Invest.* 1997; **100**: 1789-1796.
- Claret FX, Hibi M, Dhut S, Toda T, Karin M. A new group of conserved coactivators that increase the specificity of AP-1 transcription factors. *Nature.* 1996; **383**: 453-457.
- Clarke C.C, Tolin B.S., Brighton C.T. The effect of oxygen tension on proteoglycan synthesis and aggregation in mammalian growth plate chondrocytes. *J. Orthoped. Res.* 1991; **9**: 477-484.
- Cohen L, Henzel WJ, Baeuerle PA. IKAP is a scaffold protein of the I κ B kinase complex. *Nature.* 1998; **395**: 292-296.
- Colasanti M, Suzuki H. The dual personality of NO. *Trends Pharmacol. Sci.* 2000; **21**: 249-252.
- Colasanti M, Persichini T, Menegazzi M, Mariotto S, Giordano E, Calderara CM, Sogos V, Lauro GM, Suzuki H. Induction of nitric oxide synthase mRNA expression. Suppression by exogenous nitric oxide. *J. Biol. Chem.* 1995; **270**: 26731-26733.
- Colasanti M, Persichini T, Cavalieri E, Fabrizi C, Mariotto S, Menegazzi M, Lauro GM, Suzuki H. Rapid inactivation of NOS-I by lipopolysaccharide plus interferon- γ -induced tyrosine phosphorylation. *J. Biol. Chem.* 1999; **274**: 9915-9917.

Bibliografia

- Colotta F, Re F, Muzio M, Bertini R, Polentarutti N, Sironi M, Giri G, Dower SK, Sims JE, Mantovani A. Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. *Science*. 1993; **261**: 472-475.
- Conquer JA, Kandel RA, Cruz TF. Interleukin 1 and phorbol 12-myristate 13-acetate induce collagenase and PGE₂ production through a PKC-independent mechanism in chondrocytes. *Biochim. Biophys. Acta*. 1992; **1134**: 1-6.
- Corbett JA, Kwon G, Misko TP, Rodi CP, McDaniel ML. Tyrosine kinase involvement in IL-1 β -induced expression of iNOS by β -cells purified from islets of Langerhans. *Am. J. Physiol.* 1994; **267**: C48-C54.
- Corvo ML, Jorge JCS, van't Hof R, Cruz MEM, Crommelin DJA, Storm G. Superoxide dismutase entrapped in long-circulating liposomes: formulation design and therapeutic activity in rat adjuvant arthritis. *Biochim. Biophys. Acta*. 2002; **1564**: 227-236.
- Cowell S, Knauper V, Stewart ML, D'Ortho MP, Stanton H, Hembry RM, Lopez Otin C, Reynolds JJ, Murphy G. Induction of matrix metalloproteinase activation cascades based on membrane-type 1 matrix metalloproteinase: associated activation of gelatinase A, gelatinase B and collagenase 3. *Biochem. J.* 1998; **331**: 453-458.
- Cruz TF, Mills G, Pritzker KPH, Kandel RA. Inverse correlation between tyrosine phosphorylation and collagenase production in chondrocytes. *Biochem. J.* 1990; **269**: 717-721.
- Cuenda A, Rouse J, Doza YN, Meier R, Young PR, Cohen P, Lee JC. SB 203580 is a specific inhibitor of a MAP kinase homologue which is stimulated by cellular stresses and interleukin-1. *FEBS Lett.* 1995; **364**: 229-233.
- Cullinan EB, Kwee L, Nunes P, Shuster DJ, Ju G, McIntyre KW, Chizzonite RA, Labow MA. IL-1 Receptor Accessory Protein is an essential component of the IL-1 receptor. *J. Immunol.* 1998; **161**: 5614-5620.
- Cuzzocrea S, Chatterjee PK, Mazzon E, McDonald MC, Dugo L, Di Paola R, Serraino I, Britti D, Caputi AP, Thiemermann C. Beneficial effects of GW274150, a novel, potent and selective inhibitor of iNOS activity, in a rodent model of collagen-induced arthritis. *Eur. J. Pharmacol.* 2002; **453**: 119-129.
- Danen EH, Aota S, Van Kraats AA, Yamada KM, Ruiter DJ, Van Muijen GN. Requirement for the synergy site for cell adhesion to fibronectin depends on the activation state of integrin $\alpha_5\beta_1$. *J. Biol. Chem.* 1995; **270**: 21612-21618.
- Das KC, Lewis-Molock Y, White CW. Activation of NF- κ B and elevation of MnSOD gene expression by thiol reducing agents in lung adenocarcinoma (A549) cells. *Am. J. Physiol.* 1995; **269**: L588-L602.
- DaSilva J, Pierrat B, Mary JL, Lesslauer W. Blockade of p38 mitogen-activated protein kinase pathway inhibits inducible nitric-oxide synthase expression in mouse astrocytes. *J. Biol. Chem.* 1997; **272**: 28373-28380.
- de Haart M, Marijnissen WJ, van Osch GJ, Verhaar JA. Optimization of chondrocyte expansion in culture. Effect of TGF β -2, bFGF and L-ascorbic acid on bovine articular chondrocytes. *Acta Orthop. Scand.* 1999; **70**: 55-61.
- Deak M, Clifton AD, Lucocq LM, Alessi DR. Mitogen- and stress-activated protein kinase-1 (MSK1) is directly activated by MAPK and SAPK2/p38 and may mediate activation of CREB. *EMBO J.* 1998; **17**: 4426-4441.

Bibliografia

- Dean DD, Martel-Pelletier J, Pelletier J-P, Howell DS, Woessner JF Jr. Evidence for metalloproteinase and metalloproteinase inhibitor imbalance in human osteoarthritic cartilage. *J. Clin. Invest.* 1989; **84**: 678-685.
- Debets R, Timans JC, Homey B, Zurawski S, Sana TR, Lo S, Wagner J, Edwards G, Clifford T, Menon S, Bazan FF, Kastelein RA. Two novel IL-1 family members, IL-1 δ and IL-1 epsilon, function as an antagonist and agonist of NF κ B activation through the orphan receptor-related protein 2. *J. Immunol.* 2001; **167**: 1440-1446.
- del Pozo MA, Price LS, Alderson NB, Ren X-D, Schwartz MA. Adhesion to the extracellular matrix regulates the coupling of the small GTPase Rac to its effector PAK. *EMBO J.* 2000; **19**: 2008-2014.
- dela Torre A, Schroeder RA, Punzalan C, Kuo PC. Endotoxin-mediated S-nitrosylation of p50 alters NF- κ B-dependent gene transcription in ANA-1 murine macrophages. *J. Immunol.* 1999; **162**: 4101-4108.
- Demignot S, Borge L, Adolphe M. Transglutaminase activity in rabbit articular chondrocytes in culture. *Biochim. Biophys. Acta.* 1995; **1266**: 163-170.
- Demoor-Fossard M, Boittin M, Redini F, Pujol J-P. Differential effects of interleukin-1 and transforming growth factor β on the synthesis of small proteoglycans by rabbit articular chondrocytes cultured in alginate beads as compared to monolayers. *Mol. Cell. Biochem.* 1999; **199**: 69-80.
- Deng L, Wang C, Spencer E, Yang L, Braun A, You J, Slaughter C, Pickart C, Chen ZJ. Activation of I κ B kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. *Cell.* 2000; **103**: 351-361.
- Díaz-Guerra MJ, Bodelón OG, Velasco M, Whelan R, Parker PJ, Boscá L. Up-regulation of protein kinase C- ϵ promotes the expression of cytokine-inducible nitric oxide synthase in RAW 264.7 cell. *J. Biol. Chem.* 1996; **271**: 32028-32033.
- Dinant HJ, Dijkmans BAC. New therapeutic targets for rheumatoid arthritis. *Pharm. World Sci.* 1999; **21**: 49-59.
- Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood.* 1996; **87**: 2095-2147.
- Doi M, Shichiri M, Katsuyama K, Ishimaru S, Hirata Y. Cytokine-activated Jak-2 is involved in inducible nitric oxide synthase expression independent from NF- κ B activation in vascular smooth muscle cells. *Atherosclerosis.* 2002; **160**: 123-132.
- Dominice J, Levasseur C, Larno S, Ronot X, Adolphe M. Age-related changes in rabbit articular chondrocytes. *Mech. Ageing Dev.* 1986; **37**: 231-240.
- Dorsam G, Taher MM, Valerie KC, Kuemmerle NB, Chan JC, Franson RC. Diphenyleneiodonium chloride blocks inflammatory cytokine-induced up-regulation of group IIA phospholipase A₂ in rat mesangial cells. *J. Pharmacol. Exp. Therap.* 2000; **292**: 271-279.
- Dudley DT, Pang L, Decker SJ, Bridges AJ, Saltiel AR. A synthetic inhibitor of the mitogen-activated protein kinase cascade. *Proc. Natl. Acad. Sci. USA.* 1995; **92**: 7686-7689.
- Dürr J, Goodman S, Potocnik A, von der Mark H, von der Mark K. Localization of β_1 -integrins in human cartilage and their role in chondrocyte adhesion to collagen and fibronectin. *Exp. Cell Res.* 1993; **207**: 235-244.
- Duval DL, Sieg DJ, Billings RE. Regulation of hepatic nitric oxide synthase by reactive oxygen intermediates and glutathione. *Arch. Biochem. Biophys.* 1995; **316**: 699-706.

Bibliografia

- Eberhardt W, Plüss C, Hummel R, Pfeilschifter J. Molecular mechanisms of inducible nitric oxide synthase gene expression by IL-1 β and cAMP in rat mesangial cells. *J. Immunol.* 1998; **160**: 4061-4069.
- Eberhardt W, Huwiler A, Beck KF, Walpen S, Pfeilschifter J. Amplification of IL-1 β -induced matrix metalloproteinase-9 expression by superoxide in rat glomerular mesangial cells is mediated by increased activities of NF- κ B and activating protein-1 and involves activation of the mitogen-activated protein kinase pathways. *J. Immunol.* 2000; **165**: 5788-5797.
- Eberhardt W, Beck KF, Pfeilschifter J. Cytokine-induced expression of tPA is differentially modulated by NO and ROS in rat mesangial cells. *Kidney Int.* 2002; **61**: 20-30.
- Enomoto M, Leboy PS, Menko AS, Boettiger D. β_1 integrins mediate chondrocyte interaction with type I collagen, type II collagen and fibronectin. *Exp. Cell. Res.* 1993; **205**: 276-285.
- Enomoto-Iwamoto M, Iwamoto M, Nakashima K, Mukudai Y, Boettiger D, Pacifici M, Kurisu K, Suzuki F. Involvement of $\alpha_5\beta_1$ integrin in matrix interactions and proliferation of chondrocytes. *J. Bone Miner. Res.* 1997; **12**: 1124-1132.
- Eyre DR, Wu J-J, Woods PE. The cartilage collagens: structural and metabolic studies. *J. Rheumatol.* 1991; **18** (Suppl. 27): 49-51.
- Falta MT, Kotzin BL. T cells as primary players in rheumatoid arthritis. In Miossec P, van den Berg WB, Firestein GS (eds.) T cells in arthritis. Birkhäuser. Basel. 1998. 201-231.
- Farahat MN, Yanni G, Poston R, Panayi GS. Cytokine expression in synovial membranes of patients with rheumatoid arthritis and osteoarthritis. *Ann. Rheum. Dis.* 1993; **52**: 870-875.
- Farrell AJ, Blake DL, Palmer RMJ, Moncada S. Increased concentrations of nitrite in synovial fluid and serum samples suggest increased nitric oxide synthesis in rheumatic diseases. *Ann. Rheum. Dis.* 1992; **51**: 1219-1222.
- Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. *Cell.* 1996; **85**: 307-310.
- Felisaz N, Boumediene K, Ghayor C, Herrouin JF, Bogdanowicz P, Galera P, Pujol JP. Stimulating effect of diacerein on TGF- β 1 and β 2 expression in articular chondrocytes cultured with and without interleukin-1. *Osteoarthritis Cartilage.* 1999; **7**: 255-264.
- Fernandes JC, Martel-Pelletier J, Pelletier JP. The role of cytokines in osteoarthritis pathophysiology. *Biorheology.* 2002; **39**: 237-246.
- Finder JD, Petrus JL, hamilton A, Villavicencio RT, Pitt BR, Sebti SM. Signal transduction pathways of IL-1 β -mediated iNOS in pulmonary vascular smooth muscle cells. *Am. J. Physiol.* 2001; **281**: L816-L823.
- Flannery CR, Little CB, Caterson B, Hughes CE. Effects of culture conditions and exposure to catabolic stimulators (IL-1 and retinoic acid) on the expression of matrix metalloproteinases (MMPs) and disintegrin metalloproteinases (ADAMs) by articular cartilage chondrocytes. *Matrix Biol.* 1999a; **18**: 225-237.
- Flannery CR, Hughes CE, Schumacher BL, Tudor D, Aydelotte MB, Kuettner KE, Caterson B. Articular cartilage superficial zone protein (SZP) is homologous to megakaryocyte stimulating factor precursor and is a multifunctional proteoglycan with potential growth-promoting, cytoprotective and lubricating properties in cartilage metabolism. *Biochem. Biophys. Res. Commun.* 1999b; **254**: 535-541.
- Flechtenmacher J, Huch K, Thonar EJ, Mollenhauer JA, Davies SR, Schmid TM, Puhl W, Sampath TK, Aydelotte MB, Kuettner KE. Recombinant human osteogenic protein 1 is a potent stimulator

Bibliografia

- of the synthesis of cartilage proteoglycans and collagens by human articular chondrocytes. *Arthritis Rheum.* 1996; **39**: 1896-1904.
- Flescher E, Tripoli H, Salnikow K, Burns FJ. Oxidative stress suppresses transcription factor activities in stimulated lymphocytes. *Clin. Exp. Immunol.* 1998; **112**: 242-247.
- Foey A, Green P, Foxwell B, Feldmann M, Brennan F. Cytokine-stimulated T cells induce macrophage IL-10 production dependent on phosphatidylinositol 3-kinase and p70S6K: implications for rheumatoid arthritis. *Arthritis Res.* 2002; **4**: 64-70.
- Förstermann U, Kleinert H. Nitric oxide synthase: expression and expressional control of the three isoforms. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1995; **352**: 351-364.
- Förstermann U, Boissel J-P, Kleinert H. Expressional control of the "constitutive" isoforms of the nitric oxide synthase (NOS I and NOS III). *FASEB J.* 1998; **12**: 773-790.
- Forsyth CB, Pulai J, Loeser RF. Fibronectin fragments and blocking antibodies to $\alpha_2\beta_1$ and $\alpha_5\beta_1$ integrins stimulate mitogen-activated protein kinase signaling and increase collagenase 3 (matrix metalloproteinase 13) production by human articular chondrocytes. *Arthritis Rheum.* 2002; **46**: 2368-2376.
- Fortier LA, Nixon AJ, Mohammed HO, Lust G. Altered biological activity of equine chondrocytes cultured in a three-dimensional fibrin matrix and supplemented with transforming growth factor- β 1. *Am. J. Vet. Res.* 1997; **58**: 66-70.
- Fossiez F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, Pin JJ, Garrone P, Garcia E, Saeland S, Blanchard D, Gaillard C, Das Mahapatra B, Rouvier E, Golstein P, Banchereau J, Lebecque S. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J. Exp. Med.* 1996; **183**: 2593-2603.
- Franchimont P, Bassleer C. Effects of hormones and local growth factors on articular chondrocyte metabolism. *J. Rheumatol.* 1991; **18** (supp. 27): 68-70.
- Franklin RA, Tordai A, Patel H, Gardner AM, Johnson GL, Gelfand EW. Ligation of the T cell receptor complex results in activation of the Ras/Raf-1/MEK/MAPK cascade in human T lymphocytes. *J. Clin. Invest.* 1994; **93**: 2134-2140.
- Franzoso G, Bours V, Park S, Tomita Yamagushi M, Kelly K, Siebenlist U. The candidate oncoprotein Bcl-3 is an antagonist of p50/NF- κ B-mediated inhibition. *Nature.* 1992; **359**: 339-342.
- Frenkel SR, Clancy RM, Ricci JL, Di Cesare PE, Rediske JJ, Abramson SB. Effects of nitric oxide on chondrocyte migration, adhesion and cytoskeletal assembly. *Arthritis Rheum.* 1996; **39**: 1905-1912.
- Fujisawa T, Hattori T, Takahashi K, Kuboki T, Yamashita A, Takigawa M. Cyclic mechanical stress induces extracellular matrix degradation in cultured chondrocytes via gene expression of matrix metalloproteinases and interleukin-1. *J. Biochem.* 1999; **125**: 966-975.
- Furchtgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature.* 1980; **288**: 373-376.
- Galéra P, Rédini F, Vivien D, Bonaventure J, Penfornis H, Loyau G, Pujol JP. Effect of transforming growth factor- β 1 (TGF- β 1) on matrix synthesis by monolayer cultures of rabbit articular chondrocytes during the dedifferentiation process. *Exp. Cell Res.* 1992; **200**: 379-392.
- Geller DA, Nussler AK, Di Silvio M, Lowenstein CJ, Shapiro RA, Wang SC, Simmons RL, Billiar TR. Cytokines, endotoxin, and glucocorticoids regulate the expression of inducible nitric oxide synthase in hepatocytes. *Proc. Natl. Acad. Sci. USA.* 1993; **90**: 522-526.

Bibliografia

- Gemba T, Valbracht J, Alsalameh S, Lotz M. Focal adhesion kinase and mitogen-activated protein kinases are involved in chondrocyte activation by the 29-kDa amino-terminal fibronectin fragment. *J. Biol. Chem.* 2002; **277**: 907-911.
- Geng Y, Maier R, Lotz M. Tyrosine kinases are involved with the expression of inducible nitric oxide synthase in human articular chondrocytes. *J. Cell. Physiol.* 1995; **163**: 545-554.
- Geng Y, Valbracht J, Lotz M. Selective activation of the mitogen-activated protein kinase subgroups c-Jun NH₂ terminal kinase and p38 by IL-1 and TNF in human articular chondrocytes. *J. Clin. Invest.* 1996; **98**: 2425-2430.
- Geng Y, Zhou L, Thompson WJ, Lotz M. Cyclic GMP and cGMP-binding phosphodiesterase are required for Interleukin-1-induced nitric oxide synthesis in human articular chondrocytes. *J. Biol. Chem.* 1998; **273**: 27484-27491.
- Ghosh S, Karin M. Missing pieces in the NF-κB puzzle. *Cell.* 2002; **109**: S81-S96.
- Gilmore TD. The Rel/NF-κB signal transduction pathway: introduction. *Oncogene.* 1999; **18**: 6842-6844.
- Giri S, Jatana M, Rattan R, Won J-S, Singh I, Singh AK. Galactosylsphingosine (psychosine)-induced expression of cytokine-mediated inducible nitric oxide synthases via AP-1 and C/EBP: implications for Krabbe disease. *FASEB J.* 2002; **16**: 661-672.
- Glansbeek HL, van Beuningen HM, Vitters EL, van der Kraan PM, van den Berg WB. Stimulation of articular cartilage repair in established arthritis by local administration of transforming growth factor-β into murine knee joints. *Lab. Invest.* 1998; **78**: 133-142.
- Goh KC, Haque SJ, Williams BRG. p38 MAP kinase is required for STAT1 serine phosphorylation and transcriptional activation induced by interferons. *EMBO J.* 1999; **18**: 5601-5608.
- Goldring MB, Birkhead J, Sandell LJ, Kimura T, Krane SM. Interleukin 1 suppresses expression of cartilage-specific types II and IX collagens and increases types I and III collagens in human chondrocytes. *J. Clin. Invest.* 1988; **82**: 2026-2037.
- Goldring MB, Fukuo K, Birkhead JR, Dudek E, Sandell LJ. Transcriptional suppression by interleukin-1 and interferon-gamma of type II collagen gene expression in human chondrocytes. *J. Cell. Biochem.* 1994; **54**: 85-99.
- Grabowski PS, Macpherson H, Ralston SH. Nitric oxide production in cells derived from the human joint. *Br. J. Rheumatol.* 1996; **35**: 207-212.
- Gray ML, Pizzanelli AM, Grodzinsky AJ, Lee RC. Mechanical and physicochemical determinants of the chondrocyte biosynthetic response. *J. Orthop. Res.* 1988; **6**: 777-792.
- Green LC, Wagner DA, Glogowski J, Skipper PL, Wishnok JS, Tannenbaum SR. Analysis of nitrate, nitrite and [¹⁵N]nitrate in biological fluids. *Anal Biochem* 1982; **126**: 131-38.
- Greenfeder AS, Nunes P, Kwee L, Labow M, Chizzonite RA, Ju G. Molecular cloning and characterization of a second subunit of the interleukin 1 receptor complex. *J. Biol. Chem.* 1995; **270**: 13757-13765.
- Grimshaw M.J., Mason R.M. Modulation of bovine articular chondrocyte gene expression in vitro by oxygen tension. *Osteoarthritis Cartilage.* 2001; **9**: 357-364.
- Griscavage JM, Rogers NE, Sherman MP, Ignarro LJ. Inducible nitric oxide synthase from a rat alveolar macrophage cell line is inhibited by nitric oxide. *J. Immunol.* 1993; **151**: 6329-6337.
- Gross SS, Wolin MS. Nitric oxide: pathophysiological mechanisms. *Annu. Rev. Physiol.* 1995; **57**: 737-769.

Bibliografia

- Grushko G, Schneiderman R, Maroudas A. Some biochemical and biophysical parameters for the study of the pathogenesis of osteoarthritis. A comparison between processes of ageing and degeneration. *Connect. Tiss. Res.* 1989; **19**: 149-176.
- Guan Z, Baier LD, Morrison AR. p38 mitogen-activated protein kinase down-regulates nitric oxide and up-regulates prostaglandin E₂ biosynthesis stimulated by interleukin-1 β . *J. Biol. Chem.* 1997; **272**: 8083-8089.
- Guerne PA, Carson DA, Lotz M. IL-6 production by human articular chondrocytes. Modulation of its synthesis by cytokines, growth factors, and hormones in vitro. *J. Immunol.* 1990; **144**: 499-505.
- Guerne PA, Sublet A, Lotz M. Growth factor responsiveness of human articular chondrocytes: distinct profiles in primary chondrocytes, subcultured chondrocytes and fibroblasts. *J. Cell. Physiol.* 1994; **158**: 476-484.
- Guerne P-A, Blanco F, Kaelin A, Desgeorges A, Lotz M. Growth factor responsiveness of human articular chondrocytes in aging and development. *Arthritis Rheum.* 1995; **38**: 960-968.
- Guilak F, Zell RA, Erickson GR, Grande DA, Rubin CT, McLeod KJ, Donahue HJ. Mechanically induced calcium waves in articular chondrocytes are inhibited by gadolinium and amiloride. *J. Orthop. Res.* 1999; **17**: 421-429.
- Günther M, Haubeck H-D, van de Leur E, Bläser J, Bender S, Gütgemann I, Fischer D-C, Tschesche H, Greiling H, Heinrich PC, Graeve L. Transforming growth factor β 1 regulates tissue inhibitor of metalloproteinases-1 expression in differentiated human articular chondrocytes. *Arthritis Rheum.* 1994; **37**: 395-405.
- Gurjar MV, Deleon J, Sharma RV, Bhalla RC. Role of reactive oxygen species in IL-1 β -stimulated sustained ERK activation and MMP-9 induction. *Am. J. Physiol.* 2001; **281**: H2568-H2574.
- Haddad JJ. Antioxidant and prooxidant mechanisms in the regulation of redox(y)-sensitive transcription factors. *Cell. Signal.* 2002; **14**: 879-897.
- Hall A, Urban JPG, Gehl K. The effects of hydrostatic pressure on matrix synthesis in articular cartilage. *J. Orthop. Res.* 1991; **9**: 1-10.
- Han J., Lee JD, Bibb SL, Ulevitch RJ. A MAP kinase targeted by endotoxin and in mammalian cells. *Science* 1994; **265**: 808-811.
- Han Z, Boyle DL, Chang L, Bennett B, Karin M; Yang L, Manning AM, Firestein GS. c-Jun N-terminal kinase is required for metalloproteinase expression and joint destruction in inflammatory arthritis. *J. Clin. Invest.* 2001a; **108**: 73-81.
- Han Y-J, Kwon Y-G, Chung H-T, Lee S-K, Simmons RL, Billiar TR, Kim Y-M. Antioxidant enzymes suppress nitric oxide production through the inhibition of NF- κ B activation: role of H₂O₂ and nitric oxide in inducible nitric oxide synthase expression in macrophages. *Nitric Oxide.* 2001b; **5**: 504-513.
- Hardingham TE, Muir H. Hyaluronic acid in cartilage and proteoglycan aggregation. *Biochem. J.* 1974; **139**: 565-581.
- Hascall VC. Interaction of cartilage proteoglycan with hyaluronic acid. *J. Supramolec. Str.* 1977; **7**: 101-120.
- Hashimoto S, Ochs R, Komiya S, Lotz M. Linkage of chondrocyte apoptosis and cartilage degradation in human osteoarthritis. *Arthritis Rheum.* 1998; **41**: 1632-1638.
- Hato T., Pamporti N, Shattil SJ. Complementary roles for receptor clustering and conformational change in adhesive and signaling functions of integrin α IIb β 3. *J. Cell Biol.* 1998; **141**: 1685-1695.

Bibliografia

- Häuselmann HJ, Fernandes RJ, Mok SS, Schmid TM, Block JA, Aydelotte MB, Kuettner KE, Thonar EJ-MA. Phenotypic stability of bovine articular chondrocytes after long-term culture in alginate beads. *J. Cell Sci.* 1994a; **107**: 17-27.
- Häuselmann HJ, Oppiger L, Michel BA, Stefanovic-Racic, Evans CH. Nitric oxide and proteoglycan biosynthesis by human articular chondrocytes in alginate culture. *FEBS Lett.* 1994b; **352**: 361-364.
- Häuselmann HJ, Flechtenmacher J, Michal L, Thonar EJ-MA, Shinmei M, Kuettner KE, Aydelotte MB. The superficial layer of human articular cartilage is more susceptible to interleukin-1-induced damage than the deeper layers. *Arthritis Rheum.* 1996; **39**: 478-488.
- Hayashi T, Abe E, Jasin HE. Fibronectin synthesis in superficial and deep layers of normal articular cartilage. *Arthritis Rheum.* 1996; **39**: 567-573.
- He W, Pelletier JP, Martel-Pelletier J, Laufer S, Di Battista JA. Synthesis of interleukin-1 β , tumor necrosis factor- α and interstitial collagenase (MMP-1) is eicosanoid dependent in human osteoarthritis synovial membrane explants: interactions with antiinflammatory cytokines. *J. Rheumatol.* 2002; **29**: 546-553.
- Hecker M, Preiß C, Schini-Kerth VB. Induction by staurosporine of nitric oxide synthase expression in vascular smooth muscle cells: role of NF- κ B, CREB and C/EBP β . *Br. J. Pharmacol.* 1997; **120**: 1067-1074.
- Heissmeyer V, Krappmann D, Wulczyn FG, Scheidereit C. NF- κ B p105 is a target of I κ B kinases and controls signal induction of Bcl-3-p50 complexes. *EMBO J.* 1999; **18**: 4766-4778.
- Henrotin YE, De Groot DD, Labasse AH, Gaspar SE, Zheng SX, Geenen VG, Reginster JY. Effects of exogenous IL-1 β , TNF α , IL-6, IL-8 and LIF on cytokine production by human articular chondrocytes. *Osteoarthritis Cartilage.* 1996; **4**: 163-173.
- Henrotin YE, Zheng SX, Deby GP, Labasse AH, Crielaard JMR, Reginster JYL. Nitric oxide down-regulates interleukin-1 β (IL-1 β) stimulated IL-6, IL-8, and prostaglandin E₂ production by human chondrocytes. *J. Rheumatol.* 1998; **25**: 1595-1601.
- Henrotin YE, Zheng SX, Labasse AH, Deby GP, Crielaard JM, Reginster JY. Modulation of human chondrocyte metabolism by recombinant human interferon. *Osteoarthritis Cartilage.* 2000; **8**: 474-482.
- Hering TM. Regulation of chondrocyte gene expression. *Front. Biosci.* 1999; **4**: D743-761.
- Hering TM, Kollar J, Huynh TD, Varelas JB, Sandell LJ. Modulation of extracellular matrix gene expression in bovine high density chondrocyte cultures by ascorbic acid and enzymatic resuspension. *Arch. Biochem. Biophys.* 1994; **314**: 90-98.
- Herlaar E, Brown Z. p38 MAPK signalling cascades in inflammatory disease. *Mol. Med. Today.* 1999; **5**: 439-447.
- Hildebrand JD, Schaller MD, Parsons JT. Paxillin, a tyrosine phosphorylated focal adhesion-associated protein binds to the carboxyl terminal domain of focal adhesion kinase. *Mol. Biol. Cell.* 1995; **6**: 637-647.
- Hirsch MS, Lunsford LE, Trinkaus-Randall V, Svoboda KK. Chondrocyte survival and differentiation *in situ* are integrin mediated. *Dev. Dyn.* 1997; **210**: 249-263.
- Hoare GS, Marcin N, Chester AH, Yacoub MH. Role of oxidant stress in cytokine-induced activation of NF- κ B in human aortic smooth muscle cells. *Am. J. Physiol.* 1999; **277**: H1975-H1984.

Bibliografia

- Hocking D.C, Sottile J., McKeown-Longo P.J. Activation of distinct $\alpha_5\beta_1$ -mediated signaling pathways by fibronectin's cell adhesion and matrix assembly domains. *J. Cell Biol.* 1998; **141**: 241-253.
- Hollander AP, Pidoux I, Reiner A, Rorabeck C, Bourne R, Poole AR. Damage to type II collagen in aging and osteoarthritis starts at the articular surface, originates around chondrocytes, and extends into the cartilage with progressive degeneration. *J. Clin. Invest.* 1995; **96**: 2859-2869.
- Holmwall K, Camper L, Johansson S, Kimura JH, Lundgren-Akerlund E. Chondrocyte and chondrosarcoma cell integrins with affinity for collagen type II and their response to mechanical stress. *Exp. Cell Res.* 1995; **221**: 496-503.
- Homandberg GA, Wen C. Exposure of cartilage to a fibronectin fragment amplifies catabolic processes while also enhancing anabolic processes to limit damage. *J. Orthop. Res.* 1998; **16**: 237-246.
- Homandberg G.A., Kramer J., Grant D., Christianson G., Eisenstein R. Heparin-binding fragments of fibronectin are potent inhibitors of endothelial cell growth: structure-function correlations. *Biochim. Biophys. Acta.* 1986; **874**: 61-71.
- Homandberg D.A., Dunn B., Grant D., Bartley D., Eisenstein R. Synthetic peptides of the amino-terminus of fibronectin inhibit endothelial cell growth. *Cell Biol. Int. Rep.* 1989; **13**: 891-900.
- Homandberg GA, Meyers R, Xie D-L. Fibronectin fragments cause chondrolysis of bovine articular cartilage slices in culture. *J. Biol. Chem.* 1992; **267**: 3597-3604.
- Horai R, Saijo S, Tanioka H, Nakae S, Sudo K, Okahara A, Ikuse T, Asano M, Iwakura Y. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin-1 receptor antagonist-deficient mice. *J. Exp. Med.* 2000; **191**: 313-320.
- Huang J, Gao X, Li S, Cao Z. Recruitment of IRAK to the interleukin 1 receptor complex requires interleukin 1 receptor accessory protein. *Proc. Natl. Acad. Sci. USA.* 1997; **94**: 12829-12832.
- Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released by artery and vein is nitric oxide. *Proc. Natl. Acad. Sci. USA.* 1987; **84**: 9265-9269.
- Imai K, Ohta S, Matsumoto T, Fujimoto N, Sato H, Seiki M, Okada Y. Expression of membrane-type 1 matrix metalloproteinase and activation of progelatinase A in human osteoarthritic cartilage. *Am. J. Pathol.* 1997; **151**: 245-256.
- Ishibashi H, Takenoshita Y, Ishibashi K, Oka M. Age-related changes in the human mandibular condyle: a morphologic, radiologic and histologic study. *J. Oral Maxillofac. Surg.* 1995; **53**: 1016-1023.
- Ishida O, Tanaka Y, Morimoto I, Takigawa M, Eto S. Chondrocytes are regulated by cellular adhesion through CD44 and hyaluronic acid pathway. *J. Bone Miner. Res.* 1997; **12**: 1657-1663.
- Ishii H, Tanaka H, Katoh K, Nakamura H, Nagashima M, Yoshino S. Characterization of infiltrating T cells and Th1/Th2 cytokines in the synovium of patients with osteoarthritis. *Osteoarthritis Cartilage.* 2002; **10**: 277-281.
- Ishizaki Y, Burne JF, Raff MC. Autocrine signals enable chondrocytes to survive in culture. *J. Cell Biol.* 1994; **126**: 1069-1077.
- Ito CY, Kazantsev AG, Baldwin AS Jr. Three NF-kappa B sites in the I kappa B-alpha promoter are required for induction of gene expression by TNF alpha. *Nucleic Acids Res.* 1994; **22**: 3787-3792.
- Iwakura Y. Roles of IL-1 in the development of rheumatoid arthritis: considerations from mouse models. *Cytokine Growth Factor Rev.* 2002; **13**: 341-355.

Bibliografia

- Jacques C, Bereziat G, Humbert L, Corvol M, Olivier JL, Masliah J, Berenbaum F. Post-transcriptional effect of IGF-1 on IL-1 β -induced type II secreted phospholipase A2 gene expression in rabbit articular chondrocytes. *J. Clin. Invest.* 1997; **99**: 1864-1872.
- Jakob M, Démarteau O, Schäfer D, Hintermann B, Dick W, Heberer M, Martin I. Specific growth factors during the expansion and redifferentiation of adult human articular chondrocytes enhance chondrogenesis and cartilaginous tissue formation *in vitro*. *J. Cell. Biochem.* 2001; **81**: 368-377.
- Janero DR. Nitric oxide (NO)-related pharmaceuticals: contemporary approaches to therapeutic NO modulation. *Free Radic. Biol. Med.* 2000; **28**: 1495-1506.
- Janssen-Heininger YM, Macara I, Mossman BT. Cooperativity between oxidants and tumor necrosis factor in the activation of nuclear factor (NF)- κ B: requirement of Ras/mitogen-activated protein kinases in the activation of NF- κ B by oxidants. *Am J. Respir. Cell. Mol. Biol.* 1999; **20**: 942-952.
- Jiang B, Brecher P, Cohen RA. Persistent activation of nuclear factor- κ B by interleukin-1 β and subsequent inducible NO synthase expression requires extracellular signal-regulated kinase. *Arterioscler. Thromb. Vasc. Biol.* 2001; **21**: 1915-1920.
- Jin D-Y, Chae HZ, Rhee SG, Jeang K-T. Regulatory role for a novel human thioredoxin peroxidase in NF- κ B activation. *J. Biol. Chem.* 1997; **272**: 30952-30961.
- Jobanputra P, Lin H, Jenkins K, Bavington C, Brennan FR, Nuki G, Salter DM, Godolphin JL. Modulation of human chondrocyte integrins by inflammatory synovial fluid. *Arthritis Rheum.* 1996; **39**: 1430-1434.
- Jones KL, Brown M, Ali SY, Brown RA. An immunohistochemical study of fibronectin in human osteoarthritic and disease-free articular cartilage. *Ann. Rheum. Dis.* 1987; **46**: 809-811.
- Joosten LA, Helsen MM, van de Loo FA, van den Berg WB. Anticytokine treatment of established type II collagen-induced arthritis in DBA/1 mice. A comparative study using anti-TNF alpha, anti-IL-1 alpha/beta, and IL-1Ra. *Arthritis Rheum.* 1996; **39**: 797-809.
- Joosten LA, Lubberts E, Helsen MM, Saxne T, Coenen-de Roo CJ, Heinegård D, van den Berg WB. Protection against cartilage and bone destruction by systemic interleukin-4 treatment in established murine type II collagen-induced arthritis. *Arthritis Res.* 1999a; **1**: 81-91.
- Joosten LA, Helsen MM, Saxne T, van de Loo FA, Heinegård D, van den Berg WB. IL-1 alpha beta blockade prevents cartilage and bone destruction in murine type II collagen-induced arthritis, whereas TNF-alpha blockade only ameliorates joint inflammation. *J. Immunol.* 1999b; **163**: 5049-5055.
- Jovanovic D, Pelletier JP, Alaaeddine N, Mineau F, geng C, Ranger P, Martel-Pelletier J. Effect of IL-13 on cytokines, cytokine receptors and inhibitors on human osteoarthritis synovium and synovial fibroblasts. *Osteoarthritis Cartilage.* 1998; **6**: 40-49.
- Kandel RA, Petelycky M, Dinarello CA, Minden M, Pritzker KPH, Cruz TF. Comparison of the effect of interleukin 6 and interleukin 1 on collagenase and proteoglycan production by chondrocytes. *J. Rheumatol.* 1990; **17**: 953-957.
- Kanno S, Lee PC, Zhang Y, Ho C, Griffith BP, Shears LL, Billiar TR. Attenuation of myocardial ischemia/reperfusion injury by superinduction of inducible nitric oxide synthase. *Circulation.* 2000; **101**: 2742-2748.
- Karin M. How NF- κ B is activated: the role of the I κ B kinase complex (IKK) complex. *Oncogene.* 1999; **18**: 6867-6874.
- Karin M, Liu Z, Zandi E. AP-1 function and regulation. *Curr. Opin. Cell Biol.* 1997; **9**: 240-246.

Bibliografia

- Katsuyama K, Shichiri M, marumo F, Hirata Y. NO inhibits cytokine-induced iNOS expression and NF-kappaB activation by interfering with phosphorylation and degradation of I kappa B-alpha. *Arterioscler. Thromb. Vasc. Biol.* 1998; **18**: 1796-1802.
- Kempson GE, Muir H, Freeman MAR, Swanson SAV. Correlations between the compressive stiffness and chemical constituents of human articular cartilage. *Biochim. Biophys. Acta.* 1970; **215**: 70-77.
- Kempson GE, Muir H, Pollard C, Tuke M. The tensile properties of the cartilage of human femoral condyles related to the content of collagen and glycosaminoglycans. *Biochim. Biophys. Acta.* 1973; **297**: 465-472.
- Kienzle G, von Kempis J. Vascular cell adhesion molecule 1 (CD106) on primary human articular chondrocytes: functional regulation of expression by cytokines and comparison with intercellular adhesion molecule 1 (CD54) and very late activation antigen 2. *Arthritis Rheum.* 1998; **41**: 1296-1305.
- Kinashi T, Katagiri K, Watanabe S, Vanhaesebroeck B, Downward J, Takatsu K. Distinct mechanisms of $\alpha_5\beta_1$ integrin activation by Ha-Ras and R-Ras. *J. Biol. Chem.* 2000; **275**: 22590-22596.
- Kinugawa K, Shimizu T, Yao A, Kohmoto O, Serizawa T, Takahashi T. Transcriptional regulation of inducible nitric oxide synthase in cultured neonatal cardiac myocytes. *Circ. Res.* 1997; **81**: 911-921.
- Kishimoto K, Matsumoto K, Ninomiya-Tsuji J. TAK1 mitogen-activated protein kinase is activated by auto-phosphorylation within its activation loop. *J. Biol. Chem.* 2000; **275**: 7359-7364.
- Kleinert H, Wallerath T, Fritz G, Ihrig-Biedert I, Rodriguez-Pascual F, Geller DA, Förstermann U. Cytokine induction of NO synthase II in human DLD-1 cells: roles of the JAK-STAT, AP-1 and NF- κ B signalling pathways. *Br. J. Pharmacol.* 1998a; **125**: 193-201.
- Kleinert H, Euchenhofer C, Fritz G, Ihrig-Biedert I, Förstermann U. Involvement of protein kinases in the induction of NO synthase II in human DLD-1 cells. *Br. J. Pharmacol.* 1998b; **123**: 1716-1722.
- Knauper V, Will H, Lopez-Otin C, Smith B, Atkinson SJ, Stanton H, Hembry RM, Murphy G. Cellular mechanisms for human procollagenase-3 (MMP-13) activation: evidence that MT1-MMP (MMP-14) and gelatinase A (MMP-2) are able to generate active enzyme. *J. Biol. Chem.* 1996; **271**: 17124-17131.
- Knott I, Dieu M, Burton M, Houbion A, Remacle J, Raes M. Induction of cyclooxygenase by interleukin 1: comparative study between human synovial cells and chondrocytes. *J. Rheumatol.* 1994; **21**: 462-466.
- Knowles RG, Moncada S. Nitric oxide synthases in mammals. *Biochem. J.* 1994; **298**: 249-258.
- Knox P, Levick JR, McDonald J. Synovial fluid – its mass, macromolecular content and pressure in the major limb joints of the rabbit. *Q. J. Exp Physiol.* 1988; **73**: 33-45.
- Kobayashi N, Kadono Y, Naito A, Matsumoto K, Yamamoto T, Tanaka S, Inoue J. Segregation of TRAF6-mediated signaling pathways clarifies its role in osteoclastogenesis. *EMBO J.* 2001; **20**: 1271-1280.
- Koshy PJ, Henderson N, Logan C, Life PF, Cawston TE, Rowan AD. Interleukin 17 induces cartilage collagen breakdown: novel synergistic effects in combination with proinflammatory cytokines. *Ann. Rheum. Dis.* 2002; **61**: 704-713.

Bibliografia

- Kristof AS, Marks-Konczalik J, Moss J. Mitogen-activated protein kinases mediate activator protein-1-dependent human inducible nitric oxide synthase promoter activation. *J. Biol. Chem.* 2001; **276**: 8445-8452.
- Kuettner K, Thonar E, Aydelotte M. Articular cartilage – structure and chondrocyte metabolism. In Muir H, Hirohata K, Shichikawa K (eds.). *Mechanisms of articular cartilage damage and repair in Osteoarthritis*. Hans Huber publishers. Toronto. 1990. 11-30.
- Kuiper S, Joosten LA, Bendele AM, Edwards CK, Arntz OJ, Helsen MM, van de Loo FA, van den Berg WB. Different roles of tumour necrosis factor alpha and interleukin 1 in murine streptococcal cell wall arthritis. *Cytokine*. 1998; **10**: 690-702.
- Kuo PC, Abe K, Schroeder RA. Superoxide enhances interleukin 1 β -mediated transcription of the hepatocyte-inducible nitric oxide synthase gene. *Gastroenterology*. 2000; **118**: 608-618.
- Lafyatis R, Kim S-J, Angel P, Roberts AB, Sporn MB, Karin M, Wilder RL. Interleukin-1 stimulates and all-trans-retinoic acid inhibits collagenase gene expression through its 5' activator protein-1-binding site. *Mol. Endocrinol.* 1990; **4**: 973-980.
- Lai WM, Mow VC, Sun DD, Ateshian GA. On the electric potentials inside a charged soft hydrated biological tissue: streaming potential versus diffusion potential. *J. Biomech. Eng.* 2000; **122**: 336-346.
- Lakshminarayanan V, Drab-Weiss EA, Roebuck KA. H₂O₂ and tumor necrosis factor- α induce differential binding of the redox-responsive transcription factors AP-1 and NF- κ B to the interleukin-8 promoter in endothelial and epithelial cells. *J. Biol. Chem.* 1998; **273**: 32670-32678.
- Lander HM, Sehajpal P, Levine DM, Novogrodsky A. Activation of human peripheral blood mononuclear cells by nitric oxide-generating compounds. *J. Immunol.* 1993; **105**: 1509-1516.
- Lang D, Knop J, Wesche H, Raffetseder U, Kurrale R, Boraschi D, Martin MU. The type II IL-1 receptor interacts with the IL-1 receptor accessory protein: a novel mechanism of regulation of IL-1 responsiveness. *J. Immunol.* 1998; **161**: 6871-6877.
- Lapadula G, Iannone F, Zuccaro C, Grattagliano V, Covelli M, Patella V, Lo Bianco G, Pipitone V. Chondrocyte phenotyping in human osteoarthritis. *Clin. Rheumatol.* 1998; **17**: 99-104.
- LaPointe MC, Isenovi E. Interleukin-1 β regulation of inducible nitric oxide synthase and cyclooxygenase-2 involves the p42/44 and p38 MAPK signaling pathways in cardiac myocytes. *Hypertension* 1999; **33**, 276-282.
- LaPointe MC, Sitkins JR. Mechanisms of interleukin-1 β regulation of nitric oxide synthase in cardiac myocytes. *Hypertension*. 1996; **27**: 709-714.
- LeBel CP, Ali SF, McKee M, Bondy SC. Organometal-induced increases in reactive oxygen species: the potential of 2',7'-dichlorofluorescein diacetate as an index of neurotoxic damage. *Toxicol. Appl. Pharmacol.* 1990; **104**: 17-24.
- Leblanc D, Chantre P, Fournie B. Harpagophytum procumbens in the treatment of knee and hip osteoarthritis. Four-month results of a prospective, multicenter, double-blind trial versus diacerhein. *Joint Bone Spine*. 2000; **67**: 462-467.
- Lee J-I, Burckart GJ. Nuclear Factor Kappa B: important transcription factor and therapeutic target. *J. Clin. Pharmacol.* 1998; **38**: 981-993.
- Lee M, Koh WS. Raf-independent and MEKK1-dependent activation of NF- κ B by hydrogen peroxide in 70Z/3 pre-lymphocyte tumor cells. *J. Cell. Biochem.* 2003; **88**: 545-556.

Bibliografia

- Lee W, Haslinger A, Karin M, Tjian R. Activation of transcription by two factors that bind promoter and enhancer sequences of the human metallothionein gene and SV40. *Nature*. 1987; **325**: 368-372.
- Lee DA, Bentley G, Archer CW. Proteoglycan depletion alone is not sufficient to stimulate proteoglycan synthesis in cultured bovine cartilage explants. *Osteoarthritis Cartilage*. 1994; **2**: 175-185.
- Lee B-S, Kang H-S, Pyun K-H, Choi I. Roles of tyrosine kinases in the regulation of nitric oxide synthesis in murine liver cells: modulation of NF- κ B activity by tyrosine kinases. *Hepatology*. 1997a; **25**: 913-919.
- Lee FS, Hagler J, Chen ZJ, Maniatis T. Activation of I κ B α kinase complex by MEKK1, a kinase of the JNK pathway. *Cell*. 1997b; **88**: 213-222.
- Lee HS, Milward-Sadler SJ, Wright MO, Nuki G, Salter DM. Integrin and mechanosensitive ion channel-dependent tyrosine phosphorylation of focal adhesion proteins and β -catenin in human articular chondrocytes after mechanical stimulation. *J. Bone Miner. Res.* 2000; **15**: 1501-1509.
- Lee JW, Qi WN, Scully SP. The involvement of β_1 integrin in the modulation by collagen of the chondrocyte response to transforming growth factor- β 1. *J. Orthop. Res.* 2002; **20**: 66-75.
- Legendre F, Dudhia J, Pujol JP, Bogdanowicz P. JAK/STAT but Not ERK1/ERK2 Pathway Mediates Interleukin (IL)-6/Soluble IL-6R Down-regulation of Type II Collagen, Aggrecan Core, and Link Protein Transcription in Articular Chondrocytes. Association with a down-regulation of SOX-9 expression. *J. Biol. Chem.* 2003; **278**: 2903-2912.
- Lemare F, Steinberg N, Le Griel C, Demignot S, Adolphe M. Dedifferentiated chondrocytes cultured in alginate beads: restoration of the differentiated phenotype and of the metabolic responses to interleukin-1 β . *J. Cell. Physiol.* 1998; **176**: 303-313.
- Li Y, Trush MA. Diphenyleneiodonium, an NAD(P)H oxidase inhibitor, also potently inhibits mitochondrial reactive oxygen species production. *Biochem. Biophys. Res. Commun.* 1998; **253**: 295-299.
- Li WQ, Zafarullah M. Oncostatin M up-regulates tissue inhibitor of metalloproteinases-3 gene expression in articular chondrocytes via de novo transcription, protein synthesis, and tyrosine kinase- and mitogen-activated protein kinase-dependent mechanisms. *J. Immunol.* 1998; **161**: 5000-5007.
- Li WQ, Dehnade F, Zafarullah M. Oncostatin M-induced matrix metalloproteinase and tissue inhibitor of metalloproteinase-3 genes expression in chondrocytes requires Janus kinase/STAT signaling pathway. *J. Immunol.* 2001a; **166**: 3491-3498.
- Li X, Commane M, Jiang Z, Stark GR. IL-1-induced NF- κ B and c-Jun N-terminal kinase (JNK) activation diverge at IL-1 receptor-associated kinase (IRAK). *Proc. Natl. Acad. Sci. USA*. 2001b; **98**: 4461-4465.
- Li S, Strelow A, Fontana EJ, Wesche H. IRAK-4; a novel member of the IRAK family with properties of an IRAK-kinase. *Proc. Natl. Acad. Sci. USA*. 2002a; **99**: 5567-5572.
- Li X, Massa PE, Hanidu A, Peet GW, Aro P, Savitt A, Mische S, Li J, Marcu KB. IKK α , IKK β , and NEMO/IKK γ are each required for the NF- κ B-mediated inflammatory response program. *J. Biol. Chem.* 2002b; **277**: 45129-45140.
- Lin L, DeMartino GN, Greene WC. Cotranslational biogenesis of NF- κ B p50 by the 26S proteasome. *Cell*. 1998; **92**: 819-828.

Bibliografia

- Lindy O, Kontinen YT, Sorsa T, Ding Y, Santavirta S, Ceponis A, López-Otín C. Matrix metalloproteinase 13 (collagenase 3) in human rheumatoid synovium. *Arthritis Rheum.* 1997; **40**: 1391-1399.
- Little CB, Flannery CR, Hughes CE, Mort JS, Roughley PJ, Dent C, Caterson B. Aggrecanase versus matrix metalloproteinases in the catabolism of the interglobular domain of aggrecan in vitro. *Biochem. J.* 1999; **344**: 61-68.
- Lo YYC, Cruz TF. Involvement of reactive oxygen species in cytokine and growth factor induction of *c-fos* expression in chondrocytes. *J. Biol. Chem.* 1995; **270**: 11727-11730.
- Lo YYC, Wong JMS, Cruz TF. Reactive oxygen species mediate cytokine activation of c-Jun NH₂-terminal kinases. *J. Biol. Chem.* 1996; **271**: 15703-15707.
- Lo YYC, Conquer JA, Grinstein S, Cruz TF. Interleukin-1 β induction of *c-fos* and collagenase expression in articular chondrocytes: involvement of reactive oxygen species. *J. Cell. Biochem.* 1998; **69**: 19-29.
- Loeser RF. Growth factor regulation of chondrocyte integrins. Differential effects of insulin-like growth factor 1 and transforming growth factor β on $\alpha_1\beta_1$ integrin expression and chondrocyte adhesion to type VI collagen. *Arthritis Rheum.* 1997; **40**: 270-276.
- Loeser RF, Carlson CS, McGee MP. Expression of β_1 integrins by cultured articular chondrocytes and in osteoarthritic cartilage. *Exp. Cell Res.* 1995; **217**: 248-257.
- Loeser RF, Sadiev S, Tan L, Goldring MB. Integrin expression by primary and immortalized human chondrocytes: evidence of a differential role for $\alpha_1\beta_1$ and $\alpha_2\beta_1$ integrins in mediating chondrocyte adhesion to types II and VI collagen. *Osteoarthritis Cartilage.* 2000; **8**: 96-105.
- Lotz M, Blanco FJ, von Kempis J, Dudler, Maier R, Villiger PM, Geng Y. Cytokine regulation of chondrocyte functions. *J. Rheumatol.* 1995a; **22** (supp. 43): 104-108.
- Lotz M, Rosen F, McCabe G, Quach J, Blanco F, Dudler J, Solan J, Goding J, Seegmiller JE, Terkeltaub R. Interleukin 1 β suppresses transforming growth factor-induced inorganic pyrophosphate (PPi) production and expression of the PPi-generating enzyme PC-1 in human chondrocytes. *Proc. Natl. Acad. Sci. USA.* 1995b; **92**: 10364-10368.
- Lowenstein CJ, Alley EW, Raval P, Snowman AM, Snyder SH, Russell SW, Murphy WJ. Macrophage nitric oxide synthase gene: two upstream regions mediate induction by interferon- γ and lipopolysaccharide. *Proc. Natl. Acad. Sci. USA.* 1993; **90**: 9730-9734.
- Loyau G, Pujol JP. The role of cytokines in the development of osteoarthritis. *Scand J Rheumatol Suppl* 1990; **81**: 8-12.
- Lubberts E, Joosten LA, Helsen MM, van den Berg WB. Regulatory role of interleukin 10 in joint inflammation and cartilage destruction in murine streptococcal cell wall (SCW) arthritis. More therapeutic benefit with IL-4/IL-10 combination therapy than with IL-10 treatment alone. *Cytokine.* 1998; **10**:361-369.
- Lubberts E, Joosten LA, van Den Bersselaar L, Helsen MM, Bakker AC, van Meurs JB, Graham FL, Richards CD, van Den Berg WB. Adenoviral vector-mediated overexpression of IL-4 in the knee joint of mice with collagen-induced arthritis prevents cartilage destruction. *J. Immunol.* 1999; **163**: 4546-4556.
- Lubberts E, Joosten LA, van de Loo FA, van den Gersselaar LA, van den Berg WB. Reduction of interleukin-17-induced inhibition of chondrocyte proteoglycan synthesis in intact murine articular cartilage by interleukin-4. *Arthritis Rheum.* 2000; **43**: 1300-1306.

Bibliografia

- Lui KE, Panchal AS, Santhanagopal A, Dixon SJ, Bernier SM. Epidermal growth factor stimulates proton efflux from chondrocytic cells. *J. Cell. Physiol.* 2002; **192**: 102-112.
- Lukiw WJ, Bazan NG. Strong nuclear factor- κ B-DNA binding parallels cyclooxygenase-2 gene transcription in aging and in sporadic Alzheimer's disease superior temporal lobe neocortex. *J. Neurosci. Res.* 1998; **53**: 583-592.
- Lum Z-P, Hakala BE, Mort JS, Recklies AD. Modulation of the catabolic effects of interleukin-1 β on human articular chondrocytes by transforming growth factor- β . *J. Cell. Physiol.* 1996; **166**: 351-359.
- Luo L, Cruz T, McCulloch C. Interleukin 1-induced calcium signalling in chondrocytes requires focal adhesions. *Biochem. J.* 1997; **324**: 653-658.
- Luss H, DiSilvio M, Litton AL, Molina y Vedia L, Nussler AK, Billiar TR. Inhibition of nitric oxide synthesis enhances the expression of inducible nitric oxide synthase mRNA and protein in a model of chronic liver inflammation. *Biochem. Biophys. Res. Commun.* 1994; **204**: 635-640.
- MacNaul K.L., Chartrain N., Lark M., Tocci M.J., Hutchinson N.I. Discoordinate expression of stromelysin, collagenase and tissue inhibitor of metalloproteinase-1 in rheumatoid human synovial fibroblasts: synergistic effects of interleukin-1 and tumor necrosis factor- α on stromelysin expression. *J. Biol. Chem.* 1990; **265**: 17238-17245.
- Maeda S, Sawai T, Uzuki M, Takahashi Y, Omoto H, Seki M, Sakurai M. Determination of interstitial collagenase (MMP-1) in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 1995; **54**: 970-975.
- Maier R, Wisniewski HG, Vilcek J, Lotz M. TSG-6 expression in human articular chondrocytes. Possible implications in joint inflammation and cartilage degradation. *Arthritis Rheum.* 1996; **39**: 552-559.
- Malinin NL, Boldin MP, Kovalenko AV, Wallach D. MAP3K-related kinase involved in NF- κ B induction by TNF, CD95 and IL-1. *Nature.* 1997; **385**: 540-544.
- Manna SK, Zhang HJ, Yan T, Oberley LW, Aggarwal BB. Overexpression of manganese superoxide dismutase suppresses tumor necrosis factor-induced apoptosis and activation of Nuclear Transcription Factor- κ B and Activated Protein-1. *J. Biol. Chem.* 1998; **273**: 13245-13254.
- Marcus RE, Srivastava VML. Effect of low oxygen tensions on glucose metabolising enzymes in cultured articular chondrocytes. *Proc. Soc. Exp. Biol. Med.* 1973; **143**: 488-491.
- Marks-Konczalik J, Chu SC, Moss J. Cytokine-mediated transcriptional induction of the human inducible nitric oxide synthase gene requires both activator protein 1 and nuclear factor κ B-binding sites. *J. Biol. Chem.* 1998; **273**: 22201-22208.
- Marmiroli S, Bavelloni A, Faenza I, Sirri A, Ognibene A, Cenni V, Tsukada J, Koyama Y, Ruzzene M, Ferri A, Auron PE, Toker A, Maraldi NM. Phosphatidylinositol 3-kinase is recruited to a specific site in the activated IL-1 receptor I. *FEBS Lett.* 1998; **438**: 49-54.
- Maroudas A. Distribution and diffusion of solutes in articular cartilage. *Biophys. J.* 1970; **10**: 365-379.
- Maroudas A. Balance between swelling pressure and collagen tension in normal and degenerate cartilage. *Nature.* 1976; **260**: 808-809.
- Martel-Pelletier J, Faure MP, McCollum R, Pelletier JP. Plasmin, plasminogen activators and inhibitor in human osteoarthritic cartilage. *J. Rheumatol.* 1991; **18**: 1863-1871.

Bibliografia

- Martel-Pelletier J, Mineau F, Jolicoeur FC, Cloutier JM, Pelletier JP. In vitro effects of diacerhein and rhein on interleukin 1 and tumor necrosis factor- α systems in human osteoarthritic synovium and chondrocytes. *J. Rheumatol.* 1998; **25**: 753-762.
- Martel-Pelletier J, Mineau F, Jovanovic D, Di Battista JA, Pelletier JP. Mitogen-activated protein kinase and nuclear factor kappaB together regulate interleukin-17-induced nitric oxide production in human osteoarthritic chondrocytes: possible role of transactivating factor mitogen-activated protein kinase-activated protein kinase (MAPKAPK). *Arthritis Rheum.* 1999; **42**: 2399-2409.
- Martin UM, Wesche H. Summary and comparison of the signaling mechanisms of the Toll/interleukin-1 receptor family. *Biochim. Biophys. Acta.* 2002; **1592**: 265-280.
- Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-1 β . *Mol. Cell.* 2002; **10**: 417-426.
- Massaad C, Paradon M, Jacques C, Salvat C, Bereziat G, Berenbaum F, Olivier J-L. Induction of secreted type IIA Phospholipase A₂ gene transcription by interleukin-1 β . Role of C/EBP factors. *J. Biol. Chem.* 2000; **275**: 22686-22694.
- Matsukawa A, Yoshimura T, Miyamoto K, Ohkawara S, Yoshinaga M. Analysis of the inflammatory cytokine network among TNF alpha, IL-1 beta, IL-1 receptor antagonist, and IL-8 in LPS-induced rabbit arthritis. *Lab. Invest.* 1997; **76**: 629-638.
- May MJ, Ghosh S. Rel/NF- κ B and I κ B proteins: an overview. *Sem. Cancer Biol.* 1997; **8**: 63-73.
- Mayo LD, Kessler KM, Pincheira R, Warren RS, Donner DB. Vascular endothelial cell growth factor activates CRE-binding protein by signaling through the KDR receptor tyrosine kinase. *J. Biol. Chem.* 2001; **276**: 25184-25189.
- McCartney-Francis N, Allen JB, Mizel DE, Albina JE, Xie Q-W, Nathan CF, Wahl SM. Suppression of arthritis by an inhibitor of nitric oxide synthase. *J. Exp. Med.* 1993; **178**: 749-754.
- McGuire JJ, Anderson DJ, McDonald BJ, Narayanasami R, Bennett BM. Inhibition of NADPH-cytochrome P450 reductase and glyceryl trinitrate biotransformation by diphenyleneiodonium sulfate. *Biochem. Pharmacol.* 1998; **56**: 881-893.
- Melchiorri C, Meliconi R, Frizziero L, Silvestri T, Pulsatelli L, Mazzetti I, Borzì RM, Uggioni M, Facchini A. Enhanced and coordinated in vivo expression of inflammatory cytokines and nitric oxide synthase by chondrocytes from patients with osteoarthritis. *Arthritis Rheum.* 1998; **41**: 2165-2174.
- Mendler M, Eich-Bender SG, Vaughan L, Winterhalter KH. Cartilage contains mixed fibrils of collagen type II, IX, and XI. *J. Cell Biol.* 1989; **108**: 191-197.
- Mengshol JA, Vincenti MP, Coon CI, Barchowsky A, Brinckerhoff CE. Interleukin-1 induction of collagenase 3 (matrix metalloproteinase 13) gene expression in chondrocytes requires p38, c-Jun N-terminal kinase, and Nuclear Factor κ B. *Arthritis Rheum.* 2000; **43**: 801-811.
- Mengshol JA, Vincenti MP, Brinckerhoff CE. IL-1 induces collagenase-3 (MMP-13) promoter activity in stably transfected chondrocytic cells: requirement for Runx-2 and activation by p38 MAPK and JNK pathways. *Nucleic Acids Res.* 2001; **29**: 4361-4372.
- Mengshol JA, Mix KS, Brinckerhoff CE. Matrix metalloproteinases as therapeutic targets in arthritic diseases. Bull's-eye or missing the mark? *Arthritis Rheum.* 2002; **46**: 13-20.
- Mereto E, Ghia M, Brambilla G. Evaluation of the potential carcinogenic activity of Senna and Cascara glycosides for the rat colon. *Cancer Lett.* 1996; **101**: 79-83.

Bibliografia

- Meydan M, Grunberger T, Dadi H, Shahar M, Arpaia E, Lapidot Z, Leeder JS, Freedman M, Cohen A, Gazit A, Levitzki A, Roifman CM. Inhibition of acute lymphoblastic leukaemia by a Jak-2 inhibitor. *Nature*. 1996; **379**: 645-648.
- Meyer M, Schreck R, Baeuerle PA. H_2O_2 and antioxidants have opposite effects on activation of NF- κ B and AP-1 in intact cells: AP-1 as secondary antioxidant-responsive factor. *EMBO J*. 1993; **12**: 2005-2015.
- Meyer CF, Wang X, Chang C, Templeton D, Tan TH. Interaction between c-Rel and the mitogen-activated protein kinase kinase kinase 1 signaling cascade in mediating NF- κ B enhancer activation. *J. Biol. Chem.* 1996; **271**: 8971-8976.
- Michiels C, Minet E, Mottet D, Raes M. Regulation of gene expression by oxygen: NF- κ B and HIF-1, two extremes. *Free Radic. Biol. Med.* 2002; **33**: 1231-1242.
- Miesel R, Kurpisz M, Kröger H. Suppression of inflammatory arthritis by simultaneous inhibition of nitric oxide synthase and NADPH oxidase. *Free Radic. Biol. Med.* 1996; **20**: 75-81.
- Miller EJ, Lunde LG. Isolation and characterization of the cyanogen bromide peptides from the α (II) chain of bovine and human cartilage collagen. *Biochemistry*. 1973; **12**: 3153-3159.
- Miller RR, McDevitt CA. Thrombospondin is present in articular cartilage and is synthesized by articular chondrocytes. *Biochem. Biophys. Res. Commun.* 1988; **153**: 708-714.
- Milligan AS, Owens MW, Grisham MB. Augmentation of cytokine-induced nitric oxide synthesis by hydrogen peroxide. *Am. J. Physiol.* 1996; **271**: L114-L120.
- Millward-Sadler SJ, Wright MO, Lee H, Nishida K, Caldwell H, Nuki G, Salter DM. Integrin-regulated secretion of IL-4: a novel pathway of mechanotransduction in human articular chondrocytes. *J. Cell Biol.* 1999; **145**: 183-189.
- Millward-Sadler SJ, Wright MO, Davies LW, Nuki G, Salter DM. Mechanotransduction via integrins and interleukin-1 results in altered aggrecan and matrix metalloproteinase 3 gene expression in normal, but not osteoarthritic, human articular chondrocytes. *Arthritis Rheum.* 2000; **43**: 2091-2099.
- Minden A, Lin A, Claret FX, Abo A, Karin M. Selective activation of the JNK signaling cascade and c-Jun transcriptional activity by the small GTPases Rac and Cdc42Hs. *Cell*. 1995; **81**: 1147-1157.
- Miossec P. The Th1/Th2 cytokine balance in arthritis. In Miossec P, van den Berg WB, Firestein GS (eds.) T cells in arthritis. Birkhäuser. Basel. 1998. 93-109.
- Mitrovic DM, Quintero M, Starhovic A, Rychewaert A. Cell density of adult human femoral condylar articular cartilage. Joints with normal and fibrillated surfaces. *Lab. Invest.* 1983; **49**: 309-316.
- Miyamoto S, Teramoto H, Coso OA, Gutkind JS, Burbelo PD, Akiyama SK, Yamada KM. Integrin function: molecular hierarchies of cytoskeletal and signaling molecules. *J. Cell Biol.* 1995; **131**: 791-805.
- Miyazaki Y, Tsukazaki T, Hirota Y, Yonekura A, Osaki M, Shindo H, Yamashita S. Dexamethasone inhibition of TGF β -induced cell growth and type II collagen mRNA expression through ERK-integrated AP-1 activity in cultured rat articular chondrocytes. *Osteoarthritis Cartilage*. 2000; **8**: 378-385.
- Mizutani T, Layon AJ. Clinical applications of nitric oxide. *Chest*. 1996; **110**: 506-524.
- Mobasher A, Mobasher R, Francis MJ, Trujillo E, Alvarez de la Rosa D, Martín-Vasallo P. Ion transport in chondrocytes: membrane transporters involved in intracellular ion homeostasis and the regulation of cell volume, free $[Ca^{2+}]$ and pH. *Histol. Pathol.* 1998; **13**: 893-910.

Bibliografia

- Mobasher A, Carter SD, Martín-Vasallo P, Shakibaei M. Integrins and stretch activated ion channels; putative components of functional cell surface mechanoreceptors in articular chondrocytes. *Cell Biol. Int.* 2002a; **26**: 1-18.
- Mobasher A, Neama G, Bell, S, Richardson S, Carter SD. Human articular chondrocytes express three facilitative glucose transport isoforms: GLUT1, GLUT3 and GLUT9. *Cell Biol. Int.* 2002b; **26**: 297-300.
- Moldovan F, Pelletier JP, Jolicoeur FC, Cloutier JM, Martel-Pelletier J. Diacerhein and rhein reduce the ICE-induced IL-1 β and IL-18 activation in human osteoarthritic cartilage. *Osteoarthritis Cartilage*. 2000; **8**: 186-196.
- Moore AR, Greenslade KJ, Alam CA, Willoughby DA. Effects of diacerhein on granuloma induced cartilage breakdown in the mouse. *Osteoarthritis Cartilage*. 1998; **6**: 19-23.
- Moos V, Fickert S, Müller B, Weber U, Sieper J. Immunohistological analysis of cytokine expression in human osteoarthritic and healthy cartilage. *J. Rheumatol.* 1999; **26**: 870-879.
- Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, Ettlinger RE, Cohen S, Koopman WJ, Mohler K, Widmer MB, Blosch CM. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N. Engl. J. Med.* 1997; **337**: 141-147.
- Morin I, Li WQ, Su S, Ahmad M, Zafarullah M. Induction of stromelysin gene expression by tumor necrosis factor α is inhibited by dexamethasone, salicylate, and N-acetylcysteine in synovial fibroblasts. *J. Pharmacol. Exp. Therap.* 1999; **289**: 1634-1640.
- Morisset S, Patry C, Lora M, de Brum-Fernandes AJ. Regulation of cyclooxygenase-2 expression in bovine chondrocytes by interleukin 1 α , tumor necrosis factor- α , glucocorticoids, and 17 β -estradiol. *J. Rheumatol.* 1998; **25**: 1146-1153.
- Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Method* 1983; **65**: 55-63.
- Mow VC, Ratcliffe A, Poole AR. Cartilage and diarthrodial joints as paradigms for hierarchical materials and structures. *Biomaterials*. 1992; **13**: 67-97.
- Mow VC, Wang CC, Hung CT. The extracellular matrix, interstitial fluid and ions as a mechanical signal transducer in articular cartilage. *Osteoarthritis Cartilage*. 1999; **7**: 41-58.
- Mühl H, Pfeilschifter J. Amplification of nitric oxide synthase expression by nitric oxide in interleukin 1 β -stimulated rat mesangial cells. *J. Clin. Invest.* 1995; **95**: 1941-1946.
- Muir H. Proteoglycans as organizers of the intercellular matrix. *Biochem. Soc. Trans.* 1983; **11**: 613-622.
- Muir H. Biochemical basis for cartilage degeneration, destruction and loss of function in OA. In Muir H, Hirohata K, Shichikawa K (eds.). Mechanisms of articular cartilage damage and repair in Osteoarthritis. Hans Huber. Toronto. 1990. 31-42.
- Muir H. The chondrocyte, architect of cartilage. Biomechanics, structure, function and molecular biology of cartilage matrix macromolecules. *BioEssays*. 1995; **17**: 1039-1048.
- Mukhopadhyay MJ, Saha A, Dutta A, De B, Mukherjee A. Genotoxicity of sennosides on the bone marrow cells of mice. *Food Chem. Toxicol.* 1998; **36**: 937-940.
- Musti AM, Treier M, Bohmann D. Reduced ubiquitin-dependent degradation of c-Jun after phosphorylation by MAP kinases. *Science*. 1997; **275**: 400-402.

Bibliografia

- Nathan C, Xie Q-W. Regulation of biosynthesis of nitric oxide. *J. Biol. Chem.* 1994; **269**: 13725-13728.
- Nguyen KHY, Firestein GS. T cells as secondary players in rheumatoid arhritis. In Miossec P, van den Berg WB, Firestein GS (eds.) T cells in arthritis. Birkhäuser. Basel. 1998. 1-18.
- Nguyen Q, Mort JS, Roughley PJ. Preferential mRNA expression of prostromelysin relative to procollagenase and in situ localization in human articular cartilage. *J. Clin. Invest.* 1992; **89**: 1189-1197.
- Nguyen M, Dougados M, Berdah L, Amor B. Diacerhein in the treatment of osteoarthritis of the hip. *Arthritis Rheum.* 1994; **37**: 529-536.
- Niki Y, Yamada H, Seki S, kikuchi T, Takaishi H, Toyama Y, Fujikawa K, Tada N. Macrophage- and neutrophil-dominant arthritis in human IL-1 α transgenic mice. *J. Clin. Invest.* 2001; **107**: 1127-1135.
- Ninomiya-Tsuji J, Kishimoto K, Hiyama A, Inoue J, Cao Z, Matsumoto K. The kinase TAK1 can activate the NIK-I kappa B as well as the MAP kinase cascade in the IL-1 signaling pathway. *Nature.* 1999; **398**: 252-256.
- Nishimoto N, Ito A, Ono M, Tagoh H, Matsumoto T, Tomita T, Ochi T, Yoshizaki K. IL-6 inhibits the proliferation of fibroblastic synovial cells from rheumatoid arthritis patients in the presence of soluble IL-6 receptor. *Int. Immunol.* 2000; **12**: 187-193.
- Nishiya T, Uehara T, Nomura Y. Herbimycin A suppresses NF- κ B activation and tyrosine phosphorylation of JAK2 and the subsequent induction of nitric oxide synthase in C6 glioma cells. *FEBS Lett.* 1995; **371**: 333-336.
- Noguchi S, Jianmongkol S, Bender AT, Kamada Y, Demady DR, Osawa Y. Guanabenz-mediated inactivation of and enhanced proteolytic degradation of neuronal nitric oxide synthase. *J. Biol. Chem.* 2000; **275**: 2376-2380.
- O'Byrne EM, Blancuzzi V, Wilson DE, Wong M, Jeng AY. Elevated substance P and accelerated cartilage degradation in rabbit knees injected with interleukin-1 and tumor necrosis factor. *Arthritis Rheum.* 1990; **33**: 1023-1028.
- O'Donnell VB, Tew DG, Jones OTG, England PJ. Studies on the inhibitory mechanism of iodonium compounds with special reference to neutrophil NADPH oxidase. *Biochem. J.* 1993; **290**: 41-49.
- O'Shea JJ, Gadina M, Schreiber RD. Cytokine signalling in 2002: New surprises in the Jak/Stat pathway. *Cell.* 2002; **109**: S121-S131.
- Oddis CV, Simmons RL, Hattler BG, Finkel MS. Protein kinase A activation is required for IL-1-induced nitric oxide production by cardiac myocytes. *Am. J. Physiol.* 1996; **271**: C429-C434.
- Oh M, Fukuda K, Asada S, Yasuda Y, Tanaka S. Concurrent generation of nitric oxide and superoxide inhibits proteoglycan synthesis in bovine articular chondrocytes: involvement of peroxynitrite. *J. Rheumatol.* 1998; **25**: 2169-2174.
- Okada S, Kamata H, Kamata K, Yagisawa H, Hirata H. N-Acetylcysteine suppresses TNF-induced NF- κ B activation through inhibition of IkB kinases. *FEBS Lett.* 2000; **472**: 196-202.
- Okada Y, Shinmei M, Tanaka O, Naka K, Kimura A, Nakanishi I, Bayliss MT, Iwata K, Nagase H. Localization of matrix metalloproteinase 3 (stromelysin) in osteoarthritic cartilage and synovium. *Lab. Invest.* 1992; **66**: 680-690.
- Olee T, Hashimoto S, Quach J, Lotz M. IL-18 is produced by articular chondrocytes and induces proinflammatory and catabolic responses. *J. Immunol.* 1999; **162**: 1096-1100.

Bibliografia

- Osaki M, Tsukazaki T, Yonekura A, Miyazaki Y, Iwasaki K, Shindo H, Yamashita S. Regulation of c-fos gene expression and mitogenic effect of transforming growth factor- β 1 in rat articular chondrocyte. *Endocr. J.* 1999; **46**: 253-261.
- Osawa Y, Lowe ER, Everett AC, Dunbar AY, Billecke SS. Proteolytic degradation of nitric oxide synthase: effect of inhibitors and role of hsp90-based chaperones. *J. Pharmacol. Exp. Therap.* 2003; **304**: 493-497.
- Pagano PJ, Ito Y, Tornheim K, Gallop PM, Tauber AI, Cohen RA. A NADPH oxidase superoxide-generating system in the rabbit aorta. *Am. J. Physiol.* 1995; **268**: H2274-2280.
- Pahan K, Namboodiri AM, Sheikh FG, Smith BT, Singh I. Increasing cAMP attenuates induction of inducible nitric oxide synthase in rat primary astrocytes. *J. Biol. Chem.* 1997; **272**: 7786-7791.
- Pahl HL. Activators and target genes of Rel/NF- κ B transcription factors. *Oncogene.* 1999; **18**: 6853-6866.
- Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature.* 1987; **327**: 524-526.
- Palmer, RMJ, Hickery MS, Charles IG, Moncada S, Bayliss MT. Induction of nitric oxide synthase in human chondrocytes. *Biochem. Biophys. Res. Commun.* 1993; **193**: 398-405.
- Palombella VJ, Conner EM, Fuseler JW, Destree A, Davis JM, Laroux FS, Wolf RE, Huang J, Brand S, Elliott PJ, Lazarus D, McCormack T, Parent L, Stein R, Adams J, Grisham MB. Role of the proteasome and NF- κ B in streptococcal cell wall-induced polyarthritis. *Proc. Natl. Acad. Sci. USA.* 1998; **95**: 15671-15676.
- Pan J, McEver RP. Regulation of the human P-selectin promoter by Bcl-3 and specific homodimeric members of the NF- κ B/Rel family. *J. Biol. Chem.* 1995; **270**: 23077-23083.
- Pance A, Chantome A, Reveneau S, Bentrari F, Jeannin JF. A repressor in the human inducible nitric oxide synthase promoter modulates transcriptional activation. *FASEB J.* 2002; **16**: 631-633.
- Park SK, Lin HL, Murphy S. Nitric oxide regulates nitric oxide synthase-2 gene expression by inhibiting NF- κ B binding to DNA. *Biochem. J.* 1997; **322**: 609-613.
- Parkkinen JJ, Mammi MJ, Helminen HJ, Tammi M. Local stimulation of proteoglycan synthesis in articular cartilage explants by dynamic compression in vitro. *J. Orthop. Res.* 1992; **10**: 610-620.
- Parsons JT. Integrin-mediated signaling: regulation by protein tyrosine kinases and small GTP-binding proteins. *Curr. Opin. Cell Biol.* 1996; **8**: 146-152.
- Patel IR, Attur MG, Patel RN, Stuchin AS, Abagyan RA, Abramson SB, Amin AR. TNF- α convertase from human arthritis-affected cartilage: isolation of cDNA by differential display, expression of the active enzyme, and regulation of TNF- α . *J. Immunol.* 1998; **160**: 4570-4579.
- Paul A, Cuenda A, Bryant CE, Murray J, Chilvers ER, Cohen P, Gould GW, Plevin R. Involvement of mitogen-activated protein kinase homologues in the regulation of lipopolysaccharide-mediated induction of cyclo-oxygenase-2 but not nitric oxide synthase in RAW 264.7 macrophages. *Cell. Signal.* 1999; **11**: 491-497.
- Pawson T. Protein modules and signaling networks. *Nature.* 1995; **373**: 573-580.
- Pelletier J.P., Martel-Pelletier J., Howell D.S., Ghandur-Mnaymneh L., Woessner J.F. Jr. Collagenase and collagenolytic activity in human osteoarthritic cartilage. *Arthritis Rheum.* 1983; **26**: 63-68.

Bibliografia

- Pelletier JP, Mineau F, Ranger P, Tardif G, Martel-Pelletier J. The increased synthesis of inducible nitric oxide inhibits IL-1 α synthesis by human articular chondrocytes: possible role in osteoarthritic cartilage degradation. *Osteoarthritis Cartilage*. 1996; **4**: 77-84.
- Pelletier JP, Jovanovic D, Fernandes JC, Manning P, Connor JR, Currie MG, DiBattista JA, Martel-Pelletier J. Reduced progression of experimental osteoarthritis *in vivo* by selective inhibition of inducible nitric oxide synthase. *Arthritis Rheum*. 1998a; **41**: 1275-1286.
- Pelletier JP, Mineau F, Fernandes JC, Duval N, Martel-Pelletier J. Diacerhein and Rhein reduce the interleukin 1 β stimulated inducible nitric oxide synthesis level and activity while stimulating cyclooxygenase-2 synthesis in human osteoarthritic chondrocytes. *J. Rheumatol.* 1998b; **25**: 2417-2424.
- Peng H-B, Libby P, Liao JK. Induction and stabilization of I κ B α by nitric oxide mediates inhibition of NF- κ B. *J. Biol. Chem.* 1995; **270**: 14214-14219.
- Peng HB, Spiecker M, Liao JK. Inducible nitric oxide: an autoregulatory feedback inhibitor of vascular inflammation. *J. Immunol.* 1998; **161**: 1970-1976.
- Pettipher ER, Higgs GA, Henderson B. Interleukin 1 induces leukocyte infiltration and cartilage proteoglycan degradation in the synovial joint. *Proc. Natl. Acad. Sci. USA*. 1986; **83**: 8749-8753.
- Pfeilschifter J, Eberhardt W, Hummel R, Kunz D, Mühl H, Nitsch D, Plüss C, Walker G. Therapeutic strategies for the inhibition of inducible nitric oxide synthase — potential for a novel class of anti-inflammatory agents. *Cell Biol. Int.* 1996; **20**: 51-58.
- Poole AR, Pidoux I, Reiner A, Rosenberg L. An immunoelectron microscope study of the organization of proteoglycan monomer, link protein and collagen in the matrix of articular cartilage. *J. Cell Biol.* 1982; **93**: 921-937.
- Poole CA, Ayad S, Schofield JR. Chondrons from articular cartilage: I. Immunolocalization of type VI collagen in the pericellular capsule of isolated canine tibial chondrons. *J. Cell Sci.* 1988; **90**: 635-643.
- Potoka DA, Takao S, Owaki T, Bulkley GB, Klein AS. Endothelial cells potentiate oxidant-mediated Kupffer cell phagocytic killing. *Free Radic. Biol. Med.* 1998; **24**: 1217-1227.
- Pritzker KPH, Cheng PK, Renlund RC. Calcium pyrophosphate crystal deposition in hyaline cartilage. Ultrastructural analysis and implications for pathogenesis. *J. Rheumatol.* 1988; **15**: 828-835.
- Pronost S, Segond N, Macro M, Rédini F, Penifornis H, Julliene A, Moukhtar MS, Pujol JP. Modulation of interleukin-1 receptor expression by transforming growth factor- β in cultured rabbit articular chondrocytes: analysis by reverse transcription-polymerase chain reaction. *Osteoarthritis Cartilage*. 1995; **3**: 147-155.
- Pujol JP, Felisaz N, Boumediene K, Ghayor C, Herrouin JF, Bogdanowicz P, Galera P. Effects of diacerein on biosynthesis activities of chondrocytes in culture. *Biorheology*. 2000; **37**: 177-184.
- Pulai JI, Del Carlo M, Loeser RF. The $\alpha_5\beta_1$ integrin provides matrix survival signals for normal and osteoarthritic human articular chondrocytes *in vitro*. *Arthritis Rheum*. 2002; **46**: 1528-1535.
- Pulsatelli L, Dolzani P, Piacentini A, Silvestri T, Ruggeri R, Gualtieri R, Meliconi R, Facchini A. Chemokine production by human chondrocytes. *J. Rheumatol.* 1999; **26**: 1992-2001.
- Qi WN, Scully SP. Effect of type II collagen in chondrocyte response to TGF- β 1 regulation. *Exp. Cell Res.* 1998; **241**: 142-150.

Bibliografia

- Qian Y, Commane M, Ninomiya-Tsuji J, Matsumoto K, Li X. IRAK-mediated translocation of TRAF6 and TAB2 in the interleukin-1-induced activation of NF- κ B. *J. Biol. Chem.* 2001; **276**: 41661-41667.
- Rajpurohit R., Koch C.J., Tao Z., Teixeira C.M., Shapiro I.M. Adaptation of chondrocytes to low oxygen tension: relationship between hypoxia and cellular metabolism. *J. Cell. Physiol.* 1996; **168**: 424-432.
- Rathakrishnan C, Tiku K, Raghaven A, Tiku ML. Release of oxygen radicals by articular chondrocytes: a study of luminol-dependent chemiluminescence and hydrogen peroxide secretion. *J. Bone Min. Res.* 1992; **7**: 1139-1148.
- Recklies AD, Golds EE. Induction of synthesis and release of interleukin-8 from human articular chondrocytes and cartilage explants. *Arthritis Rheum.* 1992; **35**: 1510-1519.
- Reddy AS, Huang JH, Liao WS. Phosphatidylinositol 3-kinase in interleukin-1 signaling. Physical interaction with the interleukin 1 receptor and requirement in NF- κ B and AP-1 activation. *J. Biol. Chem.* 1997; **272**: 29167-29173.
- Reginato AM, Sanz-Rodriguez C, Diaz A, Dharmavaram RM, Jimenez SA. Transcriptional modulation of cartilage-specific collagen gene expression by interferon gamma and tumour necrosis factor alpha in cultured human chondrocytes. *Biochem. J.* 1993; **294**: 761-769.
- Reiling N, Ulmer AJ, Duchrow M, Ernst M, Flad HD, Hauschmidt S. Nitric oxide synthase: mRNA expression of different isoforms in monocytes/macrophages. *Eur. J. Immunol.* 1994; **24**: 1941-1944.
- Ribault D, Khatib AM, Panasyuk A, Barbara A, Bouizar Z, Mitrovic RD. Mitogenic and metabolic actions of epidermal growth factor on rat articular chondrocytes: modulation by fetal calf serum, transforming growth factor- β and tyrphostin. *Arch. Biochem. Biophys.* 1997; **337**: 149-158.
- Ritter O, schuh K, Brede M, Röthlein N, Burkard N, Hein L, Neyses L. AT₂ receptor activation regulates myocardial eNOS expression via the calcineurin-NF-AT pathway. *FASEB J.* 2003; **17**: 283-285.
- Roitt IM. Transplantation. In *Essential Immunology*. 8th edition. Blackwell Scientific Publications. Oxford. 1994. 337-360.
- Root RK, Metcalf JA. H₂O₂ release from human granulocytes during phagocytosis: relationship to superoxide anion formation and cellular catabolism of H₂O₂; studies with normal and cytochalasin B treated cells. *J. Clin. Invest.* 1977; **60**: 1266-1279.
- Rosenthal AK, Henry LA. Retinoic acid stimulates pyrophosphate elaboration by cartilage and chondrocytes. *Calcif. Tissue Int.* 1996; **59**: 128-133.
- Rossi A, Catani MV, Candi E, Bernassola F, Puddu P, Melino G. Nitric oxide inhibits cornified envelope formation in human keratinocytes by inactivating transglutaminases and activating protein 1. *J. Invest. Dermatol.* 2000; **115**: 731-739.
- Rothwarf DM, Zandi E, Natoli G, Karin M. IKK- γ is an essential regulatory subunit of the I κ B kinase complex. *Nature*. 1998; **395**: 297-300.
- Rowan AD, Koshy PJ, Shingleton WD, Degnan BA, Heath JK, Vernallis AB, Spaull JR, Life PF, Hudson K, Cawston TE. Synergistic effects of glycoprotein 130 binding cytokines in combination with interleukin-1 on cartilage collagen breakdown. *Arthritis Rheum.* 2001; **44**: 1620-1632.
- Rusyn I, Bradham CA, Cohn L, Schoonhoven R, Swenberg JA, Brenner DA, Thurman RG. Corn oil rapidly activates nuclear factor- κ B in hepatic Kupffer cells by oxidant-dependent mechanisms. *Carcinogenesis*. 1999; **20**: 2095-2100.

Bibliografia

- Sadowski T, Steinmeyer J. Differential effects of nonsteroidal antiinflammatory drugs on the IL-1 altered expression of plasminogen activators and plasminogen activator inhibitor-1 by articular chondrocytes. *Inflamm. Res.* 2002; **51**: 427-433.
- Sah RL, Kim YL, Doong JYH, Grodzinski AJ, Plaas AJ, Sandy JD. Biosynthetic responses of cartilage explants to dynamic compression. *J. Orthop. Res.* 1989; **7**: 619-636.
- Saijo S, Asano M, Horai R, Yamamoto H, Iwakura Y. Suppression of autoimmune arthritis in interleukin-1-deficient mice in which T-cell activation is impaired due to low levels of CD40 ligand and OX40 expression on T cells. *Arthritis Rheum.* 2002; **46**: 533-544.
- Sakurada S., Kato T., Okamoto T. Induction of cytokines and ICAM-1 by proinflammatory cytokines in primary rheumatoid synovial fibroblasts and inhibition by N-acetyl-L-cysteine and aspirin. *Int. Immunol.* 1996; **8**: 1483-1493.
- Sakurai H, Kohsaka K, Liu MF, Higashiyama H, Hirata Y, Kanno K, Saito I, Miyasaka N. Nitric oxide production and inducible nitric oxide synthase expression in inflammatory arthritis. *J. Clin. Invest.* 1995; **96**: 2357-2363.
- Salter DM, Hughes DE, SimpsonR, Gardner DL. Integrin expression by human articular chondrocytes. *Br. J. Rheumatol.* 1992; **31**: 231-234.
- Sandy JD, O'Neill JR, Ratzlaff LC. Acquisition of hyaluronate binding affinity *in vivo* by newly synthesised cartilage proteoglycans. *Biochem. J.* 1989; **258**: 875-880.
- Santos LL, Morand EF, Yang Y, Hutchinson P, Holdsworth SR. Suppression of adjuvant arthritis and synovial macrophage inducible nitric oxide by N-iminoethyl-L-ornithine, a nitric oxide synthase inhibitor. *Inflammation.* 1997; **21**: 299-311.
- Schaller MD, Otey CA, Hildebrand JD, Parsons JT. Focal adhesion kinase and paxillin bind to peptides mimicking beta integrin cytoplasmic domains. *J. Cell Biol.* 1995; **130**: 1181-1187.
- Scherle PA, Pratta MA, Feeser WS, Tancula EJ, Arner EC. The effects of IL-1 on mitogen-activated protein kinases in rabbit articular chondrocytes. *Biochem. Biophys. Res. Commun.* 1997; **230**: 573-577.
- Schlaepfer DD, Hunter T. Evidence for *in vivo* phosphorylation of the Grb2 SH2-domain binding site on focal adhesion kinase by Src-family protein-tyrosine kinases. *Mol. Cell. Biol.* 1996; **16**: 5623-5633.
- Schlaepfer DD, Hanks SK, Hunter T, van der Geer P. Integrin-mediated signal transduction linked to the Ras pathway by Grb2 binding to focal adhesion kinase. *Nature.* 1994; **372**: 786-791.
- Schmidt KN, Amstad P, Cerutti P, Baeuerle PA. The roles of hydrogen peroxide and superoxide as messengers in the activation of transcription factor NF- κ B. *Chemistry Biol.* 1995; **2**: 13-22.
- Schreck R, Meier B, Männel DN, Dröge, Baeuerle PA. Dithiocarbamates as potent inhibitors of Nuclear Factor κ B activation in intact cells. *J. Exp. Med.* 1992; **175**: 1181-1194.
- Scott JE. Proteoglycan-fibrillar collagen interactions. *Biochem. J.* 1988; **252**: 313-323.
- Sen CK. Redox signaling and the emerging therapeutic potential of thiol antioxidants. *Biochem. Pharmacol.* 1998; **55**: 1747-1758.
- Sen R, Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell.* 1986; **46**: 705-716.
- Shakibaei M, John T, de Souza P, Rahmanzadeh R, Merker H-J. Signal transduction by β_1 integrin receptors in human chondrocytes *in vitro*: collaboration with the insulin-like growth factor-I receptor. *Biochem. J.* 1999; **342**: 615-623.

Bibliografia

- Shakibaei M, Schulze-Tanzil G, de Souza P, John T, Rahmazadeh M, Rahmazadeh R, Merker H-J. Inhibition of mitogen-activated protein kinase kinase induces apoptosis of human chondrocytes. *J. Biol. Chem.* 2001; **276**: 13289-13294.
- Shalom-Barak T, Quach J, Lotz M. Interleukin-17-induced gene expression in articular chondrocytes is associated with activation of mitogen-activated protein kinases and NF- κ B. *J. Biol. Chem.* 1998; **273**: 27467-27473.
- Shaulian E, Karin M. AP-1 as a regulator of cell life and death. *Nature Cell Biol.* 2002; **4**: E131-E136.
- Shikhman AR, Brinson DC, Valbracht J, Lotz MK. Cytokine regulation of facilitated glucose transport in human articular chondrocytes. *J. Immunol.* 2001; **167**: 7001-7008.
- Shimizu M, Minakuchi K, Kaji S, Koga J. Chondrocyte migration to fibronectin, type I collagen, and type II collagen. *Cell Struct. Function.* 1997; **22**: 309-315.
- Shingu M; Miyauchi S, Nagai Y, Yasutake C, Horie K. The role of IL-4 and IL-6 in IL-1-dependent cartilage matrix degradation. *Br. J. Rheumatol.* 1995; **34**: 101-106.
- Shinmei M, Masuda K, Kikuchi T, Shimomura Y. Mechanisms of cartilage destruction in OA – effects of cytokines and anti-inflammatory drugs. In Muir H, Hirohata K, Shichikawa K (eds.). Mechanisms of articular cartilage damage and repair in Osteoarthritis. Hans Huber. Toronto. 1990. 62-71.
- Sims JE, Gayle MA, Slack JL, Anderson MR, Bird TA, Giri JG, Colotta F, Re F, Mantovani A, Shanebeck K, Grabstein KH, Dower SK. Interleukin 1 signaling occurs exclusively via the type I receptor. *Proc. Natl. Acad. Sci. USA.* 1993; **90**: 6155-6159.
- Smith MD, Triantafillou S, Parker A, Youssef PP, Coleman M. Synovial membrane inflammation and cytokine production in patients with early osteoarthritis. *J. Rheumatol.* 1997; **24**: 365-371.
- Smith GNJr, Myers SL, Brandt KD, Mickler EA, Albrecht ME. Diacerhein treatment reduces the severity of osteoarthritis in the canine cruciate-deficiency model of osteoarthritis. *Arthritis Rheum.* 1999; **42**: 545-554.
- Smith DE, Renshaw BR, Ketcham RB, Kubin M, Garka KE, Sims JE. Four new members expand the interleukin-1 superfamily. *J. Biol. Chem.* 2000; **275**: 1169-1175.
- Sohen S, Ooe H, Hashima M, Nonaka T, Fukuda K, Hamanishi C. Activation of histamine H1 receptor results in enhanced proteoglycan synthesis by human articular chondrocyte: involvement of protein kinase C and intracellular Ca²⁺. *Pathophysiol.* 2001; **8**: 93-98.
- Song XY, Gu M, Jin WW, Klinman DM, Wahl SM. Plasmid DNA encoding transforming growth factor-beta1 suppresses chronic disease in a streptococcal cell wall-induced arthritis model. *J. Clin. Invest.* 1998; **101**: 2615-2621.
- Šošić D, Richardson JA, Yu K, Ornitz DM, Olson EN. Twist regulates cytokine gene expression through a negative feedback loop that represses NF- κ B activity. *Cell.* 2003; **112**: 169-180.
- Spiecker M, Peng HB, Liao JK. Inhibition of endothelial vascular cell adhesion molecule-1 expression by nitric oxide involves the induction and nuclear translocation of I κ B α . *J. Biol. Chem.* 1997; **272**: 30969-30974.
- Spiecker M, Darius H, Kaboth K, Hubner F, Liao JK. Differential regulation of endothelial cell adhesion molecule expression by nitric oxide donors and antioxidants. *J. Leukocyte Biol.* 1998; **63**: 732-739.
- Spitsin SV, Koprowski H, Michaels FH. Characterization and functional analysis of the human inducible nitric oxide synthase gene promoter. *Mol. Medicine.* 1996; **2**: 226-235.

Bibliografia

- St. Clair EW. Nitric Oxide — friend or foe in arthritis? *J. Rheumatol.* 1998; **25**: 1451-1453.
- Stadler JM, Stefanovic-Racic M, Billiar TR, Curran RD, McIntyre LA, Georgescu HI, Simmons RL, Evans CH. Articular chondrocytes synthesize nitric oxide in response to cytokines and lipopolysaccharide. *J Immunol* 1991, **147**, 3915-3920.
- Stallmeyer B, Anhold M, Wetzler C, Kahlina K, Pfeilschifter J, Frank S. Regulation of eNOS in normal and diabetes-impaired skin repair: implications for tissue regeneration. *Nitric Oxide*. 2002; **6**: 168-177.
- Stefanovic-Racic M, Stadler J, Georgescu HI, Evans CH. Nitric oxide and energy production in articular chondrocytes. *J. Cell. Physiol.* 1994a; **159**: 274-280.
- Stefanovic-Racic M, Meyers K, Meschter C, Coffey JW, Hoffman RA, Evans CH. N-Monomethyl-L-arginine, an inhibitor of NOS, suppresses the development of adjuvant arthritis in rats. *Arthritis. Rheum.* 1994b; **37**: 1062-1069.
- Steiner G, Studnicka-Benke A, Witzmann G, Höfler E, Smolen J. Soluble receptors for tumor necrosis factor and interleukin-2 in serum and synovial fluid of patients with rheumatoid arthritis, reactive arthritis and osteoarthritis. *J. Rheumatol.* 1995; **22**: 406-412.
- Stuehr DJ, Fasehun OA, Kwon NS, Gross SS, Gonzalez JA, Levi R, Nathan CF. Inhibition of macrophage and endothelial cell nitric oxide synthase by diphenyleneiodonium and its analogs. *FASEB J.* 1991; **5**: 98-103.
- Stylianou E, Saklatvala J. Interleukin-1. *Int. J. Biochem. Cell Biol.* 1998; **30**: 1075-1079.
- Sun Y, Wenger L, Brinckerhoff CE, Misra RR, Cheung HS. Basic calcium phosphate crystals induce matrix metalloproteinase-1 through the Ras/mitogen-activated protein kinase/c-Fos/AP-1/metalloproteinase 1 pathway. Involvement of transcription factor binding sites AP-1 and PEA-3. *J. Biol. Chem.* 2002; **277**: 1544-1552.
- Suzuki YJ, Mizuno M, Packer L. Transient overexpression of catalase does not inhibit TNF- or PMA-induced NF- κ B activation. *Biochem. Biophys. Res. Commun.* 1995; **210**: 537-541.
- Suzuki N, Suzuki S, Duncan GS, Millar DG, Wada T, Mirtsos C, Takada H, Wakeham A, Itie A, Li S, Penninger JM, Wesche H, Ohashi PS, Mak TW, Yeh W-C. Severe impairment of interleukin-1 and Toll-like receptor signaling in mice lacking IRAK-4. *Nature*. 2002; **415**: 750-756.
- Taccoen A, Berdah L. Diacetylirhein, a new therapeutic approach of osteoarthritis. *Rev. Rhum. (Ed. Fr.)*. 1993; **60**: 83S-86S.
- Tajana G. A cartilagem articular. In O condrólio: a unidade morfológica da cartilagem articular. Um modelo para a planificação da seleção terapêutica durante a osteoartrose. Mediamix s.r.l. Milão. 1991. 22.
- Takaesu G, Kishida S, Hiyama A, Yamaguchi K, Shibuya H, Irie K, Ninomiya-Tsuji J, Matsumoto K. TAB2, a novel adaptor protein, mediates activation of TAK1 MAPKKK by linking TAK1 to TRAF6 in the IL-1 signal transduction pathway. *Mol. Cell.* 2000; **5**: 649-658.
- Taketazu F, Kato M, Gobl A, Ichijo H, ten Dijke P, Itoh J, Kyogoku M, Rönnelid J, Miyazono K, Heldin CH. Enhanced expression of transforming growth factor- β and transforming growth factor- β type II receptor in the synovial tissues of patients with rheumatoid arthritis. *Lab. Invest.* 1994; **70**: 620-630.
- Tamura T, Ohmori K. Diacerein suppresses the increase in plasma nitric oxide in rat adjuvant-induced arthritis. *Eur. J. Pharmacol.* 2001; **419**: 269-274.

Bibliografia

- Tardif G, Pelletier J-P, Dupuis M, Geng C, Cloutier JM, Martel-Pelletier J. Collagenase 3 production by human osteoarthritic chondrocytes in response to growth factors and cytokines is a function of the physiologic state of the cells. *Arthritis Rheum.* 1999; **42**: 1147-1158.
- Tardif G, Reboul P, Dupuis M, Geng C, Duval N, Pelletier JP, Martel-Pelletier J. Transforming growth factor β -induced collagenase-3 production in human osteoarthritic chondrocytes is triggered by Smad proteins: cooperation between activator protein-1 and PEA-3 binding sites. *J. Rheumatol.* 2001; **28**: 1631-1639.
- Taskiran D, Stefanovic-Racic M, Georgescu H, Evans CH. Nitric oxide mediates suppression of cartilage proteoglycan synthesis by interleukin-1. *Biochem. Biophys. Res. Commun.* 1994; **200**: 142-148.
- Tawara T, Shingu M, Nobunaga M, Naono T. Effects of recombinant human IL-1 β on production of prostaglandin E2, leukotriene B4, NAG and superoxide by human synovial cells and chondrocytes. *Inflammation.* 1991; **15**: 145-157.
- Taylor AM, Dandona P, Morrell DJ, Preece MA. Insulin like growth factor-I, protein kinase-C, calcium and cyclic AMP: partners in the regulation of chondrocyte mitogenesis and metabolism. *FEBS Lett.* 1988; **236**: 33-38.
- Taylor BS, de Vera ME, Ganster RW, Wang Q, Shapiro RA, Morris Jr SM, Billiar TR, Geller DA. Multiple NF- κ B enhancer elements regulate cytokine induction of the human inducible nitric oxide synthase gene. *J. Biol. Chem.* 1998; **273**: 15148-15156.
- Tetsuka T, Baier LD, Morrison AR. Antioxidants inhibit interleukin-1-induced cyclooxygenase and nitric oxide synthase expression in rat mesangial cells. Evidence for post-transcriptional regulation. *J. Biol. Chem.* 1996; **271**: 11689-11693.
- Tiku ML, Yan YP, Chen KY. Hydroxyl radical formation in chondrocytes and cartilage as detected by electron paramagnetic resonance spectroscopy using spin trapping reagents. *Free Radic. Res.* 1998; **29**: 177-187.
- Tiku ML, Gupta S, Deshmukh DR. Aggrecan degradation in chondrocytes is mediated by reactive oxygen species and protected by antioxidants. *Free Radic. Res.* 1999; **30**: 395-405.
- Tiku ML, Shah R, Allison GT. Evidence linking chondrocyte lipid peroxidation to cartilage protein degradation. Possible role in cartilage aging and the pathogenesis of osteoarthritis. *J. Biol. Chem.* 2000; **275**: 20069-20076.
- Togashi H, Sasaki M, Frohman E, Taira E, Ratan RR, Dawson TM, Dawson VL. Neuronal (type I) nitric oxide synthase regulates nuclear factor κ B activity and immunologic (type II) nitric oxide synthase expression. *Proc. Natl. Acad. Sci. USA.* 1997; **94**: 2676-2680.
- Tong L, Pav S, White DM, Rogers S, Crane KM, Cywin CL, Brown ML, Pargellis CA. A highly specific inhibitor of human p38 MAP kinase binds in the ATP pocket. *Nature Struct. Biol.* 1997; **4**: 311-316.
- Tortorella MD, Burn TC, Pratta MA, Abbaszade I, Hollis JM, Liu R, Rosenfeld AS, Copeland RA, Decicco CP, Wynn R, Rockwell A, Yang F, Duke JL, Solomon K, George H, Bruckner R, Nagase H, Itoh Y, Ellis DM, Ross H, Wiswall BH, Murphy K, Hillman Jr MC, Hollis GF, Newton RC, Magolda RL, Trzaskos JM, Arner EC. Purification and cloning of aggrecanase-1: a member of the ADAMTS family of proteins. *Science.* 1999; **284**: 1664-1666.
- Towle CA, Hung HH, Bonassar LJ, Treadwell BV, Mangham DC. Detection of interleukin-1 in the cartilage of patients with osteoarthritis: a possible autocrine/paracrine role in pathogenesis. *Osteoarthritis Cartilage.* 1997; **5**: 293-300.

Bibliografia

- Trujillo E, Alvarez de La Rosa D, Mobasher A, Gonzalez T, Canessa CM, Martín-Vasallo P. Sodium transport systems in human chondrocytes. II. Expression of ENaC, Na^+/K^+ /2Cl⁻ cotransporter and Na^+/H^+ exchangers in healthy and arthritic chondrocytes. *Histol. Histopathol.* 1999; **14**: 1023-1031.
- Tsukazaki T, Matsumoto T, Enomoto H, Usa T, Ohtsuru A, Namba H, Iwasaki K, Yamashita S. Growth hormone directly and indirectly stimulates articular chondrocyte cell growth. *Osteoarthritis Cartilage*. 1994; **2**: 259-267.
- Tucci MA, Tsao A, Hughes J, Baker R, Benghuzzi H. Release of inflammatory cytokines by macrophages and synovial cells challenged with tumor necrosis factor. *Biomed. Sci. Instrum.* 2002; **38**: 89-94.
- Turner CE, Burridge K. Transmembrane molecular assemblies in cell-extracellular matrix interactions. *Curr. Opin. Cell Biol.* 1991; **3**: 849-853.
- Turner CE, Glenney JRJr, Burridge K. Paxillin: a new vinculin-binding protein present in focal adhesions. *J. Cell Biol.* 1990; **111**: 1059-1068.
- Tzen C-Y, Cox RL, Scott RE. Coordinate induction of $\text{IkB}\alpha$ and NF κ B genes. *Exp. Cell Res.* 1994; **211**: 12-16.
- Urban JPG, Hall AC, Gehl KA. Regulation of matrix synthesis rates by ionic and osmotic environment of articular chondrocytes. *J. Cell. Physiol.* 1993; **154**: 262-270.
- van Beuningen HM, Glansbeek HL, van der Kraan PM, van den Berg WB. Differential effects of local application of BMP-2 or TGF- β 1 on both articular cartilage composition and osteophyte formation. *Osteoarthritis Cartilage*. 1998; **6**: 306-317.
- van de Loo FA, Joosten LA, van Lent PL, Arntz OJ, van den Berg WB. Role of interleukin-1, tumor necrosis factor alpha, and interleukin-6 in cartilage proteoglycan metabolism and destruction. Effect of in situ blocking in murine antigen- and zymosan-induced arthritis. *Arthritis Rheum.* 1995; **38**: 164-172.
- van de Loo FA, Kuiper S, van Enckevort FH, Arntz OJ, van den Berg WB. Interleukin-6 reduces cartilage destruction during experimental arthritis. A study in interleukin-6-deficient mice. *Am. J. Pathol.* 1997; **151**: 177-191.
- van den Berg WB. Growth factors in experimental osteoarthritis: transforming growth factor β pathogenic? *J. Rheumatol. Suppl.* 1995; **43**: 143-145.
- van Lent PL, Holthuysen AE, Slöetjes A, Lubberts E, van den Berg WB. Local overexpression of adeno-viral IL-4 protects cartilage from metalloproteinase-induced destruction during immune complex-mediated arthritis by preventing activation of pro-MMPs. *Osteoarthritis Cartilage*. 2002; **10**: 234-243.
- van Susante JL, Buma P, van Beuningen HM, van den Berg WB, Veth RP. Responsiveness of bovine chondrocytes to growth factors in medium with different serum concentrations. *J. Orthop. Res.* 2000; **18**: 68-77.
- Vario T, Vaheri A, von Essen R, Isomaki H, Stenman S. Fibronectin in synovial fluid and tissue in rheumatoid arthritis. *Eur. J. Clin. Invest.* 1981; **11**: 207-212.
- Vermeulen L, De Wilde G, Notebaert S, Vanden Berghe W, Haegeman G. Regulation of the transcriptional activity of the nuclear factor- κ B p65 subunit. *Biochem. Pharmacol.* 2002; **64**: 963-970.

Bibliografia

- Vermeulen L, De Wilde G, Van Damme P, Vanden Berghe W, Haegeman G. Transcriptional activation of the NF- κ B p65 subunit by mitogen- and stress-activated protein kinase-1 (MSK1). *EMBO J.* 2003; **22**: 1313-1324.
- Villiger PM, Lotz M. Differential expression of TGF beta isoforms by human articular chondrocytes in response to growth factors. *J. Cell. Physiol.* 1992; **151**: 318-325.
- Vincenti MP, Coon CI, Brinckerhoff CE. Nuclear Factor κ B/p50 activates an element in the distal matrix metalloproteinase 1 promoter in interleukin-1 β -stimulated synovial fibroblasts. *Arthritis Rheum.* 1998; **41**: 1987-1994.
- Vittur F, Grandolfo M, Fragonas E, Godeas C, Paoletti S, Pollesello P, Kvam BJ, Ruzzier F, Starc T, Mozrzymas JW. Energy metabolism, replicative ability, intracellular calcium concentration and ionic channels of horse articular chondrocytes. *Exp. Cell Res.* 1994; **210**: 130-136.
- Vivien D, Galéra P, Lebrun E, Loyau G, Pujol J-P. Differential response of cultured rabbit articular chondrocytes (RAC) to transforming growth β (TGF- β) — Evidence for a role of serum factors. *Eur. J. Cell. Biol.* 1991; **54**: 217-223.
- Vivien D, Rédini F, Galéra P, Lebrun E, Loyau G, Pujol J-P. Rabbit articular chondrocytes (RAC) express distinct TGF- β receptor phenotypes as a function of the cell cycle. *Exp. Cell Res.* 1993; **205**: 165-170.
- Walakovits LA, Moore VL, Bhardwaj N, Gallick GS, Lark MW. Detection of stromelysin and collagenase in synovial fluid from patients with rheumatoid arthritis and posttraumatic knee injury. *Arthritis Rheum.* 1992; **35**: 35-42.
- Wang C, Deng L, Hong M, Akkaraju GR, Ji I, Chen ZJ. TAK1 is a ubiquitin-dependent kinase of MKK and IKK. *Nature.* 2001; **412**: 346-351.
- Wary KK, Mainiero F, Isakoff SJ, Marcantonio EE, Giancotti FG. The adaptor protein Shc couples a class of integrins to the control of cell cycle progression. *Cell.* 1996; **87**: 733-743.
- Watanabe S., Georgescu H.I., Mendelow D., Evans C.H. Chondrocyte activation in response to factor(s) produced by a continuous line of lapine synovial fibroblasts. *Exp. Cell Res.* 1986; **167**: 218-226.
- Webb GR, Westacott CI, Elson CJ. Osteoarthritic synovial fluid and synovium supernatants up-regulate tumor necrosis factor receptors on human articular chondrocytes. *Osteoarthritis Cartilage.* 1998; **6**: 167-176.
- Weinberg JB, Granger DL, pisetsky DS, Seldin MF, Misukonis MA, Mason SN, Pippen AM, Ruiz P, Wood ER, Gilkeson GS. The role of nitric oxide in the pathogenesis of spontaneous murine autoimmune disease: increased nitric oxide production and nitric oxide synthase expression in MRL-lpr/lpr mice, and reduction of spontaneous glomerulonephritis and arthritis by orally administered N^G-monomethyl-L-arginine. *J. Exp. Med.* 1994; **179**: 651-660.
- Weisser J, Rahfoth B, Timmermann A, Aigner T, Bräuer R, von der Mark K. Role of growth factors in rabbit articular cartilage repair by chondrocytes in agarose. *Osteoarthritis Cartilage.* 2001; **9** (suppl. A): S48-54.
- Wesche H, Korherr C, Kracht M, Falk W, Resch K, Martin MU. The Interleukin-1 Receptor Accessory Protein (IL-1RAcP) is essential for IL-1-induced activation of Interleukin-1 Receptor-associated Kinase (IRAK) and Stress-activated Protein Kinases (SAP Kinases). *J. Biol. Chem.* 1997a; **272**: 7727-7731.
- Wesche H, Henzel WJ, Shillinglaw W, Li S, Cao Z. MyD88: an adapter that recruits IRAK to the IL-1 receptor complex. *Immunity.* 1997b; **7**: 837-847.

Bibliografia

- Wesselborg S, Bauer MKA, Vogt M, Schmitz ML, Schulze-Osthoff K. Activation of transcription factor NF- κ B and p38 mitogen-activated protein kinase is mediated by distinct and separate stress effector pathways. *J. Biol. Chem.* 1997; **272**: 12422-12429.
- Westacott CI, Whicher JT, Barns IC, Thompson D, Swan AJ, Dieppe PA. Synovial fluid concentration of five different cytokines in rheumatic disease. *Ann Rheum Dis* 1990; **49**: 676-81.
- White LA, Brinckerhoff CE. Two activator protein-1 elements in the matrix metalloproteinase-1 promoter have different effects on transcription and bind JunD, c-Fos, and Fra-2. *Matrix Biol.* 1995; **14**: 715-725.
- Wilkins RJ, Hall AC. Control of matrix synthesis in isolated bovine chondrocytes by extracellular and intracellular pH. *J. Cell. Physiol.* 1995; **164**: 474-481.
- Wolfe AM. The epidemiology of rheumatoid arthritis: a review. *Bull. Rheum. Dis.* 1968; **19**: 518-530.
- Woodgett JR, Avruch J, Kyriakis JM. Regulation of nuclear transcription factors by stress signals. *Clin. Exp. Pharmacol. Physiol.* 1995; **22**: 281-283.
- Woods VL, Schreck PJ, Gesink DS, Pacheco HO, Amiel D, Akeson WH, Lotz M. Integrin expression by human articular chondrocytes. *Arthritis Rheum.* 1994; **37**: 537-544.
- Woods JS, Ellis ME, Dieguez-Acuña FJ, Corral J. Activation of NF- κ B in normal kidney epithelial (NRK52E) cells is mediated via a redox-insensitive, calcium-dependent pathway. *Toxicol. Appl. Pharmacol.* 1999; **154**: 219-227.
- Wotton SF, Jeacocke RE, Maciewicz RA, Wardale RJ, Duance VC. The application of scanning confocal microscopy in cartilage research. *Histochem. J.* 1991; **23**: 328-335.
- Wright MO, Stockwell RA, Nuki G. Response of plasma membrane to applied hydrostatic pressure in chondrocytes and fibroblasts. *Connect. Tissue Res.* 1992; **28**: 49-70.
- Wright M, Jobanputra P, Bavington C, Salter DM, Nuki G. Effects of intermittent pressure-induced strain on the electrophysiology of cultured human chondrocytes: evidence for the presence of stretch-activated membrane ion channels. *Clin. Sci. (Lond).* 1996; **90**: 61-71.
- Wright MO, Nishida K, Bavington C, Godolphin JL, Dunne E, Walmsley S, Jobanputra P, Nuki G, Salter DM. Hyperpolarization of cultured human chondrocytes following cyclical pressure-induced strain: evidence for a role of $\alpha_5\beta_1$ as a chondrocyte mechanoreceptor. *J. Orthop. Res.* 1997; **15**: 742-747.
- Xiao G, Harhaj EW, Sun SC. NF- κ B-inducing kinase regulates the processing of NF- κ B2 p100. *Mol. Cell.* 2001; **7**: 401-409.
- Xie D-L, Meyers R, Homandberg GA. Fibronectin fragments in osteoarthritic synovial fluid. *J. Rheumatol.* 1992; **19**: 1448-1452.
- Xie Q-W, Wishnani R, Nathan C. Promoter of the mouse gene encoding calcium-independent nitric oxide synthase confers inducibility by interferon γ and bacterial lipopolysaccharide. *J. Exp. Med.* 1993; **177**: 1779-1784.
- Xie Q-W, Kashiwabara Y, Nathan C. Role of transcription factor NF- κ B/Rel in induction of nitric oxide synthase. *J. Biol. Chem.* 1994; **269**: 4705-4708.
- Yamamoto K, Arakawa T, Ueda N, Yamamoto S. Transcriptional roles of nuclear factor κ B and nuclear factor-interleukin-6 in the tumor necrosis factor α -dependent induction of cyclooxygenase-2 in MC3T3-E1 cells. *J. Biol. Chem.* 1995. **270**: 31315-31320.

Bibliografia

- Yamanishi Y, Boyle DL, Clark M, Maki RA, Tortorella MD, Arner EC, Firestein GS. Expression and regulation of aggrecanase in arthritis: the role of TGF- β . *J. Immunol.* 2002; **168**: 1405-1412.
- Yamin TT, Miller DK. The interleukin-1 receptor-associated kinase is degraded by proteasomes following its phosphorylation. *J. Biol. Chem.* 1997; **272**: 21540-21547.
- Yea C, Cross AR, Jones OT. Purification and some properties of the 45 kDa diphenylene iodonium-binding flavoprotein of neutrophil NADPH oxidase. *Biochem. J.* 1990; **265**: 95-100.
- Yoshizumi M, Perrella MA, Burnett JC Jr, Lee ME. Tumor necrosis factor downregulates an endothelial nitric oxide synthase mRNA by shortening its half-life. *Circ. Res.* 1993; **73**: 205-209.
- Zafarullah M, Martel-Pelletier J, Cloutier J-M, Gedamu L, Pelletier J-P. Expression of *c-fos*, *c-jun*, *jun-B*, metallothionein and metalloproteinase genes in human chondrocyte. *FEBS Lett.* 1992; **306**: 169-172.
- Zandi E, Rothwarf DM, Delhase M, Hayakawa M, Karin M. The I κ B kinase complex (IKK) contains two kinase subunits, IKK α and IKK β , necessary for I κ B phosphorylation and NF- κ B activation. *Cell.* 1997; **91**: 243-252.
- Zhong H, Voll RE, Ghosh S. Phosphorylation of NF-kappa B p65 by PKA stimulates transcriptional activity by promoting a novel bivalent interaction with the coactivator CBP/p300. *Mol. Cell.* 1998; **1**: 661-671.
- Zhou LZ, Johnson AP, Rando TA. NF- κ B and AP-1 mediate transcriptional responses to oxidative stress in skeletal muscle cells. *Free Radic. Biol. Med.* 2001; **31**: 1405-1416.
- Zídek Z. Role of cytokines in the modulation of nitric oxide production by cyclic AMP. *Eur. Cytokine Netw.* 2001; **12**: 22-32.
- Zouki C, József L, Oullet S, Paquette Y, Filep JG. Peroxynitrite mediates cytokine-induced IL-8 gene expression and production by human leukocytes. *J. Leukoc. Biol.* 2001; **69**: 815-824.