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The NDR/LATS protein kinases in neurobiology: Key regulators of cell proliferation, differentiation and migration in the ocular and central nervous system

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ABSTRACT

Nuclear Dbf2-related (NDR) kinases are a subgroup of evolutionarily conserved AGC protein kinases that regulate various aspects of cell growth and morphogenesis. There are 4 NDR protein kinases in mammals, LATS1, LATS2 and STTK8/NDR1, STK38L/NDR2 protein kinases. LATS1 and 2 are core components of the well-studied Hippo pathway, which play a critical role in the regulation of cell proliferation, differentiation, and cell migration via YAP/TAZ transcription factor. The Hippo pathways play an important role in nervous tissue development and homeostasis, especially with regard to the central nervous system (CNS) and the ocular system. The ocular system is a very complex system generated by the interaction in a very tightly coordinated manner of numerous and diverse developing tissues, such as, but not limited to choroidal and retinal blood vessels, the retinal pigmented epithelium and the retina, a highly polarized neuronal tissue. The retina development and maintenance require precise and coordinated regulation of cell proliferation, cell death, migration, morphogenesis, synaptic connectivity, and balanced homeostasis. This review highlights the emerging roles of NDR1 and NDR2 kinases in the regulation of retinal/neuronal function and homeostasis via a noncanonical branch of the Hippo pathway. We highlight a potential role of NDR1 and NDR2 kinases in regulating neuronal inflammation and as potential therapeutic targets for the treatment of neuronal diseases.

1. Introduction

Nuclear Dbf2-related (NDR) kinases are a subgroup of evolutionarily conserved AGC protein kinases known to regulate various aspects of cellular growth and morphogenesis (Tamaskovic, Bichsel, and Ã 2003) (Table 1). NDR kinases were first identified in yeasts and *Drosophila melanogaster* as critical regulators of cellular proliferation and polarized morphogenesis (Hergovich, 2016). In *Saccharomyces cerevisiae*, Ndr kinases function in two distinct and evolutionarily conserved signaling networks, known as the Mitotic Exit Network (MEN), in which the

Abbreviations: LATS, Large Tumor Suppressor; STK38, Serine/Threonine Kinase 38; STK38L, Serine/Threonine Kinase 38 like; Ndr, Nuclear Dbf2-Related; ONL, Outer Nuclear Layer; OPL, Outer Plexiform Layer; INL, Inner Nuclear Layer; IPL, Inner Plexiform Layer; GCL, Ganglion Cell layer; NFL, Nerve Fiber Layer; MEN, Mitotic Exit Network; RAM, Regulation of Ace2 and polarized Morphogenesis; MST, Mammalian STE20-Like Protein Kinase; YAP, Yes-Associated Protein; p-YAP, Phosphorylated Yap; TAZ, WW Domain Containing Transcription Regulator 1; p-TAZ, Phosphorylated Taz; AAK1, AP-2 Associated Kinase; TRIAD, Transcriptional Repression-Induced Atypical cell Death; SINE, Short Interspersed Nuclear Element; Erd, Early Retinal Degeneration disease; PAX6, Paired box 6; HUD, Hu antigen D; GAD65, Glutamate Decarboxylase 65 kDa isoform; ROS, Reactive Oxygen Species; NF-κB, Nuclear Factor Kappa B; MEKK2, Mitogen-Activated Protein Kinase Kinase Kinase 2; MAPK, Mitogen-Activated Protein Kinase; CXCL2, Chemokine (C-X-C motif) Ligand 2; CCL20, Chemokine (C-C motif) Ligand 20.

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Table 1
Comparative list of Hippo kinases from *S. pombe*, *S. cerevisiae*, *C. elegans*, Drosophila and mammals.

Protein Symbol				
Mammals	*Drosophila*	*C.elegans*	*S. cerevisiae*	*S. pombe*
MST 1/2	Hpo	Cst-1/2	Cdc15	Sid1 / Cdc7
LATS 1/2	Wts	Wts-1	Dbf2/Dbf20	Sid2
NDR 1/2	Trc	Sax-1	Cbk1	Orb6
YAP/TAZ	Yki	Yap-1	-	-

terminal kinases are the paralogous kinases Dbf2 and Dbf20, and the Regulation of Ace2 and polarized Morphogenesis (RAM) network, in which the terminal kinase is Cbk1. The corresponding networks in *Schizosaccharomyces pombe*, are the Septation Initiation Network (SIN) and Morphogenesis Orb6 Network (MOR). In Drosophila, the equivalent networks to the yeast MEN/SIN and RAM/MOR pathways are the Hippo and Germinal Center Kinase III (GckIII) pathways (Hergovich et al., 2006; Stoepel et al., 2005).

In *Drosophila melanogaster,* the kinases Warts (Wts, mammalian LATS ortholog) and Tricornered (Trc, mammalian NDR ortholog) are the orthologs of the budding yeast MEN and RAM kinases and form the highly conserved Hippo signaling pathway, starting with the upstream kinase Hippo (He et al., 2005; Hergovich, 2013). The *Caenorhabditis elegans* kinases sensory axon guidance-1 (Sax-1) and c Large Tumor Suppressor (cLats) are the orthologs of the budding yeast nuclear Dbf2-related kinases (Table 1). In mammals, there are four Ndr kinases: Large Tumor Suppressor (LATS) 1, LATS2 (mammalian orthologs of the drosophila Warts), NDR1 and NDR2, also known as Serine-Threonine Kinase 38 (STK38) and Serine-Threonine Kinase like (STK38L) and mammalian orthologs of the drosophila Tricornered.

LATS1 and LATS2 are the paralogous terminal kinases of the well-studied Hippo pathway. The core of the hippo pathway is a kinase cascade, wherein the highly conserved Ste20-like kinases MST1 and MST2 (ortholog of Drosophila Hippo) phosphorylate and activate the kinases LATS1 and LATS2, which sequentially phosphorylate their substrates (Fig. 1). In mammals, the main substrates of the Hippo signaling are the paralogous transcription co-factors Yes-associated protein (YAP) and WW Domain Containing Transcription Regulator 1 (TAZ). YAP/TAZ are regulated via numerous mechanisms. When phosphorylated, YAP and TAZ, are excluded from the nucleus and either targeted for degradation, retained in the cytoplasm or at cell junctions (Fig. 2). When dephosphorylated, YAP/TAZ enter the nucleus and promote transcription via an association with the TEAD transcription factors.

Studies have shown that the mammalian NDR1 and NDR2 paralogous kinases are regulated by the MST1 and MST2 kinases and can function via YAP/TAZ in some tissues such as the intestinal epithelium-as a non-canonical or parallel branch of Hippo pathway. However, NDR1 and NDR2 can be activated by other kinases and have many other known substrates which indicates that NDR1 and NDR2 likely also function via a distinct Ndr signaling pathway to the Hippo signaling (Fig. 1). This is like what we observe in yeast and Drosophila.

As in *C. elegans* and drosophila, LATS and NDR kinases have been implicated in development via the phosphorylation of numerous substrates involved in the control of proliferation, (cell death, polarized morphogenesis, cellular differentiation and tissue homeostasis (Cornils et al., 2011; Tamaskovic et al., 2003), intracellular vesicle trafficking, dendrite growth regulation of pyramidal neurons, and spine development (Ultanir et al., 2012), endocytosis and membrane recycling (Roşianu et al., 2023) (Figs. 1 and 3). The serine/threonine kinases are also known to be regulated by chemical signals such as cyclic AMP (Cass et al., 1999), lipids (Leonard and Hurley, 2011) or by specific cellular events such as oxidative stress (Diallo and Prigent, 2011; Enomoto et al., 2012; McCubrey et al., 2000) and play a role in many diseases, especially in cancer (Brognard and Hunter, 2011) and neurodegenerative diseases (Chan and Ye, 2013; Monaco and Vallano, 2005). However, several functions of LATS and NDR kinases are still poorly understood and several of their substrates are to be discovered and studied.

In this review, we will present the most important players of the LATS/NDR pathway and their functions and regulation in the neuronal tissues with a main focus on NDR kinases and the retina. We will extrapolate the retinal functions of these kinases from results obtained in the brain which share an embryonic origin with retinal cells.

2. The ocular system

The eye is a complex organ responsible for collecting and transforming light into electrochemical signals that are then transported to the brain, thus giving rise to the sense of vision. The retina, the innermost layer of the eye and considered as part of the central nervous system, having the same embryonic origin of the brain, is composed of several types of cells (neurons, glia and endothelial cells). The neurons are organized in three main cell layers separated by two plexiform layers, which correspond to the regions that contain the synapses between the various types of retinal neurons. From the outermost zone towards the innermost zone, we find the retinal pigment epithelium cell layer, the outer nuclear layer (ONL), the outer plexiform layer (OPL), the inner nuclear layer (INL), the inner plexiform layer (IPL) and finally the ganglion cell layer (GCL), whose axons form the nerve fiber layer (NFL). These axons converge to the optic disc where they bundle together and form the optic nerve, responsible for carrying visual information from

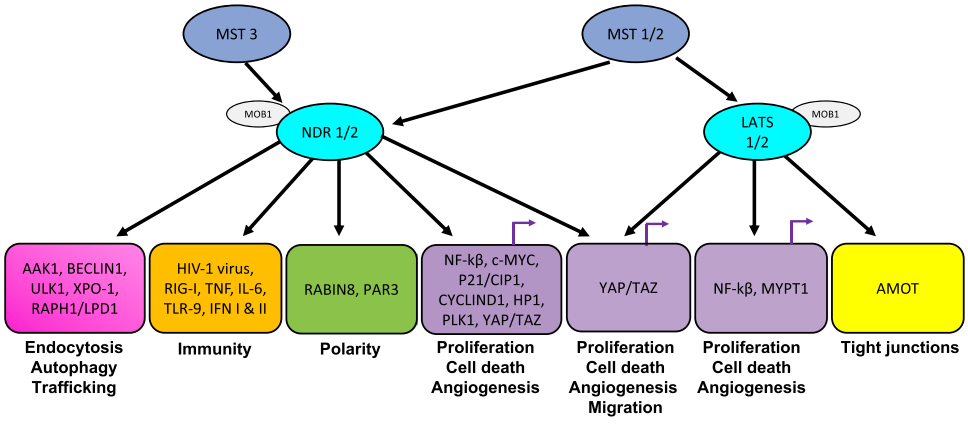

Fig. 1. Summary of mammalian NDR/LATS kinase signaling pathway, their substrates, and cellular functions. Classically, the core cassette of the Hippo pathway includes the AGC serine/threonine protein kinases LATS1/2, functioning downstream of Ste20-like kinases MST1/2 to regulating the transcriptional co-activators YAP and TAZ (purple), their major effectors as well as several other substrates such as SNAIL, AMOT. Moreover, the AGC serine/threonine NDR1/2 kinases, functioning downstream of Ste20-like kinases MST1–3, can also act as YAP/TAZ kinases. However, the list of the NDR1/2 kinases binding partners and substrates has been expanded recently, to include NF-κB, BECLIN 1, RAPH1 and many more. Therefore, the functions of NDR kinases range from autophagy, immunity regulation to cell cycle control.

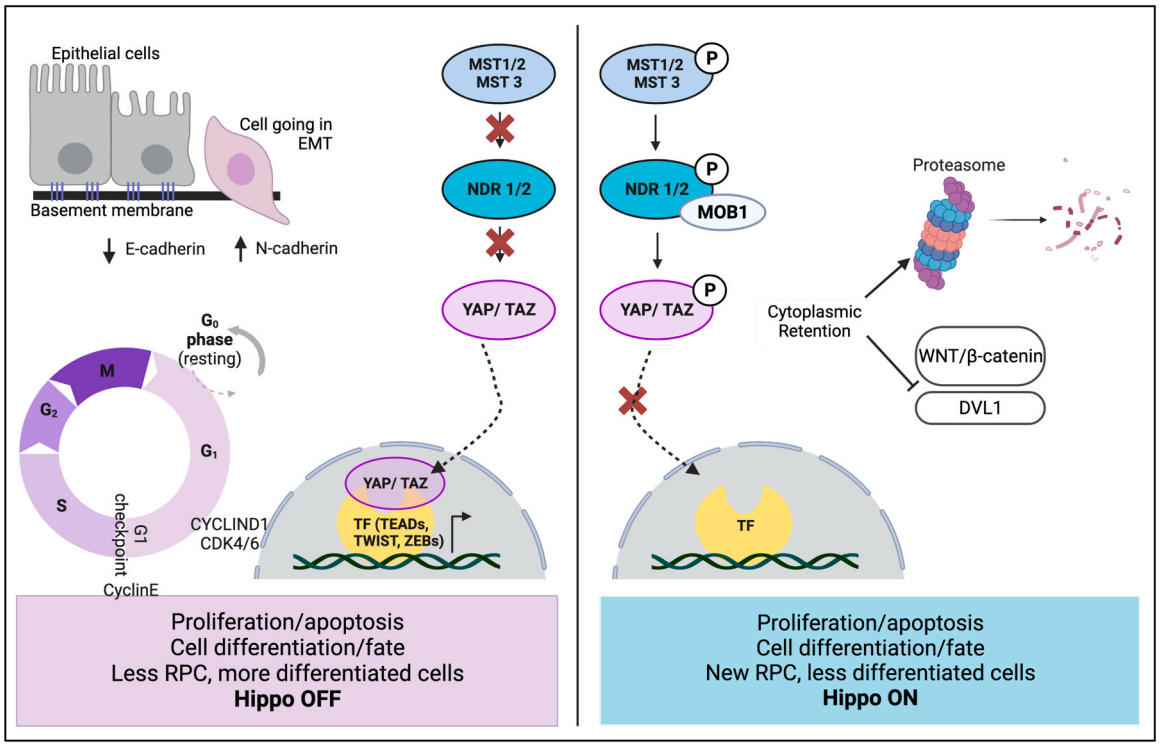

Fig. 2. Regulation of the YAP/TAZ co-transcription factors by NDR1/2 signaling in neuronal cells. Left: Hippo pathway is OFF. The NDR1/2 kinases are not phosphorylated and thus not activated, leading to the translocation of the no phosphorylated YAP and/or TAZ co-transcriptional factors to the nucleus and the transcription of genes involved in cell cycle and cell differentiation. In particular, YAP/TAZ can promote the epithelial-mesenchymal transition. Right: Hippo pathway is ON. The NDR1/2 kinases are phosphorylated and activated by the MST kinases, inhibiting the co-transcriptional activity of YAP/TAZ and promoting the cytoplasmic retention of their phosphorylated forms or the inhibition of the Wnt/β-catenin pathways involved in cell proliferation. Created with BioRender.com.

the retina to the brain (Fig. 4). Therefore, the retina is a complex and highly polarized neuronal tissue requiring precise and coordinated regulation of cell proliferation, migration, morphogenesis, and synaptic connectivity. For that reason, it is not surprising that the Hippo pathway is an important player in the development and homeostasis of the tissues of the ocular and central nervous system.

3. Functions of the LATS kinases in neuronal tissues

LATS1 and LATS2 kinases have been known to regulate the size of various organs by controlling the proliferation/apoptosis balance and cell migration. Therefore, they are important players in the development and homeostasis of the central nervous system.

3.1. LATS1/2 kinases are fundamental for neuronal cell proliferation and cell death

In the brain, controlled neural stem cell proliferation and differentiation generate neurons and glial cells during development and, in some specific brain regions, throughout life. The Hippo kinases Ste20-like kinases MST1 and MST2 (orthologs of Drosophila Hippo) and the LATS1/2 kinases (orthologs of Drosophila Warts) play an important role in the expansion and differentiation during the development of the CNS and in the maintenance of the differentiated adult CNS (Cao et al., 2008) by influencing the G2/M transition. It has been demonstrated that the downregulation of LATS2 kinase expression is linked to several gliomas (astrocytomas, oligodendrogliomas and glioblastomas) and marks the transition from low- to high-grade glioma by controlling the G1/S progression and the cell migration speed. Glioma cells with downregulated Lats2 show a decrease in phosphorylated forms of the co-factors YAP (p-YAP) and TAZ (p-TAZ) and an increase of the YAP/TAZ nuclear localization where they carry their transcription co-factor activity. Nuclear YAP/TAZ can bind several transcription factors such as TEADs, RUNXs, and SMADs, and regulate the transcription of the neural precursor gene such as PAX3, the cell cycle genes CDK4, CDK6, CyclinD1, CyclinE, or the epithelial-mesenchymal transition (EMT) genes Twist, E-Cadherin and N-Cadherin (Fig. 2). Together, these results showed that LATS2 play a major role in glioma progression via its substrates YAP/-TAZ (Guo et al., 2019; Lignitto et al., 2013; Ouyang et al., 2020). Similarly, it has been also shown that LATS1 and LATS2 kinases play a role in the progression of the Schwann cell-lineage-derived sarcomas and the pituitary gland tumorigenesis via their substrate YAP/TAZ. A reduction or a loss of LATS1/2 expression induces a loss of p-YAP and p-TAZ expression, an increase of the YAP/TAZ nuclear form (non--phosphorylated form) and promotes cellular hyperproliferation and a cancerous, progenitor-like phenotype (Brandt et al., 2019; Lodge et al., 2019; Wu et al., 2018). The Hippo pathway can also cross-react with several other pathways in tumorigenic cells such as glioma cells. The phosphorylated form of YAP and TAZ can inhibit the Wnt/β-catenin pathways, regulating cell proliferation and glioma development. Indeed, YAP can sequester β-Catenin in the cytoplasm (Imajo et al., 2012) while TAZ can inhibit the phosphorylation of disheveled (DVL) protein (Denysenko et al., 2016; Nusse and Clevers, 2017). In conclusion, the Hippo kinases LATS1/2 play an important role in neuronal cell proliferation during developmental processes and adulthood.

While LATS kinases are important regulators of the cell cycle, they are also crucial for the regulation of several forms of cell death. In Huntington's disease, phosphorylated YAP causes excitotoxicity and calcium signal disturbances, mitochondrial dynamics changes, transcriptional interference, cytoskeletal disruption, and improper protein processing. In Huntington's and Alzheimer's diseases, nuclear YAP can interact with the P73, a structural and functional homologue of the P53 tumor suppressor protein, promoting ballooning cell death and transcriptional repression-induced atypical cell death (TRIAD), while YAP/

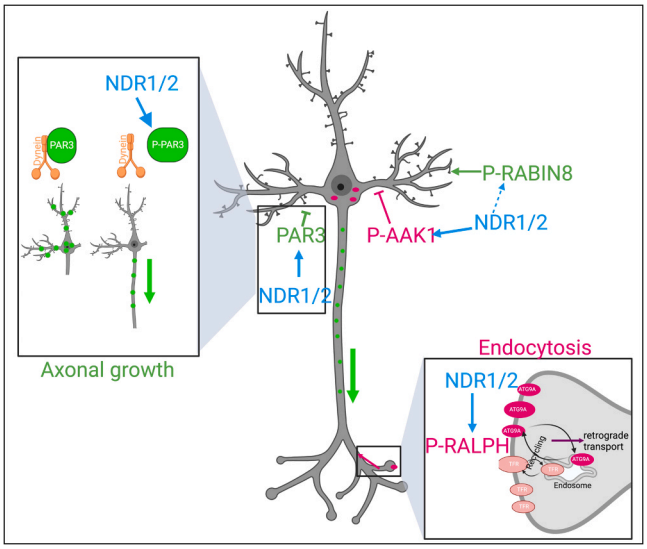

Fig. 3. NDR1/2 play a central role in the regulation of neuronal polarity in brain and retina. This schematic diagram depicts the functions of several substrates of NDR1/2 kinases in neuronal polarity and membrane trafficking events affected by NDR1/2 in neurons. NDR1/2 kinases can restrain proximal dendrite branching via their substrate AAK1 (pink) while promoting synapse development and increase in spine head diameter via RABIN8 (green). In the left zoom, unphosphorylated PAR3 can binds to dynein and is distributed uniformly to all neurites of the developing neuron. NDR, in conjunction with RASSF5, prevent the interaction of phosphorylated (Ser383) PAR3, with dynein and its retrograde transport to the soma, therefore restricting PAR3 (green) to axon tips, promoting axon formation. In the right zoom, NDR1/2 kinases regulate endocytosis of the trans-membrane autophagy protein ATG9A (pink), via their substrate RAPH1/LPD, causing axonal retrograde ATG9A transport. Created with BioRender.com.

P73/BAX mediate apoptosis and intracellular Aβ-induced neuron necrosis (Jin et al., 2020).

In cortical and striatal neurons, LATS1 and the kinase PLK1 control the TEAD/YAP-dependent specific necrosis called TRIAD, by controlling the balance of cytoplasmic and nuclear YAP. Activated PLK1 promotes neuronal apoptosis while activated LATS induces necrosis and inhibits apoptosis. In cortical neurons of patients with Huntington's disease, the activation of LATS only strongly pushes toward TRIAD.

3.2. LATS1/2 kinases functions in the neuroretina

The mechanisms underlying the LATS1/2 kinases functions in ocular development and homeostasis in different animal models are largely unknown. Studies using the drosophila Lats – Wts demonstrate their key role in the development of the eye. Wts is involved in the differentiation of the r8 ommatidium via the mutually exclusive cross-repression between Wts and the growth regulator Melted (Melt), permitting color vision in Drosophila (Jukam et al., 2013). Yoichi Asaoka et al. have demonstrated that, in Zebrafish, YAP activity, probably regulated by LATS1/2 kinases, suppresses photoreceptor cell differentiation via its interactions with transcription factor RX1, acting upstream of OTX, CRX and Rhodopsin (Asaoka et al., 2014).

Although YAP function during early ocular development is understood, the underlying mechanisms in different animal models are largely unknown, except for Drosophila.

The mammalian Lats1 gene was first identified in the canine retina by Akhmedov et al., who characterized two different retinal variants, the truncated mRNA version or Lats1S (3.4 kb) and the long version (Lats1L; 7.5 kb) (Akhmedov et al., 2005). Lats1L is more abundantly expressed in mammalian retinas than Lats1S. Both Lats1 mRNA are expressed in cone photoreceptors as well as in retinal cells from the INL and GCL. Immunolocalization of LATS1 showed labeling in INL, GCL and the NFL. In CD-1 mice, LATS1/2 are robustly and increasingly expressed in the developing retina, from postnatal day 0 (P0) to later postnatal stages. This increased expression is associated with a decreased expression of their substrate YAP confirming that YAP is negatively regulated by LATS proteins to control and limit retinal proliferation (Zhang et al., 2012). However, LATS1/2 are also associated with abnormal retinal homeostasis. In dogs, the gene responsible for autosomal dominant cone dystrophy is in the same region than the Lats1 locus suggesting LATS1 as a novel putative candidate for future cone dystrophy studies (Akhmedov et al., 2005). Moreover, retinas from dogs with early retinal degeneration disease (erd), a disease associated with concomitant aberrant proliferation and apoptosis of the photoreceptors, present a diffuse labeling of LATS1 in the S-cones. These results demonstrate that LATS1 protein is expressed in the newly generated hybrid and aberrant rods/S-cones observed in erd dogs (Gardiner et al., 2016).

In mouse developed retinas, LATS1/2 prevents the activation of the co-transcription factors YAP/TAZ in quiescent Müller cells (Rueda et al., 2019). Interestingly, even if Yap has not been directly linked to retinoblastoma initiation, numerous studies report a downregulation of LATS2 kinase in human retinoblastoma tumors, suggesting that the loss of YAP inhibition by LATS2 is a factor in the development of the disease (Chakraborty et al., 2007). A similar mechanism occurs in the ciliary

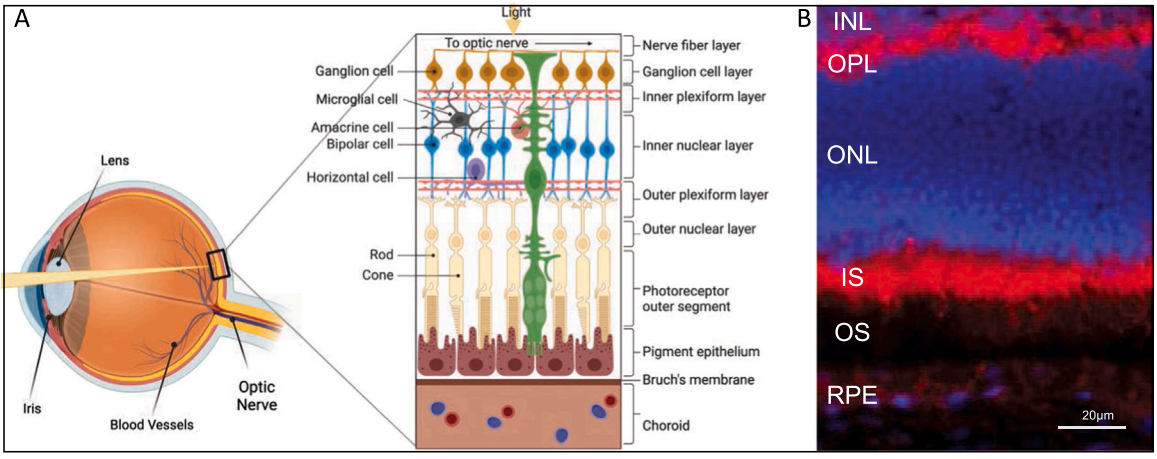

Fig. 4. Expression of the hippo pathways components in the ocular system. (A) Schematic of the ocular system (left) and retina organization (right). Created with BioRender.com. (B) Expression of NDR2 kinase (red) in the photoreceptors andOPL. Nuclei were labeled with Dapi. Scale bar:

margin (CM), where the neurofibromin2 (Nf2)-Hippo-Yap/Taz feedback circuit promotes cell proliferation and tissue growth in the post-natal mouse eye (Curto and McClatchey, 2008; Moon et al., 2018). In humans, the ocular diseases congenital retinal coloboma and Sveinsson's chorioretinal atrophy are linked to the Hippo-Yap/Taz pathway (Miesfeld et al., 2015). Both present a loss of choroid, RPE, and photoreceptors. Moreover, several studies demonstrated that YAP impacts the cell-cycle exit of the retinal progenitor cells during development without affecting their cell fate determination. YAP plays also an important role in the regulation of Müller cell homeostasis and the maintenance of cone photoreceptors during aging (Masson et al., 2020). Interestingly, YAP/TAZ seems to also have an important role in endothelial cells (ECs), regulating the retinal angiogenesis. YAP is highly expressed in vascular ECs of the developing mouse retina (Choi et al., 2015). Yap knockout (KO) mice present developmental arrest with vascular defects in the yolk sac (Morin-Kensicki et al., 2006).

Finally, the Hippo pathway has been shown to be also involved in metabolism adaptation to the microenvironment and availability of nutrients as demonstrated by many cancer cells (Ardestani et al., 2018; Lee, Cho, and Jho, 2022). For example, diabetic rats present a decreased phosphorylated (activated) MST1/2 level in the IPL, associated with an increased retinal LATS1/2 expression and a reduced expression of P-YAP in the photoreceptor layer when compared to non-diabetic rats. Therefore, the Hippo pathway could play an important role in the progression of diabetic retinopathy (Hao et al., 2017).

4. Functions of the NDR kinases in neuronal tissues

The NDR pathway is considered as the non-canonical branch of the Hippo pathway. It is constituted of the MST1 and MST2 kinases which phosphorylate the NDR1 (STK38) and NDR2 (STK38L) kinases in association with MOB1 co-factor (Fig. 1). NDR1 and NDR2 were identified in budding yeast *S. cerevisiae* as Cbk1, the terminal nuclear serine-threonine kinase of the RAM/MOR signaling network (Hergovich et al., 2006; Hergovich et al., 2005; Yu and Guan, 2013) (Table 1). Mammalian NDR kinases are tissue growth regulators, implicated in cell proliferation, cell cycle progression and cell death. NDR kinases can also control various cellular mechanisms such as tissue homeostasis, polarized morphogenesis, cell differentiation, or secretion events, via their numerous substrates (Fig. 1).

Mammalian NDR1 and NDR2 kinases share ~85 % of protein identity and ~90 % protein sequence similarity with each other. Both NDR kinases are similarly structured with an N-terminal S100B/calmodulin binding site, a catalytic kinase domain which contains a non-consensus nuclear localization signal and a phosphorylation site necessary for kinase activation. Both mammalian Ndr1 and Ndr2 kinase genes are constituted of 14 exons with conserved intron-exon boundaries. The exon 1 is a noncoding exon containing the 5′-untranslated region, the exon 2 contains the start codon and the exons 4–14 are the coding sequence for the protein kinase and contain the stop codon. NDR1 and NDR2 protein kinases have a different pattern of expression which suggest tissue-specific functions. NDR1 is widely expressed in all tissues with a predominance in the immune system while NDR2 is mainly expressed in the gastrointestinal tract (Stegert et al., 2004). Several studies have demonstrated that both NDR1 and NDR2 play a role in the neuronal tissues such as the brain and the retina. But their functions are still poorly understood, and many of their substrates are to be discovered.

4.1. NDR kinases roles in neuronal polarity

The asymmetric distribution of neuronal molecules is an important regulator of neuronal differentiation. It permits the establishment of a polarized neuron with a single axon and several dendrites from an unpolarized neuron made of multiple short neurites (Banker, 2018). Yeast Ndr regulates vesicle trafficking, polarized secretion and morphogenesis which are essential for neuronal cell development and function. Moreover, mutations in *Drosophila* and *C. elegans* Ndr kinase homologs (Trc and Sax-1) are known to cause defects in neuronal tiling and dendritic spine morphology while overexpression of Ndr kinases promotes neurite formation and branching, influences integrin trafficking and integrin-dependent neurite growth in hippocampal neurons. Mammalian NDR1 and NDR2 are involved in the establishment of polarity in neurons. In the hippocampus, the NDR kinases, under the control of the tumor suppressor RASSF5, prevent the formation of supernumerary axons by regulating the interaction between the cytoskeletal motor protein dynein and the polarity protein PAR3 (Hergovich et al., 2006; Yang et al., 2014; Zallen et al., 2000) (Fig. 3 left). NDR2 kinase also regulates dendritic growth of hippocampal neurons by phosphorylating integrins, causing their translocation to the neurite tips where they promote neurite extension (Rehberg et al., 2014). NDR1/2 kinases can also control endocytosis and axonal retrograde transport of the trans-membrane autophagy protein ATG9A (Fig. 3 right), which plays an essential role in axonal homeostasis by coupling the synaptic vesicle cycle with autophagy (Roşianu et al., 2023).

NDR1 and NDR2 are also implicated in dendritic spine morphogenesis, interneuron vesicle trafficking and synapse function via their substrate AP-2 associated kinase-1 (AAK1), an alpha-adaptin binding protein and a clathrin-coated vesicle trafficking regulator (Conner and Schmid, 2002; Ultanir et al., 2012) (Figs. 1, 3). AAK1 is a known controller of NUMB, a membrane-bound protein, which plays an important role in neurogenesis by regulating the density and length of dendritic protrusions. Moreover, AAK1 is known to localize at the presynaptic terminals where it participates in synaptic vesicles recycling as well as in clathrin-coated pits and at the leading edge of polarized cells. Based on the role of AAK1's yeast orthologue on destabilizing actin cytoskeleton at endocytic zones and its regulation by Cbk1p (the phosphorylated form of NDR1/2's yeast orthologue), it has been hypothesized that NDR1/2 could destabilize actin via AAK1 phosphorylation regulation, causing dendritic loss of hippocampal neurons. Interestingly, Ndr 1 and Ndr2 single KO mice retinas present a similar phenotype with (a) the observation of decreased expression of AAK1 protein expression in the photoreceptors, the OPL and IPL and (b) the downregulation of genes involved in synapse function and modulation in Ndr2 KO retinas, demonstrating a role of NDR kinases in interneuron neurite and synapse functions. Intriguingly, these data suggest that both NDR1 and NDR2 kinases are required to maintain wild type levels of retinal AAK1 (Léger et al., 2018).

4.2. Functions of the NDR kinases in the neuroretina

A naturally occurring SINE insertion in exon 4 of the Stk38l gene causes retinal cell proliferation and apoptosis. These dogs also present an increase of the Hippo kinases LATS1 and LATS2, which may be an attempt of the retina to counterbalance the aberrant photoreceptors proliferation. The disease progression is accompanied by concurrent increases in photoreceptor proliferation and apoptosis, promoting progressive retinal strata disorganization, early retinal degeneration (erd) and ultimately blindness before 6 months old. These dogs present also aberrant rods/S-cone hybrids, generated by the proliferation of the photoreceptors accompanied by rhodopsin mislocalization (Gardiner et al., 2016; Goldstein et al., 2010).

Ndr2 and Ndr1 KO mice present a similar retinal phenotype with concomitant increased apoptosis and cell proliferation of terminally differentiated retinal neurons. NDR2 kinase is prominently localized in the synapse-rich inner and outer plexiform layers (Léger et al., 2018) as well as punctate in the outer segment of the photoreceptors. Ndr1 or Ndr2 deletion induces the cycling of a subset of terminally differentiated PAX6-positive amacrine cells, associated with a decreasing number of GABAergic (GAD65), HUD and PAX6-positive amacrine cells in the INL and the GCL. The apparent decrease in PAX6-positive, HUD-positive and GABAergic amacrine cells in Ndr1 and Ndr2 KO mice may be a

consequence of increased cell death, as suggested by elevated active caspase 3 expression in the INL or may reflect a role for NDR kinases in promoting cell differentiation or controlling the expression of amacrine cell markers (Table 2). Therefore, NDR kinases are involved in the maintenance of amacrine cells by ensuring the appropriate gene expression and/or by controlling their proliferation and cell death, probably via a combination of transcriptional and posttranscriptional mechanisms. However, the mechanisms underlying the role of NDR1 and NDR2 kinases in mouse differentiated retina are unknown. One possibility is that YAP is the effector of the observed cycling amacrine cells, delaying their cell-cycle exit (Hamon et al., 2018; Kim et al., 2016; Masson et al., 2020) (Fig. 2). NDR1 and NDR2 could also negatively regulate amacrine cell proliferation via indirect mechanisms or via another unidentified substrate. We hypothesize that NDR1 and NDR2 regulate amacrine cell functions via their substrate AAK1, which is known to regulate NOTCH signaling both important for retinal interneuron development (Gupta-Rossi et al., 2011). Table 3.

Alternatively, RNA sequencing analysis of Ndr2 KO retinas demonstrated an increased expression of genes associated with oxidative stress, and mitochondrial dysfunction (Table 2) which may be an indirect consequence of misregulated interneuron homeostasis and increased apoptosis in the INL. Further analyses of putative NDR substrates are necessary to elucidate the precise molecular mechanisms of NDR kinases in modulating amacrine cell proliferation (Léger et al., 2018).

5. NDR kinases roles in inflammation

5.1. NDR kinases in immune response

As presented earlier, the Hippo pathway possesses a role in regulating cell proliferation, survival, and differentiation, controlling organ size and tissue homeostasis. However, these functions can also be applied to the regulation of the proliferation and differentiation of the immune cells during injury and pathogen-induced tissue immune response. Numerous studies have shown that the components of the Hippo signaling have a role in innate and/or adaptive immunity. For example, MST1 can regulate B- and T-cells functions via the modulation FOXP3 acetylation, LATS1/2 kinases enhanced anti-viral responses (Zhang et al., 2017) and inhibits the pro-inflammatory response. These functions are probably mediated by YAP/TAZ. Indeed, YAP/TAZ promotes the maturation and recruitment of T-regulatory cells (Treg). Moreover, YAP/TAZ triggers a pro-inflammatory response by inducing IL-6 expression and reducing arginase-I (ARG1) expression via its interaction with the histone deacetylase 3 (HDAC3)-nuclear receptor corepressor 1 (NCoR1) repressor complex (Xie et al., 2021).

In recent years, it has been demonstrated that NDR1/2 plays an important role in inflammation. NDR1 kinase is known to participate in immunity by binding P65 NF-κB subunit and by positively regulating IL-17- and TNF-mediated inflammation in macrophages, which are members of the mononuclear phagocyte system, a major component of innate immunity. On the other hand, NDR2 negatively regulates IL-17-associated inflammation by promoting degradation of SMURF1-mediated MEKK2, suppressing the expression of IL-17-induced MAPK and of IL-17-induced expression of IL-6, CXCL2, and CCL20 and by decreasing NF-κB activation (Ye et al., 2020). However, the role of NDR kinases on inflammatory response is not known in immune-privileged tissues such as the retina.

Table 2
Table presenting the expression of the Hippo pathways components in the ocular system.

Hippo component	Expression in mammalian ocular system
MST1	Blood vessels (Endothelial cells)
MST2	Photoreceptors, Blood vessels (Endothelial cells)
LATS1	RPE, INL (mostly Müller cells), GCL, NFL, Endothelial cells
LATS2	RPE, OPL (synapses between photoceptors and bipolar cells), INL (Müller cells), Endothelial cells
NDR1	Choroid layer/RPE, Microglial cells
NDR2	Choroid layer/RPE, Photoreceptors (punctats in inner segment), OPL, IPL, Microglial cells
YAP	Choroid layer, INL (Müller cells), Blood vessels (Endothelial cells), Microglial cells
TAZ	Choroid layer, INL (mostly Müller cells), Blood vessels (Endothelial cells), Microglial cells

5.2. NDR kinases in neuronal inflammation

Gene enrichment of the differentially upregulated genes in Ndr2 KO retinas highlighted the putative role of the NDR2 kinase in "oxidative phosphorylation" (cytochrome c), "respiratory by electron transport chain" (NAD(P)H:quinone oxidoreductase) and "translation", linked with oxidative, mitochondrial stress and inflammation (Léger et al., 2018). A deeper analysis of the differentially expressed genes in Ndr2 KO retinas realized with Ingenuity Pathway Analysis software highlighted the putative role of the NDR2 kinase in the inflammation pathways Eukaryotic Translation Initiation Factor 2A (EIF2A) and C-X-C Motif Chemokine Receptor 4 (CXCR4), linked with oxidative and mitochondrial stress (Fig. 5A). This analysis underlines a role of NDR2 kinases in ophthalmic and metabolic diseases (Fig. 5B). This analysis is supported by previous studies showing that Hippo signaling can interact with the EIF2AP-ATF4 pathway under oxidative stress (Rajesh et al., 2016). Oxidative and mitochondrial stress often arise from an imbalance between the generation of reactive oxygen species (ROS) produced by the cellular metabolism and the endogenous and exogenous cellular detoxification mechanisms. The retina possesses a high metabolic and oxidative phosphorylation rate compared to other central nervous system tissues due to the extremely high oxygen consumption (Crooks and Kolb, 1992; Eells, 2019; Quinlan et al., 2013). The light-induced signal transduction pathways can cause rhodopsin photobleaching promoting protein oxidation and lipid peroxidation and ROS (Grimm et al., 2000). This is interesting as we demonstrated that the Ndr1 and Ndr2 KO mice present a rod and cone opsin mislocalization in the outer nuclear and inner plexiform layers, mislocalization that could contribute to elevated ROS production and a correlative increased expression of free radical scavenging enzymes, such as NAD(P)H:quinone oxidoreductase (Léger et al., 2018) (Table 2, Fig. 5 C). While healthy retinal neurons maintain homeostasis in the presence of moderate oxidative stress, an aberrant increase in ROS caused by constant exposure to light, mislocalized opsin or retinal defects can lead to activation of inflammatory factors and apoptotic pathways causing cell death, metabolic defects and visual impairment, which are observed in Ndr2 defected dogs (erd) and mice (Ndr2 KO) (Table 2, Fig. 5D).

Finally, it is highly possible that Ndr loss-of-function impairs the functions of the retinal mononuclear phagocytes e.g. the microglia via the activation of the NF-κB signaling pathway as observed in colon. This is supported by the fact that MST1, an upstream kinase of the pathway is known to play an important role on ischemia-reperfusion-induced neuroinflammation and injury by directly and indirectly controlling the NF-κB signaling and brain microglial activation (Zhao et al., 2016). Moreover, in brain, YAP negatively controls the expression of the suppressor of cytokine signaling 3 (SOCS3), and subsequently the JAK/-STAT pathway in astrocytes and its driven microglial activation necessary for the appropriate blood-brain barrier functions. Astrocytic activated YAP is also implicated in the prevention of demyelination and microglia-induced neuroinflammation control in the spinal cord and in the optic nerve through the TGF-β pathway as well as in the brain of Alzheimer's disease (AD) patients via the production of pro-inflammatory factors such as IL-1β, IL-12, and TNF (Mia and Singh, 2022; Xie et al., 2021).

Table 3
Impact of Ndr2 or Ndr1 kinase deletion in dog and mouse on retinal phenotype, cell proliferation/apoptosis, differentiation, neuronal stress, and function.

Topics	Erd dog	Ndr2 KO mice	Ndr1 KO mice
Ndr kinase	SINE insertion in exon 4 of Ndr2 gene	LoxP targeting exon 7 of Ndr2 gene	2 lines: CRISPR Indel in exon 4 or exon 6
	No kinase activity	No Protein expression	No Protein expression
Retinal phenotype	Progressive retinal strata disorganization	Rod and rod-driven bipolar cell response of dark-adapted 1 month old animal: normal	Rod and rod-driven bipolar cell response of dark-adapted 1 month old animal: normal
	Blindness before 6 months old	Mixed rod-cone responses of dark-adapted 1 month old animal: normal	Mixed rod-cone responses of dark-adapted 1 month old animal: normal
	Aberrant rod/S-cone hybrids	Visual placement evaluation of 1 month old animal: normal	Visual placement evaluation of 1 month old animal: normal
	Rhodopsin mislocalization	Rhodopsin mislocalization	Rhodopsin mislocalization
Proliferation/Apoptosis	Aberrant photoreceptors proliferation and apoptosis		Aberrant photoreceptors proliferation
		Aberrant amacrine cell proliferation and apoptosis	Aberrant amacrine cell proliferation and apoptosis
Cell fate and differentiation	Decreasing number of Pax6-positive cells	Decreasing number of GABAergic (GAD65), HUD and PAX6-positive amacrine cells in the INL and the GCL	Decreasing number of GABAergic (GAD65), HUD and PAX6-positive amacrine cells in the INL and the GCL
Enhanced neuronal stress		Up-regulated genes: “structural constituents of eye lens” (crystallin), “ubiquinol-cytochrome-c reductase activity” and “NADH dehydrogenase (quinone) activity", "Respiratory electron transport chain", "Oxidative phosphorylation".	Validated by RTqPCR
Decreased function and modulation of the synapses		Down-regulated genes: ”regulation of synaptic plasticity” and “synapse organization”, “nervous system development” and “muscle contraction”	Validated by RTqPCR
		Decrease (>50 %) in Aak1 immunofluorescence levels	Decrease (>50 %) in Aak1 immunofluorescence levels

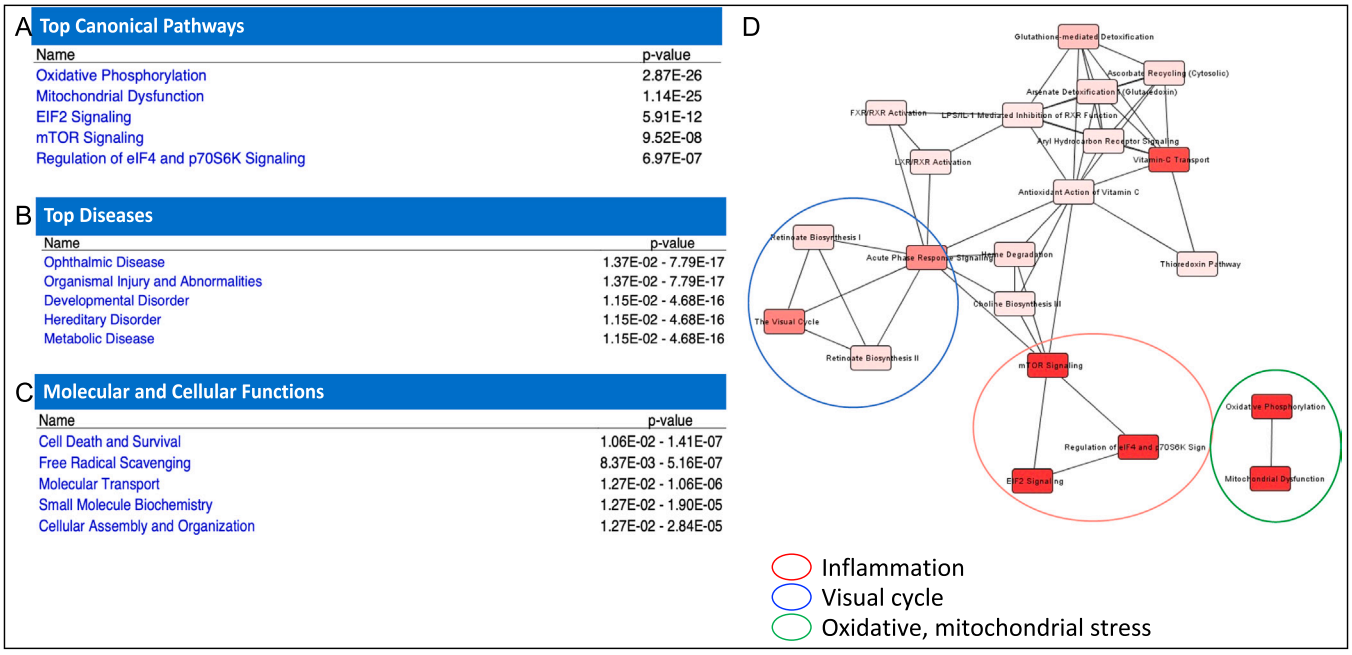

Fig. 5. Ingenuity pathway analysis (IPA) network and canonical pathway analysis for the differentially regulated genes in mouse Ndr2 KO highlighted the role of NDR2 kinase in inflammation regulation. (A) The top canonical pathways determined by IPA are associated with inflammation as well as oxidative and mitochondrial stress. (B) Top diseases caused by a Ndr2 deletion identified by IPA. (C) Molecular and cellular functions observed in Ndr2 KO retinas showed that NDR2 kinase is especially important for the regulation of cell death and survival and free radical scavenging linked with oxidative stress and inflammation. (D) Depiction of the main canonical pathway webs highlighted by IPA. The first one (green circle) appear devoted to the regulation of the oxidative and mitochondrial stress while the second one (red) highlight inflammation. The third (blue circle) is centered to visual cycle. Canonical pathway red symbol gradient relates to the p-value for the likelihood of the association between the differentially genes in our experiment and the pathway. The smaller the p-value, the darker the red shading and the stronger the association. For a more detailed explanation, see http://qiagen.force.com/KnowledgeBase/articles/Basic_Technical_Q_A/Legend.

6. Concluding remarks and future perspectives

Like the Hippo kinases LATS1 and LATS2, NDR1 and NDR2 kinases are important players in the homeostasis of brain and retina. NDR1 and NDR2 are involved in the apoptosis and cell proliferation regulation of mammalian brain and neuroretina. NDR1 and NDR2 kinases are also involved in the amacrine differentiation and/or maintenance probably via a combination of transcriptional and posttranscriptional mechanisms. Further analyses are necessary to identify the NDR substrates and the precise molecular mechanisms by which NDR modulates amacrine cell proliferation and differentiation. Moreover, we demonstrated that loss of NDR signaling might impair retinal interneuron vesicle trafficking and neuronal signaling in retinas via diminished AAK1 level/activity, which is supported by the role of NDR1/2 kinases in intracellular vesicle trafficking, dendrite growth regulation of pyramidal neurons, and spine development via its substrate AAK1. Finally, we showed that Ndr2 KO animals present markers of elevated retinal stress such as increased expression of genes associated with oxidative stress, mitochondrial dysfunction, protein misfolding, and cytoskeleton changes. These results may be an indirect consequence of misregulated interneuron homeostasis and increased apoptosis in the INL or direct evidence of impaired retinal inflammation. This last hypothesis is supported by the fact that NDR kinase has recently been discovered as an immune regulator that could play an important role in retinal microglia activation. Therefore, it is crucial to investigate the functions of NDR1 and NDR2 kinases in the regulation of the neuroimmune system and their role as potential therapeutic targets for the treatment of neuronal diseases.

CRediT authorship contribution statement

Paulo Santos: Writing, Reviewing and Editing; Beatriz Fazendeiro: Writing, Figures, Reviewing and Editing; Francis Luca: Reviewing and Editing; António Francisco Ambrósio: Reviewing and Editing; Hélène Léger: Conceptualization, Writing, Figures, Reviewing and Editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The RNA sequencing data were already published (Léger et al., 2018) and the article is cited in the review.

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