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JB Review

The growing role of the Hippo–NDR kinase signalling in neuronal development and disease

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The nuclear Dbf2-realted (NDR) family members are highly conserved serine/threonine protein kinases that function in concert with the Hippo signalling pathway to play crucial roles in regulation of cell proliferation and survival in non-neuronal cells. Recent studies employing a range of animal models have implicated NDR kinases as regulators of multiple aspects of development in post-mitotic neurons including progenitor proliferation, fate specification and circuit formation, all of which are crucial for neuronal functions. This review summarizes the recent advances in our understanding of the neuronal functions of NDR kinases and discusses their association with neuronal diseases.

Keywords: Down's Syndrome/Mps one binder/ mammalian sterile 20-kinase/nuclear Dbf2-related/ Target of rapamycin/warts.

Abbreviations: MOB, Mps one binder; MST, mammalian sterile 20-like; NDR, nuclear Dbf2-realted; TOR, Target of rapamycin; Wts, warts/lats kinase.

The NDR (Nuclear Dbf2-related) family is an evolutionarily conserved subclass of the AGC (protein kinase A, G and C) group of kinases (*1*, *2*). The NDR kinases can be further classified into two families based on their structures and functions, the Ndr family and the Wts/Lats family (hereafter designated the Wts family; Fig. 1). Human and other vertebrate genomes encode two Ndr (Ndr1 and Ndr2) and Wts (Lats1 and Lats2) kinases, whereas one member of each family is found in invertebrates including *Caenorhabditis elegans* (SAX-1 and LATS) and *Drosophila* (Trc and Wts).

Ndr and Wts family kinases have been characterized for their roles in cell proliferation and survival in non-neuronal cells. In particular, recent studies in multiple organisms have established that the Hippo–Wts kinase pathway plays the central role in organ size control by promoting cell-cycle exit and apoptosis (*3*, *4*). Analyses of different model systems have also suggested that Ndr signalling and Wts signalling are likely to be involved in additional cellular functions such as centrosome duplication (*5*, *6*), chromosome alignment (*7*), cell polarity control (*8–11*) and cytoskeletal organization (*12*). Although both the Ndr and Wts family kinases are also known to be abundant in the brain (*13–17*), the neuronal functions of these kinases remain poorly understood. However, several recent findings have suggested that the NDR family members are crucial regulators of different stages of neuronal development. In the present article, we review the current advances in our understanding of NDR functions in neurons, including progenitor proliferation control, neural fate specification, neurite outgrowth/branching and receptive field determination. We will also discuss how these mechanisms may play a role in neural diseases.

The NDR family kinases and signal transduction

The NDR kinases are major regulators of cell proliferation and apoptosis. In neurons, however, these enzymes appear to play broader roles including neural fate specification, neurite outgrowth/branching and receptive field determination. Several excellent reviews published recently have discussed the signal transduction pathways that are involved in NDR activity, the cellular processes regulated by NDR kinases, as well as the proteins that interact with these kinases (*1*, *3*, *4*, *18*). Thus, this review here provides a brief summary of the current knowledge of NDR actions in the nervous system.

Genetic studies of the Ndr kinases in yeast and invertebrates have established that Ndr family kinases play an evolutionarily conserved role in cell morphogenesis, presumably by controlling Rho GTPase signalling (*9*, *10*, *19–23*). In parallel, pathological studies of the human Ndr kinases, Ndr1 and Ndr2, have uncovered a potential relationship between these factors and tumour development. As an example, human Ndr1 has been found to be up-regulated in progressive ductal carcinoma and some melanoma cell lines (*24*, *25*). Similarly, the Ndr2 levels are increased in a metastatic lung cancer cell line (*26*). These observations suggest that the Ndr kinases might have proto-oncogenic activity. On the other hand, recent studies have also indicated that mammalian Ndr1 and Ndr2 mediate apoptosis downstream of tumour suppressors MST kinases and RASSFs (*27*, *28*). Consistently, a recent report has suggested that Ndr1 knockout mice are predisposed to the development of T-cell lymphomas (*29*). Thus, Ndr kinases seem to function in the regulation of cell growth and apoptosis, although the precise underlying mechanisms have yet to be established.

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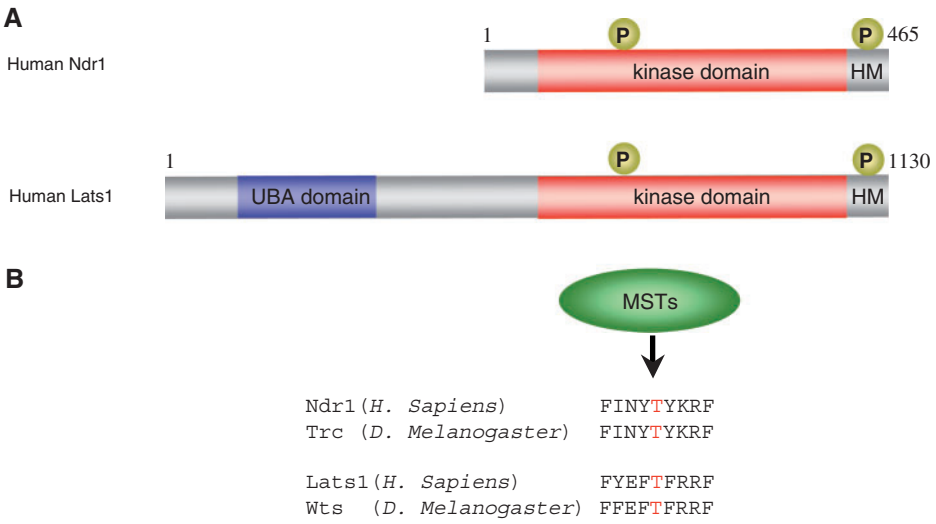

Fig. 1 (A) Molecular structures of NDR family kinases. NDR family can be further divided into two groups; Ndr family and Wts/Lats family. The primary structures of human Ndr1 of the Ndr family and human Lats1of the Wts/Lats family are shown. Compared to the Ndr family members, Wts/Lats family members contain additional domains at N-terminal. UBA, ubiquitin associated; HM, hydrophobic motif; MST, mammalian ste20-like kinase. (B) MST kinases directly phosphorylate NDR kinases at the Thr residue in the C-terminal hydrophobic motif.

The mechanism of Wts signalling action in growth control is relatively well understood. Wts kinases control cell growth by phosphorylating the transcriptional repressor YAP at multiple Ser residues, leading to suppression of its activity (*30*) (Fig. 2). In *Drosophila*, when Yorkie (a fly homologue of YAP) is not inhibited, it localizes in the nucleus, forms complexes with transcription factors such as Scalloped (a fly homologue of TEAD), and induces the expression of target genes including the cell-cycle regulator *cyclin E*, the inhibitor of apoptosis *diap*, the growth promoter *Myc* and the growth and cell-survival promoting miRNA *bantam*, all of which drive cell proliferation and survival (*30–40*). YAP is thus a growth promoter, whereas Wts acts as a tumour suppressor by suppressing YAP. In mammals, many studies that have uncovered a connection between Wts signalling and organ size control have done so by employing a YAP overexpression strategy that mimics pathway inactivation and shown that the induction of YAP expression in the adult mouse liver leads to a dramatic increase in liver mass as a result of increased cell numbers (*41*, *42*). The results of these studies have inferred that Wts signalling plays a crucial role in organ size control through the regulation of YAP activity. However, further confirmation is needed to determine which phenotypes induced by YAP overexpression are associated with Wts signalling, since recent studies have shown also that YAP is regulated by additional signalling mechanisms, such as the α-catenin and 14-3-3 pathways (*43*).

Lats2-deficient mice die during embryonic development due to defects in proliferation control and in the maintenance of genomic stability (*14*), whereas Lats1-null mice spontaneously develop tumours and are hypersensitive to carcinogenic treatments (*16*). In addition, the down-regulation of Lats1 and Lats2 levels has been reported in association with human sarcomas, ovarian carcinoma, breast cancer and acute

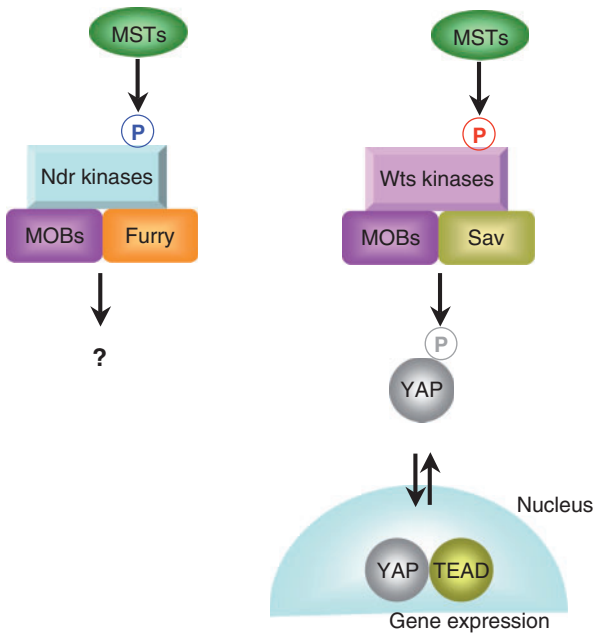

Fig. 2 Schematic diagrams of the Ndr and the Wts-signalling pathways in mammals. The Ndr family kinases function as a complex with a scaffold protein Furry (left), whereas the Wts family kinases associate with a cofactor Salvador/WW45 (Sav) (right). MOBs are shared activators for both family kinases. MST kinases phosphorylate both Ndr and Wts kinases for their full activation. The activated Wts kinases then inactivate the transcriptional factor YAP by phosphorylation, because the phosphorylated YAP binds to 14-3-3 and are sequestered in the cytosol.

lymphoblastic leukaemia (*44–46*). These observations suggest the possibility that, similar to Wts in *Drosophila*, the mammalian Wts family kinases might also function as tumour suppressors in mammals.

Regulation of NDR kinase activity

The activities of the NDR kinases are promoted following phosphorylation of the Ser and Thr residues in

their activation loop and the C-terminal hydrophobic motif, respectively (Fig. 1). In addition to these two critical residues, several Ser/Thr residues appear to be phosphorylated in human Ndr1 and Ndr2 (*15*, *47*). The Ser residue in the active loop is likely to be autophosphorylated, whereas the Thr phosphorylation in the hydrophobic domain is mediated by upstream kinases (*15*, *48*). Recent studies in multiple model organisms indicate that the mammalian Ste20-like (MST) kinases directly phosphorylate NDR kinases at the Thr residue in the C-terminal hydrophobic motif. For example, the *Drosophila* MST kinase Hippo phosphorylates Trc (a fly homologue of Ndr kinases) as well as Wts *in vivo* and *in vitro* (*39*, *49*). Similarly, MSTs can directly phosphorylate the Thr of Ndr1, Ndr2, Lats1 and Lats2 in the hydrophobic motif (*28*, *50*, *51*).

The target of rapamycin (TOR) kinase is also implicated in Thr phosphorylation in the hydrophobic motif of Ndr kinases. TOR is an evolutionarily conserved Ser/Thr protein kinase that functions in two distinct multiprotein complexes referred as TOR complex 1 (TORC1) and complex 2 (TORC2). TORC1 is composed of TOR, Raptor and LST8 (also known as GβL) whereas TORC2 contains TOR, Rictor, LST8 and Sin1 (*52–54*). TORC1 regulates translation and cell growth by phosphorylating ribosomal S6 kinase (S6K) and eukaryote initiation factor 4E-binding protein (4E-BP1) in a rapamycin-sensitive manner. The function of TORC2 is less well-defined than that of TORC1, but some studies suggest that TORC2 is involved in actin cytoskeleton reorganization (*55*, *56*). A recent report has shown that TORC2, but not TORC1, forms a complex with Ndr1 in HeLa cells (*57*). Further genetic and biochemical analyses indicate that TORC2 is required for Ndr phosphorylation on the Thr residue of its hydrophobic domain, a region that is critical for Ndr activity both *in vivo* and *in vitro*, although direct phosphorylation by TORC2 has yet to be determined.

In addition to the Ser/Thr phosphorylation, both the Ndr and Wts kinases require multiple activator proteins for maximum activation (Fig. 2). The MOB (Mps-One Binder) activator proteins bind to the conserved N-terminal domain preceding the catalytic domain and promote full activation of NDR kinases (*58–61*). Although the precise mechanisms underlying their activation remains elusive, MOBs appear to induce structural changes in the kinase domain of NDR proteins, leading to the release of autoinhibition (*62*). Interestingly, MOBs are phosphorylated by MST kinases at multiple Ser/Thr residues, which likely enhances their ability to activate NDR kinases (*27*, *63–65*). RASSFs, proteins with a Ras-association domain, also play a regulatory role in both the Ndr and Wts pathways, but the identity of the underlying mechanisms remains controversial (*28*, *66*, *67*).

Although MOBs and RASSFs are required for the activation of both Ndr and Wts kinases, Furry is only required by the Ndr family kinases. Furry is an evolutionarily conserved large protein that is known to interact physically and genetically with Ndr kinases (*19*, *23*, *68–70*). Chiba and colleagues have demonstrated that Furry protein is associated with microtubules as well as Ndr1 in HeLa cells and that this association is critical for the precise alignment of mitotic chromosomes (*7*). In *Drosophila* bristles, Furry seems to be highly mobile, suggesting a potential role in the recruitment and/or transport of Ndr kinases in bristles (*71*). The Wts kinases require different sets of activator/scaffold proteins for their activity control. For example, the WW domain-containing protein Salvador/WW45 forms a complex with and activates Wts kinases (*37*), whereas the LIM protein Ajuba associates with and suppresses Wts kinase activity (*72*).

Proliferation control of neural progenitor cells

Given that the NDR kinases play critical roles in cell growth control, one might speculate that they are involved also in the control of neural stem/progenitor cells. Indeed, the Wts kinase signalling pathway mediates progenitor cell proliferation and survival in multiple tissues including the nervous system. In the developing vertebrate neural tube, neural progenitor cells reside along the ventricle and form a pseudostratified epithelium. With their ability to carry out multiple rounds of cell division and to produce progeny of different fates, neural progenitor cells ultimately give rise to the vast numbers and diverse types of neurons and glial cells that constitute the mature nervous system (*73*). The inhibition of Wts signalling in the developing neuroepithelium of chick embryos via the overexpression of dominant-negative kinases or YAP causes expansion of the neural progenitor pool in the spinal cord (*74*, *75*). Conversely, the loss of YAP or TEAD function results in a reduction of the progenitor population, presumably due to increased cell death. These data suggest that the Wts pathway likely regulates the number of neural progenitor cells by affecting their proliferation and survival. The Wts pathway plays similar roles in tissues outside of the brain. For example, YAP expression is restricted to the intestinal crypts and the basal layer of the skin, where progenitor cells reside, in both the adult human and mouse (*41*, *76*). Attenuation of the Wts signalling expands the progenitor pool at the expense of differentiated cells. Thus, Wts signalling likely plays general roles in maintaining an undifferentiated progenitor cell population. Recent studies in *Drosophila* and mouse models suggest a potential role of the Wts pathway in the control of the stem-cell proliferation during tissue regeneration (*77–81*). However, further studies will be required to address whether the Wts pathway is involved in control of the neural stem-cell population.

The *Drosophila* Wts kinase was originally isolated as a tumour suppressor via genetic screens (*82*, *83*), and subsequent studies implicate Wts dysfunction in tumour progression in multiple human tissues (*44–46*). Consistently, the aberrant control of Wts signalling in neural precursor cells is likely to be associated with the development of medulloblastomas, the most common solid malignancies in childhood that arise in the developing cerebellum (*75*).

Medulloblastoma has further been shown to be associated with activation of the Sonic hedgehog (Shh) signalling pathway, and YAP has now been identified as an up-regulated factor in human Shh-associated medulloblastoma. Shh induces YAP expression in granule neuron precursors. Furthermore, the overexpression of YAP in granule neuron precursors significantly increases their proliferation, whereas a knockdown of YAP in the presence of Shh leads to a significant decrease in cell division. The mechanism by which Shh interacts with the Wts signalling pathway remains to be determined. Since the level of phosphorylated Wts seems to be reduced in mouse medulloblastomas, Shh may suppress Wts kinase activity, leading to YAP activation. A possibility exists that the Wts pathway could be a target for medulloblastoma therapies aimed at eliminating the recurrence of these lesions.

Neural fate specification

In the neural progenitor cells, the Wts pathway appears to inhibit cell-cycle progression by suppressing cyclin genes including *cyclin D1*. However, unlike the inhibition of the Wts pathway or YAP overexpression, the constitutive expression of cyclin D1 only transiently increases the neural progenitor number, and cells forced to express cyclin D1 undergo a few extra rounds of mitosis but eventually exit the cell cycle (*84*). This suggests that the Wts pathway likely induces factors that promote neuronal differentiation. In fact, activation of the Wts pathway up-regulates the neurogenic bHLH factor *NeuroM* and leads to precocious neuronal differentiation whereas repressing the Wts pathway inhibits the expression of *NeuroM* (*74*). It is thus likely that Wts signalling promotes neuronal differentiation as well as cell-cycle exit, thereby leading to the maintenance of the progenitor population. Consistent with these *in vivo* data, YAP promotes pluripotency and inhibits differentiation in mouse embryonic stem (ES) cells, partly in a Wts-dependent manner (*85*). Chromatin immunoprecipitation and deep sequencing have further revealed that YAP controls genes that are known to be important in ES cells such as Polycomb group genes, *Nanog*, *Oct4 and Sox2*.

A previous genetic study in *Drosophila* photoreceptors has provided further evidence in support of Wts kinases functioning in cell fate decisions (*86*). Throughout the animal kingdom, colour vision is made possible by the presence of specific photosensitive proteins within optic neurons. Control of the production of rhodopsins in the correct spatial and temporal manner is vital for proper visual development. Although the molecular pathways that activate neuronal development are largely known, the genes that control the expression of specific rhodopsins, and hence colour vision, are poorly understood. Colour vision in *Drosophila* relies on the comparison between two colour-sensitive photoreceptors, R7 and R8, which contain different rhodopsins. A genetic screen has identified *wts* as the gene that is both necessary and sufficient for R8 fate specification. This cell fate control requires not only Wts but also Hippo and Salvador, suggesting a role for the Hippo–Wts tumour suppressor pathway in fate specification. This function of the Hippo–Wts pathway in fate specification appears also to be independent of cell growth control, since neither the cell number, size, nor shape is altered in $wts^{-/-}$ photoreceptors.

An important question that arises is how the Wts signalling governs the neural fate choice in post-mitotic neurons. Several lines of observations suggest that Notch signalling and Wnt signalling are potential downstream targets of Wts signalling-mediated cell fate specification (*87*, *88*). It has also been well established that the Notch and Wnt signals play critical roles in maintaining progenitor fates in the early neural tube (*89–91*). In the mouse intestine, both Notch and Wnt signals seem to be stimulated shortly after YAP activation (*41*). In addition, Wts activity likely influences differentiation of *Drosophila* optic neuroepithelial cells into neuroblasts by modulating Notch signalling (*92*, *93*). The future identification of direct targets of YAP/TEAD transcription factors in neural precursor cells will further our understanding of how Wts signalling controls neural cell fates.

Neurite outgrowth and branching

Ndr kinases regulate neurite outgrowth and branching during circuit formation in both the invertebrate and vertebrate nervous systems. In an earlier study, Stork *et al.* (*17*) screened for genes that are induced in the mouse amygdala during fear memory consolidation and isolated Ndr2 as a potential candidate. Since Ndr2 overexpression facilitates neurite outgrowth in rat PC12 cells and in mouse primary cultured neurons, they proposed that it might have a role in neurite remodelling during fear memory consolidation. In *Drosophila* and *C. elegans* sensory neurons, Ndr kinase is required for dendrite branching (*19*, *23*). In these cases, Ndr kinases likely promote neurite outgrowth/branching through Rho family GTPase-dependent cytoskeletal remodelling in neurites.

Specification of receptive fields in sensory neurons

During development, sensory neurons establish their specific dendritic fields in particular places. In some sensory neurons, dendrite–dendrite interactions have a profound influence on the size and shape of the dendritic fields and may play a particularly important role in determining the boundaries of receptive fields. For example, mammalian retinas contain more than 50 distinct functional classes of neurons, each of which completely but non-redundantly covers the retina surface, akin to tiles on a floor (*94–96*). This is most likely to ensure efficient and unambiguous representation of the view field. Sensory neurons in *Drosophila* and *C. elegans* also form tile arrangements (Fig. 3), suggesting that tiling may be a general mechanism by which dendritic fields are organized (*97–99*).

Several lines of evidence have demonstrated that like-repels-like dendritic interactions underlie tiling behaviour and shape the dendritic fields of sensory

neurons (*97*, *98*). First, at interfaces where dendritic arbors of two *Drosophila* sensory neurons converge, as well as within the arbors of a single neuron, terminal dendrites avoid contact with each other. Second, the production of supernumerary sensory neurons does not perturb this tiling behaviour. Rather, the extra neuron partitions the receptive field with neighbouring neurons. Lastly, laser ablation of the sensory neurons in *Drosophila* embryos causes the remaining neurons to expand their dendritic fields to occupy the territory of the ablated neuron.

Genetic screens in *Drosophila* and *C. elegans* sensory neurons have identified the Ndr family kinase (Trc and SAX-1 for *Drosophila* and *C. elegans*, respectively) as an essential component of dendritic tiling (*19*, *100*). In *trc* mutants, dendrites of class IV sensory neurons no longer show their characteristic turning or retracting response when they encounter dendrites of neighbouring class IV dendrites. This results in extensive overlap of their dendrites and therefore loss of tiling (Fig. 3). Furthermore, Trc kinase activity is essential for tiling control *in vivo*. Because Trc is present in the soma, axons and major dendritic branches of the sensory neurons, one likely scenario is that Trc functions in the dendrites to mediate the tiling response.

Once dendritic arbors are established by like-repels-like dendritic repulsion, arbors of class IV neurons maintain the tiling of the body wall throughout the larval stage. Laser ablation of larval class IV neurons after dendritic fields are established results in only limited invasion of the unoccupied space by terminal dendrites of neighbouring class IV neurons. Thus, additional mechanisms likely ensure that the complete and non-redundant coverage of the receptive fields by class IV dendrites is maintained. Genetic screens in class IV neurons have identified the tumour suppressor Wts kinase as an essential component for the dendrite maintenance. Loss of Wts function causes a progressive defect in the maintenance of dendritic tiling, resulting in large gaps in the receptive fields (*49*). Time-lapse studies suggest that the primary defect is in terminal dendrites, indicating that Wts likely functions to stabilize these dendrites. Genetic evidence suggests that the Polycomb repressor complex for transcriptional silencing functions downstream of the Wts kinase-signalling pathway (*101*). The question then arises as to how the establishment and maintenance of dendritic fields is coordinated. In *Drosophila* sensory neurons, the *Drosophila* MST kinase Hippo can directly phosphorylate and regulate both Trc, which functions in the establishment of dendritic tiling, and Wts, which functions in the maintenance of dendritic tiling (*49*). Furthermore, *hippo* mutants have defects in both the establishment and maintenance of dendritic fields. It is thus likely that the Hippo–NDR pathway plays a role in the coordination of dendrite dynamics and stabilization (Fig. 3). Since Hippo, Wts and Ndr kinases are evolutionarily conserved and are highly expressed in the vertebrate brain, the role of the corresponding signalling pathway may be conserved in mammals.

A similar progressive reduction in dendritic arborization of the cortical neurons is often observed in

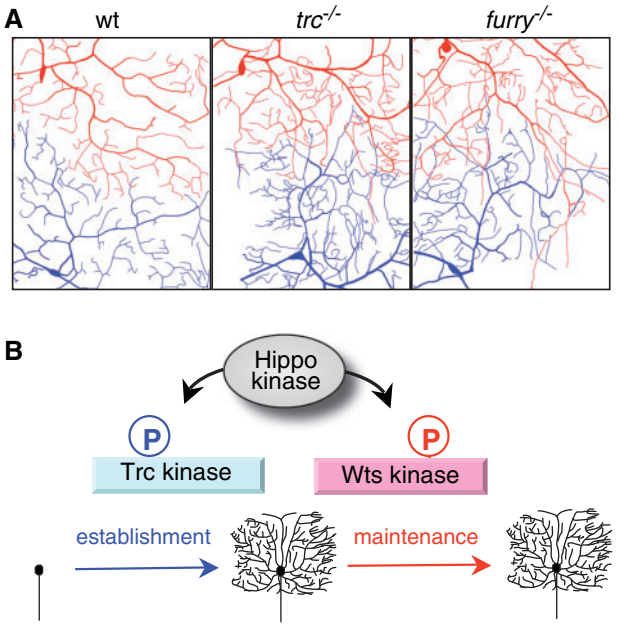

Fig. 3 (A) Dendritic tiling observed in *Drosophila* sensory neurons. Dendrites of adjacent homotypic neurons rarely send their branches into the dendritic fields of their neighbouring fields (wt). In *trc* and *furry* mutants, however, dendrites often invade neighbouring fields. Thus, the Trc kinase signalling mediates the like-repels-like response of dendritic branches of *Drosophila* sensory neurons. (B) The Hippo pathway coordinates establishment and maintenance of dendritic fields of *Drosophila* class IV sensory neurons. In the early developmental stage, Hippo phosphorylates Trc (the fly homologue of Ndr kinase) to establish the dendritic tiling of class IV sensory neurons. Once the dendritic fields are established, Hippo then phosphorylates Wts to maintain the dendritic fields. In *wts* mutants, dendrites initially tile the fields normally but progressively lose branches at later larval stages.

mental retardation diseases (*102*). For instance, Down's syndrome (DS) causes a progressive reduction in dendrite arborization of cortical neurons that begins postnatally. Quantitative analysis of dendrites in pyramidal neurons of the prefrontal cortex of 2.5-month-old infants has revealed no significant differences in dendrite development between normal and DS cases, whereas basilar dendrites of cortical pyramidal neurons are shorter than normal in DS subjects that are >4 months. Subsequent to this age, there is a steady decrease so that the dendritic branching and length in DS individuals >2 years are significantly reduced relative to controls, suggesting that DS affects the maintenance of dendritic arbors in postnatal neurons. It is thus possible that a dysfunction of the Hippo–Wts pathway may be associated with these diseases.

Neurodegeneration

A recent report has suggested that there is a neuroprotective role for the Wts signalling pathway in polyglutamine (PolyQ)-mediated neurodegeneration in *Drosophila* (*103*). In *Drosophila* mutants of the Wts pathway, photoreceptor cells show progressive degeneration in the adult stage. This neurodegeneration is not a secondary effect of overproliferation, because

mutations that induce growth in photoreceptor cells do not necessarily cause neurodegeneration. Histochemical and genetic data have further suggested that Wts signalling is likely to be required for autophagic flux in neurons, which promotes the clearance of polyQ proteins.

Perspectives

This review presents the most recent advances in our understanding of the role of NDR family kinases in neurons. The evidence indicates that the functions of these kinases go well beyond a simple control of cell proliferation and further studies are needed to properly elucidate these roles. Although many upstream regulators and downstream targets of these factors have been isolated in proliferating cells, it remains uncertain whether the NDR kinases function in the same context in neurons. In terms of its dendrite maintenance and neuroprotective roles, the Wts pathway probably utilizes downstream targets distinct from YAP. In addition, the Ndr and Wts pathways share upstream regulators including MSTs, MOBs and RASSFs, implying that a functional cross talk occurs between the two pathways. It will be important to determine when, where, and which target proteins are activated during particular phases of neuronal development and in different types of neurons. This information will also yield a better understanding of the molecular events that underlie some aspects of mental retardation and neurodegenerative disorders.

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Conflict of interest
None declared.

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