Published in final edited form as:

J Peripher Nerv Syst. 2021 March ; 26(1): 4–16. doi:10.1111/jns.12431.

The Hippo pathway: Horizons for innovative treatments of peripheral nerve diseases

M. Laura Feltri^{1,2}, Michael R. Weaver¹, Sophie Belin³, Yannick Poitelon³

¹Hunter James Kelly Research Institute, Department of Biochemistry, Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York

²Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York

³Department of Neuroscience and Experimental Therapeutics, Albany Medical College, Albany, New York

Abstract

Initially identified in *Drosophila*, the Hippo signaling pathway regulates how cells respond to their environment by controlling proliferation, migration and differentiation. Many recent studies have focused on characterizing Hippo pathway function and regulation in mammalian cells. Here, we present a brief overview of the major components of the Hippo pathway, as well as their regulation and function. We comprehensively review the studies that have contributed to our understanding of the Hippo pathway in the function of the peripheral nervous system and in peripheral nerve diseases. Finally, we discuss innovative approaches that aim to modulate Hippo pathway components in diseases of the peripheral nervous system.

Keywords

Hippo; nerve injury and regeneration; neurofibromatosis; peripheral neuropathy; schwann cell; YAP/TAZ

1 | COMPONENTS, REGULATORS, AND FUNCTION OF THE HIPPO PATHWAY

1.1 | Canonical Hippo pathway components

In mammalian cells, the core components of the Hippo pathway are Serine/Threonine kinases; mammalian sterile 20-like (MST1 and MST2) kinases, large tumor suppressor (LATS1 and LATS2) kinases, the adaptor proteins Salvador homolog 1 (SAV1) and Mps one binder kinase activator proteins (MOB1A and MOB1B) (Figure 1). These proteins were grouped into one signaling pathway - the Hippo pathway - named after observing that mutants of their *Drosophila* orthologues had a “hippopotamus” appearance, caused by the overgrowth of tissues due to hypercellularity.¹⁻⁵ The main function of the Hippo pathway

is to negatively regulate the activity of the transcription coactivator Yes-associated protein 1 (YAP, encoded by *YAP1*) and its paralog, transcriptional coactivator with PDZ-binding motif (TAZ, encoded by *WWTR1*) (Figure 1). YAP and TAZ have many similarities in their structures, functions and regulations, yet they are not completely redundant^(6,7; and reviewed in⁸). In this review, we use the term YAP/TAZ when it has been shown that YAP and TAZ share the mentioned regulations or functions. However, we use YAP or TAZ when data is available only for either YAP or TAZ. The central axis of the Hippo pathway is a phosphorylation cascade from MST1/MST2-LATS1/LATS2 to YAP/TAZ. Mechanistically, MST1/MST2 form heterotetramers with SAV1 to promote MST1/MST2 activation by trans-autophosphorylation^(9,10). Phosphorylated MST1/MST2-SAV1 heterotetramers then phosphorylate MOB1A/MOB1B and the hydrophobic motif of LATS1/LATS2 kinases.¹¹ Phosphorylation on MOB1A/MOB1B promotes their interaction with LATS1/LATS2 and the autophosphorylation of LATS1/LATS2 on their activation loop. Both phosphorylation of the hydrophobic LATS1/LATS2 motif by MST1/MST2 and autophosphorylation of LATS kinases activation loop are critical for their activation (reviewed in¹²). Activated LATS1/LATS2 directly phosphorylate YAP and TAZ at multiple sites. Phosphorylated YAP/TAZ bind to 14-3-3 proteins and are then sequestered in the cytoplasm, resulting in their inhibition. Additional phosphorylation of YAP/TAZ by casein kinase 1 leads to YAP/TAZ ubiquitination and degradation by the proteasome.^{13,14} In addition, YAP can also be degraded by autophagy.¹⁵ Because TAZ has a rapid turnover, with a half-life of less than 2 hours, it has been suggested that protein degradation, rather than cytoplasmic sequestration, may be the main route for TAZ inhibition.¹³ In contrast, YAP is a relatively stable protein, thus it may be inhibited primarily by cytoplasmic sequestration. Interestingly, it was also shown that YAP may have a cytoplasmic function, namely to promote cell migration by favoring activation of CDC42.^{16,17} To sum up, once activated, the Hippo pathway inhibits YAP/TAZ nuclear localization through their phosphorylation (reviewed in¹⁸).

On the other hand, when the Hippo pathway is inactive/off, YAP/TAZ are not phosphorylated and are instead translocated into the nucleus, where they promote gene transcription¹⁴ (Figure 1). YAP and TAZ are transcriptional co-regulators, but do not contain DNA-binding domains and TEAD family transcription factors are the primary binding partners of YAP/TAZ.¹⁹ TEADs mediate the main transcriptional output of the Hippo pathway in mammalian cells.²⁰ As detailed below, YAP/TAZ/TEAD-mediated gene expression regulates many cellular processes, spanning from proliferation to migration and to cell differentiation. In the absence of nuclear YAP/TAZ, TEAD transcription factors function as repressors by binding to VGLL4 (transcription cofactor vestigial-like protein 4), repressing target gene expression.^{21,22}

1.2 | Upstream signals regulating the canonical Hippo pathway

The central role of the Hippo pathway is to influence the localization and protein stability of the effectors YAP/TAZ. A multitude of extracellular, intracellular and non-biological stimuli can activate the Hippo pathway and regulate YAP/TAZ transcriptional activity. Here we briefly present the most understood mechanisms that regulate the Hippo pathway. For a comprehensive review detailing all signals and regulators of the Hippo pathway, see.²³

Cell polarity is essential for a wide range of cellular processes, such as synaptic communication between neurons or myelin formation (reviewed in²⁴⁻²⁶). The Crumbs complex is a key regulator of cell polarity and contains CRB proteins (CRBs), which are necessary to organize apicobasal polarity and the associated cytoplasmic proteins PALS1 and PATJ.²⁷ CRBs act as scaffold proteins for multiple components of the Hippo pathway such as LATs/YAP/TAZ, and play a role in YAP/TAZ cytoplasmic localization.²⁸⁻³⁰ Consistent with the key role of cell polarity proteins in promoting activation of the Hippo pathway, components of tight junctions or adherens junction complexes regulate Hippo signaling.³¹ For example, loss of E-cadherins, α - or β -Catenin can result in increased YAP transcriptional activity.^{32,33} CRB proteins also recruit to the plasma membrane other known Hippo regulators such as Angiomotins (AMOTs) or Neurofibromin 2 (NF2), also called Merlin or Schwannomin.^{29,34-37} Angiomotins were first reported to promote the activation of the Hippo pathway³⁸ through the sequestration of YAP/TAZ (see Section 1.3). However, a further report has also suggested that Angiomotins may serve as direct YAP activators by preventing its phosphorylation.³⁹ *NF2* is a tumor suppressor gene, whose loss of function causes Neurofibromatosis type 2, a disorder characterized by the development of tumors in the peripheral nervous system (PNS) (see Section 3.1).⁴⁰ NF2 is a positive regulator of the Hippo pathway through several mechanisms. NF2 binds and recruits LATS proteins to the cell membrane where they get activated by the MST1/MST2/SAV1 complex.⁴¹ In addition, NF2 also binds and inhibits the ubiquitination and degradation of LATS proteins.⁴²

Cells can sense stiffness of the extracellular matrix (ECM) through focal adhesion complexes that link the ECM to the actin cytoskeleton, and consequently change cell behavior such as migration and spreading (reviewed in⁴³). Physical forces such as stress or strain that physiologically impact cell density, stiffness of the extracellular environment and cell geometry are now known to regulate the localization and activation of YAP/TAZ through mechanisms that are both dependent or independent (see Section 1.3 below) of the Hippo pathway.⁴⁴⁻⁴⁶ In response to ECM stiffness or cell spreading, YAP/TAZ transcriptional activity is regulated, making them essential effectors of mechanical stimuli into the cell.⁴⁴ Integrin signaling has been revealed to inhibit LATS1/LATS2 activity and thus facilitates YAP nuclear translocation and transcriptional activation through the β 1-integrin-FAK-Src-PI3K-PDK1 pathway.⁴⁷ The Src-Rac1-PAK pathway also inhibits the phosphorylation of YAP by LATS1/LATS2 downstream of β 1-integrin, through phosphorylation of NF2.⁴⁷

In addition to local and mechanical signals (eg, cell polarity, cell-cell contact and ECM stiffness), paracrine or endocrine signals can also regulate the Hippo pathway. For example, ligands of G-protein-coupled receptors such as sphingosine 1-phosphate and lysophosphatidic acid have been shown to inhibit LATS1/LATS2 through G-proteins.⁴⁸ Similarly, epidermal growth factor signaling inactivates the Hippo pathway through the epidermal growth factor receptor (EGFR) and both the PI3K-PDK1 and the Ras-Raf-MAPK signaling pathways.^{49,50} Activation of the EGFR-RAS-MAPK pathway increases the phosphorylation of the Ajuba family proteins, promoting their interaction with LATS proteins, and thus preventing LATS-dependent YAP phosphorylation.^{51,52}

In addition to the MAPK signaling pathway, the Hippo pathway interacts with many other signaling pathways, such as the Wnt/ β -catenin and Notch pathways. Most studies have focused on the crosstalk between the Hippo signaling and the Wnt/ β -catenin signaling pathway due to their critical roles in tumorigenesis (see Section 3).⁵³ When Wnt signaling is activated, β -catenin induces the transcriptional up-regulation of YAP. Yet, (i) when the Hippo pathway is activated, YAP inhibits Wnt signaling by sequestering β -catenin in the cytoplasm; (ii) when the Hippo pathway is inactive, nuclear YAP up-regulates Wnt/ β -catenin signaling.^{54,55} In addition, the Notch receptor and ligand Jagged1 are direct target genes of YAP, and the Notch intracellular domain enhances the transcriptional activity of YAP/TAZ.^{56,57}

Finally, the Hippo pathway is also regulated by dephosphorylation events, such as by striatin-interacting phosphatase and kinase (STRIPAK) complexes. The phosphatase component of STRIPAK complexes is protein phosphatase 2A (PP2A). PP2A interacts with and dephosphorylates MST1/MST2 kinases and the functionally related kinase MAP4K4, which leads to the dephosphorylation of YAP/TAZ.^{10,58-62} The interaction of STRIPAK complexes with MAP4K4, and possibly with MST1/MST2, is regulated in part by RhoA activity-dependent NF2 association with STRIPAK components.⁵⁸

1.3 | Hippo pathway-independent regulation of YAP/TAZ

While the cytoplasmic retention of phosphorylated YAP/TAZ is a consistent outcome of Hippo pathway activation, in several studies the cytoplasmic-nuclear shuttling of YAP was shown to be independent from the Hippo pathway.^{44,63,64} Thus, it is currently proposed that in addition to canonical Hippo signaling (i), kinases other than LATS1/LATS2 may also regulate YAP/TAZ transcriptional activity (reviewed in⁶⁵), and (ii) YAP/TAZ cytoplasmic-nuclear shuttling may also be regulated independently of their phosphorylation.^{66,67}

Among Hippo- independent YAP/TAZ regulation, the role of several kinases or binding proteins have been elucidated. This is the case for several receptor tyrosine kinases (GFRE, RET, MERTK, PYK2), phosphofructokinase (PFK1), AMP-activated protein kinase (AMPK), the pre-mRNA splicing factor 4 kinase (PRP4K) and Nemo-like kinase (NLK), which have been shown to directly phosphorylate a subset of LATS sites on YAP/TAZ and either phosphorylate YAP/TAZ or promote their exclusion from the nucleus.⁶⁸⁻⁷¹ For example, AMPK is a key cellular metabolic sensor that is activated by a high AMP to ATP ratio. PFK1 is an enzyme regulating the first step of glycolysis. Their regulation of YAP/TAZ indicates that YAP/TAZ can be regulated by metabolic pathways.^{72,73} In addition to phosphorylation, YAP/TAZ are also regulated by a variety of molecules that can sequester YAP/TAZ. Cell-cycle kinase (CDK1), α -catenin, Claudin18 and protein tyrosine phosphatase non-receptor type 14 (PTPN14) directly bind to YAP to sequester it in the cytoplasm or at the plasma membrane.^{23,37,74,75}

Finally, several recent studies have shown that mechanical cues can induce regulation of YAP/TAZ also independently of their phosphorylation by the Hippo pathway.^{44,45,76,77} Physical forces lead to the reorganization of the actin cytoskeleton, and to activation of Rho GTPase.^{76,78} Knockdown of actin capping protein (CAPZB) causes an increase in F-actin, and an increase in nuclear YAP/TAZ coupled with an increase in expression of

YAP/TAZ target genes.⁴⁴ Reverse regulations also exist, as YAP promotes the expression of the Rho guanine exchange factor ARHGEF17 that activates the RhoA-actomyosin axis. Thus, YAP and RhoA signals are likely to be mutually regulated by feedback loops.^{79,80} Spectrin, a cytoskeletal protein associated to actin filaments, also plays an important role in the activation of YAP.⁸¹⁻⁸³ While the mechanical regulation of YAP/TAZ independently of the Hippo pathway was controversial for some time, recent studies have started to clarify its mechanisms. Actomyosin fibers connecting focal adhesions to the LINC (Linker of the Nucleoskeleton and Cytoskeleton) complex of the nuclear envelope, may regulate YAP import in the nucleus by opening nuclear pores.^{66,67} Interestingly, in this model it was also suggested that NF2 forms a complex with YAP/TAZ to mediate their nuclear export.⁸⁴

2 | THE HIPPO SIGNALING PATHWAY IN PERIPHERAL NERVE DEVELOPMENT

YAP, TAZ and TEADs regulates gene expression that leads cells to respond to their environment in an exquisitely cell and context-specific manner. The PNS is formed from the soma and axons of sensory and autonomic neurons, and from the axons of motor neurons which exit the central nervous system (CNS) at motor exit points. These axons are ensheathed by glial cells and surrounded by blood vessels, endoneurial fibroblasts, perineurial and epineurial cells. Many of these cell types derive from the neural crest. Here we will briefly review the developmental steps from the neural crest to PNS components in which the Hippo pathway is known to be involved (Figure 2).

2.1 | Neural crest cells

Neural crest cells originate after closure of the neural tube and expand and migrate extensively in the whole organism. Depending on the anterior/posterior region from which they delaminate, neural crest cells are classified into cranial, cardiac, vagal, trunk or sacral. The region of origin and path of migration greatly influence the fate of neural crest cells, which includes PNS components, melanocytes, chromaffin organs, smooth muscle cells, cardiac cells, facial bone and cartilage (reviewed in⁸⁵). YAP promotes human neural crest cell fate and migration.⁸⁶ In addition, the Hippo pathway regulates migration and differentiation of neural crest cells into smooth muscle cells, craniofacial and dental structures and melanocytes.⁸⁷⁻⁹¹ Most of the neural crest-derived PNS cells, including sensory and autonomic neurons, all Schwann cells, satellite cells and endoneurial fibroblasts, originate from trunk neural crest cells. The Hippo pathway is active in trunk neural crest cells.^{92,93}

To our knowledge, there are no published reports on the Hippo pathway in terminal Schwann cells at the neuromuscular junction. Thus, only the studied roles of Hippo pathway components in Schwann cell, sensory neuron precursors and fibroblasts are reviewed below.

2.2 | Dorsal root ganglia neurons and satellite cells

After delamination from the neural tube, some neural crest cells migrate ventrally between the neural tube and the somites, where they coalesce to form dorsal root ganglia (DRG) neurons and glia.^{94,95} DRG neurons send axons centrally to form spinal roots and synapse

with sensory neurons in the spinal cord, and peripherally to sensory terminal. Satellite glia tightly surround the soma of DRG neurons, probably providing metabolic and electrical support, similar to astrocytes in the CNS (reviewed in⁹⁶). DRG neurons and satellite glia derive from a common neural crest precursor, in separate waves spanning embryonic day (E) E11.5 to E13.5 in the mouse, that give rise to different subsets of DRG neurons and to satellite cells.⁹⁷⁻⁹⁹ Elegant work involving expression in vivo and deletion or hyperactivation of members of the Hippo pathway revealed that YAP is expressed in immature DRG neurons, glia precursors, and satellite cells, but not in mature DRG neurons. Inhibition of YAP, mediated by NF2 positive regulation of the Hippo pathway (see Section 1.2), prevents over-expansion of the precursor cell population and increases the number of glial cells while deleting NF2 causes neuron depletion.⁹³ This suggests that YAP may favor glia differentiation. Inhibition of the differentiation of various neuronal types by YAP transcriptional activity is also suggested by several studies showing that softer matrices and tissues, which inhibit YAP dephosphorylation, favor neuronal differentiation and axonal growth.¹⁰⁰

2.3 | Schwann cells

Trunk neural crest precursors that migrate ventrally give rise to DRG neurons and Schwann cells.¹⁰¹ Schwann cells migrate to the periphery along neuronal projections, while progressively changing their spatial association with axons and differentiating into Schwann cells precursors, immature Schwann cells, promyelinating Schwann cells and finally into mature myelinating Schwann cells or Remak (non-myelin forming) Schwann cells (Figure 2). It is important to mention that some Schwann cells, especially those myelinating dorsal and ventral nerve roots, derive from a different population of neural crest derivatives, boundary cap cells, that transiently localize and preserve the boundary between the CNS and PNS at sensory entry points and motor exit points,^{102,103} and reviewed in.¹⁰⁴ Boundary cap cells are in part molecularly distinct from Schwann cells, and share many characteristics with a similar population of cells, motor exit point cells, characterized in the zebrafish¹⁰⁵ and reviewed in.¹⁰⁶

Schwann cells precursors (E12.5-E15.5 in the mouse) surround large bundles of mixed caliber axons.¹⁰⁷ Immature Schwann cells (E16.5-early postnatal) start penetrating nerve bundles and recognize axons destined to be myelinated (usually larger than 1 μ m), based on the amount of Neuregulin 1 type III on the surface of axons.^{108,109} By progressive proliferation to match the number of axons and segregation, immature Schwann cells reach a 1:1 relationship with larger axons start to myelinate. Collectively, this process is called radial sorting of axons by Schwann cells, and spans from perinatal times to post-natal day (P) 10 in the mouse. Finally, when all axons larger than 1 μ m have been isolated, small axons remain ensheathed in smaller bundles that differentiate into Remak bundles, around P15 in the mouse, surrounded by non-myelin forming Schwann cells (Figure 2). Radial sorting is highly dependent on signals from basal lamina components laminin 211, 411 and collagen XV,¹¹⁰⁻¹¹² which are transmitted through the laminin receptors integrins $\alpha 6\beta 1$ and $\alpha 7\beta 1$, dystroglycan and GPR126.¹¹³⁻¹¹⁵ It has been shown that one way by which laminin signals promote radial sorting is by regulating the cytoskeleton through FAK, ILK, CDC42, Pinch, and RAC1, allowing the formation of lamellipodia-like processes from Schwann cells

that interact with, recognize and sort axons.¹¹⁶⁻¹²⁰ Other mechanisms involve regulation of cAMP levels and PKA cross-talk with the Neuregulin pathway.^{121,122} Detailed reviews of Schwann cell development can be found elsewhere.¹²³⁻¹²⁶

Recent work from several laboratories has highlighted how inhibition of the Hippo pathway, with consequent activation of YAP/TAZ, is essential for multiple steps of normal Schwann cell development, including radial sorting, proliferation and subsequent myelination.^{92,127,128} YAP/TAZ are expressed throughout the Schwann cell lineage, but TAZ expression is higher between P3 and P15, the period corresponding to active radial sorting and myelination.^{127,128} Nuclear localization of YAP/TAZ, denoting that they are active, is detected in vivo in mice at all times examined, from E16.5 to adulthood (P60), suggesting that YAP/TAZ may be required throughout the life of a Schwann cell.^{28,92,127,128} Deletion of both alleles of YAP/TAZ specifically in Schwann cells using Schwann-cell specific Cre (*Mpz-Cre*)^{92,128} or *Dhh-Cre*,¹²⁷ which recombine Schwann cell precursors at E13.5 and E12.5, respectively, profoundly impairs radial sorting of axons, preventing immature Schwann cells from reaching the promyelinating stage (1:1 relationship with axons) and therefore preventing myelination. Interestingly, homozygous deletion of only YAP causes virtually no radial sorting problems, while deletion of TAZ causes moderate radial sorting arrest, suggesting that TAZ is more important for radial sorting than YAP. However, YAP/TAZ are functionally redundant, as deletion of one of two YAP alleles in the context of TAZ deletion aggravates the radial sorting phenotype.^{92,127,128}

As for other cell types and as introduced in part 1 in this review, the inhibition of the Hippo pathway in Schwann cells to promote radial sorting of axons is probably caused by multiple mechanical and chemical stimuli. Peripheral nerves traverse every tissue of the body and thus must possess mechanical resistance and elasticity. These are provided by abundant extracellular matrix, including collagen fibers, that renders nerves among the stiffer (after bones) and most elastic tissues in the body.¹²⁹ Throughout all their developmental steps, Schwann cells are subjected to mechanical stimulation due to various forces, including axonal stretching and elongation and basal lamina polymerization and stiffening. It thus likely that some of these mechanical stimuli promote Schwann cell development through activation of YAP/TAZ. Like other cells, Schwann cells are mechanosensitive^{128,130} and activate YAP/TAZ in response to increased matrix stiffness^{128,130} and axonal stretching during nerve elongation,²⁸ but also in response to laminin 111 and 211. Laminins likely inhibit the Hippo pathway and activate YAP/TAZ through mechanoreceptors, such as integrin $\alpha 6 \beta 1$, which in turn regulate the actin cytoskeleton via RAC1 activation.^{119,128,131,132} Downstream of YAP/TAZ, radial sorting is promoted via the transcriptional activation of several genes required for this process, including genes encoding for regulators of proliferation (G α proteins, ErbB2/3 receptors), SOX10, ZEB2, laminin $\gamma 1$ and the laminin receptors integrin $\alpha 6 \beta 1$ and dystroglycan. In several of these cases, TAZ and TEAD1 bind directly to enhancers of these genes.^{127,133} It is possible that other Laminin receptors such as GPR126/cAMP are also involved in regulating the Hippo pathway in Schwann cells.

YAP/TAZ also have a role in myelination, after radial sorting is complete, however some findings suggest that the regulation of myelination by the Hippo pathway and

YAP/TAZ is complex and subject to multiple levels of cross-regulation. Studies in mice clearly indicate that YAP/TAZ promote myelination in concert with SOX10 by targeting enhancers of the master myelin-promoting transcription factor EGR2/KROX20 and of genes coding for myelin proteins and lipid synthesis regulators.^{28,92,127,128,133,134,200} However, the absence of NF2 causes transient hypomyelination, but whether this is due to the lack of Hippo-mediated repression of YAP/TAZ is unknown.¹³⁵ In addition, deletion of TEAD4 downstream of HDAC3 causes remarkable hypermyelination in mice, increases PI3K and ERK signaling and promotes upregulation of myelin-related genes,¹³⁶ suggesting that TEAD1 and TEAD4 may have opposite functions in myelination. This, and the fact that TAZ seems more important during development than YAP,¹²⁸ suggest that specific components of the Hippo pathway may have specific effects. Interestingly, YAP and TAZ act differently in the nucleus, as only TAZ forms liquid-liquid interphase biomolecular condensates that are associated with super enhancers, while YAP does not, indicating potentially different nuclear functions (reviewed in¹³⁷). It is also possible that YAP or TAZ interact with TEAD4 to inhibit precocious myelination during radial sorting, in a way similar to the inhibitory effect of laminin on Neuregulin 1 type III signaling, to ensure the timely and correct amount of myelin formation.¹²¹ More transcriptomic and epigenetic experiments on single gene mutants or after activation of single components will be required to dissect these possibilities. Furthermore, a better understanding of the intersection between specific components of the Hippo pathway and other promyelinating pathways such as those activated by Neuregulins is also of interest. As mentioned, NF2 is a particularly important tumor suppressor in Schwann cells, and it is a known activator of the Hippo pathway at different levels. NF2 also cross-talks with integrins and antagonizes RAC1.^{131,138} However, how NF2 and RAC1, and possibly NF2 and CRB3, regulate each other is only partially understood. Finally, CRB3-FRMD6/willin, upstream regulators of the Hippo pathway, localize at the nodes of Ranvier and regulate the elongation of myelin segments (internodal length) during development through YAP.²⁸

2.4 | Endoneurial fibroblasts

Endoneurial fibroblasts are neural crest derived, and play crucial roles during nerve regeneration, by communicating with Schwann cells via EphB signaling to coordinate segregation and collective migration of both cell types.¹³⁹ Interestingly, FRMD6/willin, an upstream activator of the Hippo pathway, is highly expressed in endoneurial fibroblasts, where it appears to inhibit YAP/TAZ activation to promote collective migration necessary for regeneration.¹⁴⁰ This is remarkably similar to the role of NF2 in Schwann cells after injury.¹³⁵ Thus, is possible that the specificity of activation of the Hippo pathway in Schwann cells and fibroblasts after injury may be achieved using cell-specific receptors.

3 | THE HIPPO PATHWAY IN PNS DISEASES

As the Hippo pathway controls so many PNS cells and their function during nerve development, we would expect that components of this pathway contribute also to peripheral nerve pathology. So far, the most prominent roles for the Hippo pathway are reported in tumorigenesis, nerve injury and repair and in neuropathic pain, which will be reviewed

below (Figure 2). In contrast, the role of the Hippo pathway in acquired or inherited neuropathies are largely unexplored, so we will only speculate briefly about this topic.

3.1 | Tumorigenesis

Early indications of a link between a defective Hippo pathway and tumorigenesis were suggested by the overgrowth phenotypes of *Drosophila* Hippo pathway mutants, observations of elevated tumorigenesis in LATS kinases mutant mice, and an association between the NF2 tumor suppressor and Hippo signaling.¹⁴¹ Subsequent observations have shown that elevated nuclear YAP/TAZ levels were associated with a wide variety of tumors, including in the PNS.^{134,142}

Tumors of peripheral nerve, schwannomas and neurofibromas, are benign in the vast majority of clinically symptomatic cases (reviewed in ¹⁴³), with lesser percentages made up of other benign tumors and of malignant tumors such as malignant peripheral nerve sheath tumors (MPNSTs), lymphoma and metastases.¹⁴⁴ MPNSTs are frequent in the context of neurofibromatosis. For patients with neurofibromatosis type 2 (NF-2), the clinical presentation is characterized by the development of multiple schwannomas and meningiomas.^{42,145,146} Because the *NF2* gene was shown to function upstream of the Hippo pathway, there are numerous evidences that strongly suggest that YAP/TAZ are involved in schwannoma tumorigenesis and NF-2 pathophysiology.^{135,147-150} A very recent study confirmed this hypothesis by demonstrating that Hippo signaling and YAP/TAZ are required for schwannoma formation.¹⁵¹ For patients with neurofibromatosis type 1 (NF-1), the incidence of malignancy is significantly greater. About 10% of patients with NF-1 will develop a MPNST during their lifetimes, and nearly 50% of patients with MPNST have NF-1.¹⁵² Several studies have demonstrated evidence for alterations of the Hippo pathway in MPNSTs. Analysis from MPNST samples shows an increase in the copy number of Hippo pathway effectors (ie, *TAZ*, *CTGF* and *BIRC5*) and loss of gene loci of YAP/TAZ activity inhibitors (ie, *LATS2* and *AMOTL2*).¹³⁴

Transcriptome sequencing of human MPNST samples also revealed elevated YAP-activated gene expression in MPNST when compared to normal nerves and NF1-associated benign tumors.^{153,154} Furthermore, the YAP signature is present in MPNST samples regardless of their NF-1 genetic status, suggesting that activation of the YAP/TAZ is common to both genetic and sporadic MPNSTs. Importantly, ablation of both LATS kinases in Schwann cells in genetic mouse models abolished the regulation of YAP and TAZ, which remained active in the nucleus, causing the development of aggressive nerve-associated tumors, similar to human MPNSTs in their pathological and invasive characteristics.¹³⁴ Together, these studies validate the role of the Hippo pathway in MPNST tumorigenesis, likely in combination with other oncogenic pathways, such as EGFR-RAS, WNT, GPCR or PI3K signaling, and with changes in the tumor microenvironment, such as inflammation and increased ECM stiffness.

3.2 | Traumatic injury

YAP/TAZ proteins play key roles in wound repair and regeneration. This is due to their roles in promoting cell differentiation and organ growth, and to their activation by loss of tissue integrity, as it happens in damaged tissues. Indeed, activation of YAP/TAZ proteins

occurs both in response to changes in cell-cell contact, cell density, and cell stretching that can accompany wounding. Following traumatic injury, the peripheral nerve starts a series of events distal to the site of the injury (Wallerian degeneration reviewed in¹⁵⁵), which includes the degeneration of axons, infiltration of macrophages, and reprogramming of Schwann cells to transdifferentiate and assume a repair Schwann cell phenotype, which facilitates axonal regeneration through formation of tubular guidance structures (Bands of Büngner) and functional repair of the peripheral nerve.¹⁵⁶ Recent data indicated that both YAP and TAZ regulate peripheral nerve regeneration, but in different contexts. The Hippo pathway activator NF2 is crucial for the generation of repair Schwann cells, as nerves deficient for NF2 display a severe impairment of Bungers band formation, axon regrowth and remyelination. Consistently, *NF2*-null nerves present with activation of YAP following nerve injury in Schwann cells.¹³⁵ Despite the fact that YAP in Schwann cell itself is not necessary for axonal regrowth or remyelination following injury, further removal of YAP in of *NF2*-Schwann cells null crushed nerves leads to normal axonal regrowth and functional recovery after injury.¹³⁵ Thus, Schwann cell YAP may have a role in axonal regrowth following traumatic nerve injury. Ablation of TAZ alone does not affect axonal regrowth, rather, it delays remyelination after nerve injury. This phenotype is amplified in the injured nerve of animals lacking both YAP/TAZ, which present a failure in remyelination.^{157,158} This failure to remyelinate is due to YAP/TAZ being necessary in repair Schwann cells for their redifferentiation into myelinating Schwann cells.¹⁵⁸ Thus, YAP/TAZ are both regulating developmental and post-traumatic myelin formation, yet while absence of TAZ cannot be compensated by YAP, YAP absence seems to be compensated by the expression of TAZ in Schwann cells.

3.3 | Neuropathic pain

Neuropathic pain may be due to genetic mutations in ion channels or may be a consequence of lesions or inflammation of the nervous system, and accounts for about 10% of chronic pain cases.¹⁵⁹ The transmission of nociception in unmyelinated C fibers and small thinly myelinated A δ fibers depends on mechanosensitive ion channels at sensory terminals such as Piezo ion channels, transient receptor potential (TRP) channels and sodium channels (eg, Nav1.7-1.9) (reviewed in¹⁶⁰). While a conventional role for YAP/TAZ directly at the synaptic terminal of neurons is unlikely due to the distance between the neuronal cell bodies and synaptic terminals, a functional role for the Hippo pathway was suggested by upregulation of FRMD6 in sensory neurons cell bodies in the dorsal root ganglion after injury,¹⁶¹ and further in the spinal dorsal horn of the CNS.¹⁶² Interestingly, peripheral glia associated with these afferent fiber's terminals may also act as sensors. Activation of skin-resident glial cells at the sensory terminals are both necessary and sufficient for mechanical pain sensation.¹⁶³ These newly identified nociceptive glial cells are sensitive to mechanical stimulation, a known regulator of YAP/TAZ.¹⁶³ In addition, Piezo channels can modulate activation of YAP/TAZ.¹⁶⁴ These studies suggest new mechanisms to target the Hippo pathway and specific glial cells involved in pain perception (see Section 4.2).

3.4 | Speculation on inherited neuropathies

Peripheral neuropathies are common, affecting up to 8% of people over 55 years of age (reviewed in¹⁶⁵). Neuropathies can be acquired, such as diabetic neuropathies,

or inherited, such as Charcot-Marie-Tooth. Despite different pathogenic mechanisms, neuropathies eventually converge on a common phenotype characterized by loss of nerve fibers and increased ECM. It is likely that these changes dysregulate the mechanosensitive Hippo pathway, potentially increasing Schwann cell proliferation and impeding recovery. Even though studies on the potential role of the Hippo pathway in acquired and inherited peripheral neuropathies are currently lacking, one could make the argument that dysregulation of the Hippo pathway is a potential contributor to inherited neuropathies due to altered expression of Peripheral Myelin Protein 22 (PMP22) in Charcot Marie Tooth 1A (CMT1A) and Hereditary Neuropathy with Liability to Pressure Palsy (HNPP).¹⁶⁶⁻¹⁷⁰ As the disease name suggests, in HNPP innocuous mechanical pressure causes conduction block and demyelination (reviewed in¹⁷¹). While normal myelinated fibers can withstand remarkable compression without loss of integrity and quickly reverse to normal shape, PMP22 null nerves have less elasticity.¹²⁹ The possible multiple roles of PMP22 in myelinated fiber elasticity and resistance, at cellular junctions and in the cell-cycle make it an ideal candidate to be intimately linked to the Hippo pathway, which is also regulated by mechanical signals and junctional proteins and tied to proliferation. Interestingly, the YAP/TAZ co-transcription factor TEAD1 directly regulates PMP22 gene expression.¹³³ Thus, a putative dysregulation of the Hippo pathway may further contribute to dysregulated PMP22 expression caused by genetic copy number variation of PMP22.

4 | INNOVATIVE THERAPIES BASED ON THE HIPPO PATHWAY

4.1 | Drug based therapies

Targeting of the Hippo pathway with drug-based therapies is of great significance due to its roles in cancer biology and tissue regeneration. Interestingly, these fields usually have opposite goals, with cancer research pursuing drugs to reduce YAP/TAZ-TEAD transcriptional activity and regenerative medicine pursuing drugs to increase YAP/TAZ-TEAD transcriptional activity. To date, most studies have investigated small molecules or peptides capable of activating the Hippo pathway for cancer treatment and these drugs have been extensively reviewed.¹⁷²⁻¹⁷⁴ Due to the considerable amount and variety of these small molecules and peptides, Pobbati et al. have classified Hippo-modifying drugs into three groups (see Figure 3). Group I drugs target the upstream regulators of YAP/TAZ, enhancing LATS1/LATS2-dependent phosphorylation of YAP/TAZ, thus reducing YAP/TAZ transcriptional activity (see Table 1). This group includes many compounds that are already U.S. Food and Drug Administration (FDA)-approved (eg, pazopanib, dasatinib, dobutamine, losartan) and therefore hold potential for drug repurposing. However, these compounds are not specific to the Hippo pathway and dysregulate broad signaling downstream of cell surface receptors and intracellular kinases. Group II drugs directly modify the YAP/TAZ-TEAD interaction, by targeting TEAD or YAP (see Table 1). Thus, these drugs are more directed towards the Hippo/YAP/TAZ pathway. Nevertheless, verteporfin, a commonly used disruptor of the YAP/TAZ-TEAD interaction, also does not solely target YAP and may target other proteins.^{184,185} Finally, group III drugs (eg, celecoxib) target the genes regulated by YAP/TAZ-TEAD (see Figure 3). Using these drugs can be challenging as they target only one of the many proteins regulated by YAP/TAZ. Combinatory use of group I, II and III drugs could also be considered.

The therapeutic potential for Hippo pathway modulation in the context of PNS diseases is of interest for neuropathies such as HNPP, CMT1A, and MPNSTs (see Section 3). Upstream Hippo pathway activation (Group I drugs) or direct inhibition of the YAP/TAZ-TEAD interaction (Group II drugs) may alleviate the oncogenic effects of high YAP transcriptional activity in MPNSTs. In addition, celecoxib, a cyclooxygenase-2 (COX-2) inhibitor that has been FDA approved since 1998, is a particularly exciting example of a widely available Group III Hippo-modifying drug with potential to treat Schwann cell-derived tumors. Treatment in vitro with celecoxib has been shown to reduce cell proliferation of *NF2*-null schwannoma tumor cells in a dose-dependent manner.¹⁴⁸ Moreover, when these cells were implanted into mouse sciatic nerves as an in vivo schwannoma tumor model, tumorigenesis was markedly reduced following 10 days of once daily oral celecoxib administration. Further studies will be needed to clarify the therapeutic potential and side effect profile of the use of Hippo-modifying drugs in PNS diseases.

4.2 | Mechanical based therapies

Peripheral nerves are often damaged by compression, stretch, and avulsion. There are many proposed methods of speeding nerve regeneration, including physical methods, such as electrical stimulation,¹⁸⁶ magnetic field stimulation,¹⁸⁷ laser stimulation¹⁸⁸ and ultrasound therapy.¹⁸⁹ It is possible that the Hippo pathway and YAP/TAZ are stimulated by the application of physical stimuli. First, in vitro studies have shown that application of low-intensity ultrasound can regulate the Hippo pathway and YAP/TAZ.¹⁹⁰⁻¹⁹² Second, in vitro studies in Schwann cells have shown that ultrasound regulates signaling pathways upstream of the Hippo pathway.^{193,194} Finally, extensive studies provide evidence that low-intensity ultrasound activates and promotes Schwann cell proliferation, a major outcome of the Hippo pathway (reviewed in¹⁹⁵).

Similarly, application of an electromagnetic field to cultured Schwann cells promotes their proliferation and migration, at least in part through the Hippo pathway. Colciago et al., have shown that the expression of genes known to be upstream or downstream mediators of the Hippo pathway was altered in Schwann cells, leading to dysregulation of YAP.¹⁹⁶ While further studies are needed to support this hypothesis, the physical control of the Hippo pathway and YAP/TAZ opens potential new avenues for the treatment of peripheral neuropathies. However, because of the implication of the Hippo pathway in tumorigenesis, ectopic activation of the Hippo pathway and YAP/TAZ in physiological and pathological contexts should be carefully controlled.^{197,198}

5 | CONCLUSIONS AND OPEN QUESTIONS

The Hippo pathway and YAP/TAZ rapidly came to the forefront of PNS biology and pathology only in the last few years. In light of the multitude of stimuli and signals regulating the Hippo pathway, and of the major role that it plays in many developmental and pathological systems, one of the challenges now faced by the scientific community is to understand how the signals that converge on the Hippo pathway, YAP and TAZ, regulate each other in feed-back loops (reviewed in¹⁹⁹), how integration with other major cellular signaling pathways occurs, the extent of cell-specificity and context-specificity and the

different and overlapping roles of single components of the Hippo pathway. This specific understanding will allow more targeted and specific modulation of YAP and TAZ activity in peripheral nerve disease.

ACKNOWLEDGEMENTS

We apologize for the work that we did not have the space to discuss. We thank all members of the Feltri, Wrabetz, Poitelon & Belin laboratories for their work and discussion. Work on the Hippo pathway is funded by grant number R01NS45630 in the Feltri laboratory and R01NS110627 in the Poitelon laboratory.

Funding information

National Institute of Neurological Disorders and Stroke, Grant/Award Numbers: R01NS110627, R01NS45630

REFERENCES

1. Harvey KF, Pfleger CM, Hariharan IK. The *Drosophila* Mst ortholog, hippo, restricts growth and cell proliferation and promotes apoptosis. *Cell*. 2003;114:457–467. [PubMed: 12941274]
2. Jia J, Zhang W, Wang B, Trinko R, Jiang J. The *Drosophila* Ste20 family kinase dMST functions as a tumor suppressor by restricting cell proliferation and promoting apoptosis. *Genes Dev*. 2003;17:2514–2519. [PubMed: 14561774]
3. Pantalacci S, Tapon N, Leopold P. The Salvador partner hippo promotes apoptosis and cell-cycle exit in *Drosophila*. *Nat Cell Biol*. 2003;5:921–927. [PubMed: 14502295]
4. Udan RS, Kango-Singh M, Nolo R, Tao C, Halder G. Hippo promotes proliferation arrest and apoptosis in the Salvador/warts pathway. *Nat Cell Biol*. 2003;5:914–920. [PubMed: 14502294]
5. Wu S, Huang J, Dong J, Pan D. Hippo encodes a Ste-20 family protein kinase that restricts cell proliferation and promotes apoptosis in conjunction with Salvador and warts. *Cell*. 2003;114:445–456. [PubMed: 12941273]
6. Gaffney CJ, Oka T, Mazack V, et al. Identification, basic characterization and evolutionary analysis of differentially spliced mRNA isoforms of human YAP1 gene. *Gene*. 2012;509:215–222. [PubMed: 22939869]
7. Kanai F, Marignani PA, Sarbassova D, et al. TAZ: a novel transcriptional co-activator regulated by interactions with 14-3-3 and PDZ domain proteins. *EMBO J*. 2000;19:6778–6791. [PubMed: 11118213]
8. Reggiani F, Gobbi G, Ciarrocchi A, Sancisi V. YAP and TAZ Are Not Identical Twins. *Trends in Biochemical Sciences*. 2021;46(2):154–168. 10.1016/j.tibs.2020.08.012. [PubMed: 32981815]
9. Praskova M, Khoklatchev A, Ortiz-Vega S, Avruch J. Regulation of the MST1 kinase by autophosphorylation, by the growth inhibitory proteins, RASSF1 and NORE1, and by Ras. *Biochemical Journal*. 2004;381(2):453–462. 10.1042/bj20040025.
10. Bae SJ, Ni L, Osinski A, Tomchick DR, Brautigam CA, Luo X. SAV1 promotes hippo kinase activation through antagonizing the PP2A phosphatase STRIPAK. *Elife*. 2017;6.
11. Chan EH, Nousiainen M, Chalamalasetty RB, Schafer A, Nigg EA, Sillje HH. The Ste20-like kinase Mst2 activates the human large tumor suppressor kinase Lats1. *Oncogene*. 2005;24:2076–2086. [PubMed: 15688006]
12. Furth N, Aylon Y. The LATS1 and LATS2 tumor suppressors: beyond the hippo pathway. *Cell Death Differ*. 2017;24:1488–1501. [PubMed: 28644436]
13. Liu CY, Zha ZY, Zhou X, et al. The hippo tumor pathway promotes TAZ degradation by phosphorylating a phosphodegron and recruiting the SCF{beta}-TrCP E3 ligase. *J Biol Chem*. 2010;285:37159–37169. [PubMed: 20858893]
14. Zhao B, Li L, Tumaneng K, Wang CY, Guan KL. A coordinated phosphorylation by Lats and CK1 regulates YAP stability through SCF(beta-TRCP). *Genes Dev*. 2010;24:72–85. [PubMed: 20048001]

15. Lee YA, Noon LA, Akat KM, et al. Autophagy is a gatekeeper of hepatic differentiation and carcinogenesis by controlling the degradation of yap. *Nat Commun.* 2018;9:4962. [PubMed: 30470740]
16. Althoff MJ, Nayak RC, Hegde S, et al. Yap1-scribble polarization is required for hematopoietic stem cell division and fate. *Blood.* 2020;136:1824–1836. [PubMed: 32483624]
17. Sakabe M, Fan J, Odaka Y, et al. YAP/TAZ-CDC42 signaling regulates vascular tip cell migration. *Proc Natl Acad Sci U S A.* 2017;114:10918–10923. [PubMed: 28973878]
18. Meng Z, Moroishi T, Guan KL. Mechanisms of hippo pathway regulation. *Genes Dev.* 2016;30:1–17. [PubMed: 26728553]
19. Vassilev A, Kaneko KJ, Shu H, Zhao Y, DePamphilis ML. TEAD/TEF transcription factors utilize the activation domain of YAP65, a Src/-yes-associated protein localized in the cytoplasm. *Genes Dev.* 2001;15:1229–1241. [PubMed: 11358867]
20. Zhao B, Ye X, Yu J, et al. TEAD mediates YAP-dependent gene induction and growth control. *Genes Dev.* 2008;22:1962–1971. [PubMed: 18579750]
21. Guo T, Lu Y, Li P, et al. A novel partner of scalloped regulates hippo signaling via antagonizing scalloped-Yorkie activity. *Cell Res.* 2013;23:1201–1214. [PubMed: 23999857]
22. Koontz LM, Liu-Chittenden Y, Yin F, et al. The hippo effector Yorkie controls normal tissue growth by antagonizing scalloped-mediated default repression. *Dev Cell.* 2013;25:388–401. [PubMed: 23725764]
23. Ma S, Meng Z, Chen R, Guan KL. The hippo pathway: biology and pathophysiology. *Annu Rev Biochem.* 2019;88:577–604. [PubMed: 30566373]
24. Arimura N, Kaibuchi K. Neuronal polarity: from extracellular signals to intracellular mechanisms. *Nat Rev Neurosci.* 2007;8:194–205. [PubMed: 17311006]
25. Nelson WJ. Adaptation of core mechanisms to generate cell polarity. *Nature.* 2003;422:766–774. [PubMed: 12700771]
26. Tricaud N. Myelinating Schwann cell polarity and mechanically-driven myelin sheath elongation. *Front Cell Neurosci.* 2017;11:414. [PubMed: 29354031]
27. Bazellieres E, Aksenova V, Barthelemy-Requin M, Massey-Harroche D, Le Bivic A. Role of the crumbs proteins in ciliogenesis, cell migration and Actin organization. *Semin Cell Dev Biol.* 2018;81:13–20. [PubMed: 29056580]
28. Fernando RN, Cotter L, Perrin-Tricaud C, et al. Optimal myelin elongation relies on YAP activation by axonal growth and inhibition by Crb3/hippo pathway. *Nat Commun.* 2016;7:12186. [PubMed: 27435623]
29. Szymaniak AD, Mahoney JE, Cardoso WV, Varelas X. Crumbs3-mediated polarity directs airway epithelial cell fate through the hippo pathway effector yap. *Dev Cell.* 2015;34:283–296. [PubMed: 26235047]
30. Varelas X, Samavarchi-Tehrani P, Narimatsu M, et al. The crumbs complex couples cell density sensing to hippo-dependent control of the TGF-beta-SMAD pathway. *Dev Cell.* 2010b;19:831–844. [PubMed: 21145499]
31. Assemat E, Bazellieres E, Pallesi-Pocachard E, Le Bivic A, Massey-Harroche D. Polarity complex proteins. *Biochim Biophys Acta.* 2008;1778:614–630. [PubMed: 18005931]
32. Kim NG, Gumbiner BM. Adhesion to fibronectin regulates hippo signaling via the FAK-Src-PI3K pathway. *J Cell Biol.* 2015;210:503–515. [PubMed: 26216901]
33. Schlegelmilch K, Mohseni M, Kirak O, et al. Yap1 acts downstream of alpha-catenin to control epidermal proliferation. *Cell.* 2011;144:782–795. [PubMed: 21376238]
34. Chan SW, Lim CJ, Chong YF, Pobbati AV, Huang C, Hong W. Hippo pathway-independent restriction of TAZ and YAP by angiomin. *J Biol Chem.* 2011;286:7018–7026. [PubMed: 21224387]
35. Leung CY, Zernicka-Goetz M. Angiomin prevents pluripotent lineage differentiation in mouse embryos via hippo pathway-dependent and -independent mechanisms. *Nat Commun.* 2013;4:2251. [PubMed: 23903990]
36. Wang W, Huang J, Chen J. Angiomin-like proteins associate with and negatively regulate YAP1. *J Biol Chem.* 2011;286:4364–4370. [PubMed: 21187284]

37. Zhao B, Li L, Lu Q, et al. Angiomotin is a novel hippo pathway component that inhibits YAP oncoprotein. *Genes Dev.* 2011;25:51–63. [PubMed: 21205866]
38. Adler JJ, Johnson DE, Heller BL, et al. Serum deprivation inhibits the transcriptional co-activator YAP and cell growth via phosphorylation of the 130-kDa isoform of Angiomotin by the LATS1/2 protein kinases. *Proc Natl Acad Sci U S A.* 2013;110:17368–17373. [PubMed: 24101513]
39. Moleirinho S, Guerrant W, Kissil JL. The Angiomotins—from discovery to function. *FEBS Lett.* 2014;588:2693–2703. [PubMed: 24548561]
40. Gusella JF, Ramesh V, MacCollin M, Jacoby LB. Merlin: the neurofibromatosis 2 tumor suppressor. *Biochim Biophys Acta.* 1999;1423:M29–M36. [PubMed: 10214350]
41. Yin F, Yu J, Zheng Y, Chen Q, Zhang N, Pan D. Spatial organization of hippo signaling at the plasma membrane mediated by the tumor suppressor Merlin/NF2. *Cell.* 2013;154:1342–1355. [PubMed: 24012335]
42. Li W, Cooper J, Zhou L, et al. Merlin/NF2 loss-driven tumorigenesis linked to CRL4(DCAF1)-mediated inhibition of the hippo pathway kinases Lats1 and 2 in the nucleus. *Cancer Cell.* 2014;26:48–60. [PubMed: 25026211]
43. Burridge K. Focal adhesions: a personal perspective on a half century of progress. *FEBS J.* 2017;284:3355–3361. [PubMed: 28796323]
44. Dupont S, Morsut L, Aragona M, et al. Role of YAP/TAZ in mechanotransduction. *Nature.* 2011;474:179–183. [PubMed: 21654799]
45. Zhao B, Li L, Wang L, Wang CY, Yu J, Guan KL. Cell detachment activates the hippo pathway via cytoskeleton reorganization to induce anoikis. *Genes Dev.* 2012;26:54–68. [PubMed: 22215811]
46. Zhao B, Wei X, Li W, et al. Inactivation of YAP oncoprotein by the hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes Dev.* 2007;21:2747–2761. [PubMed: 17974916]
47. Sabra H, Brunner M, Mandati V, et al. β 1 integrin-dependent Rac/group I PAK signaling mediates YAP activation of yes-associated protein 1 (YAP1) via NF2/merlin. *J Biol Chem.* 2017;292:19179–19197. [PubMed: 28972170]
48. Yu FX, Zhao B, Panupinthu N, et al. Regulation of the hippo-YAP pathway by G-protein-coupled receptor signaling. *Cell.* 2012;150:780–791. [PubMed: 22863277]
49. Fan R, Kim NG, Gumbiner BM. Regulation of hippo pathway by mitogenic growth factors via phosphoinositide 3-kinase and phosphoinositide-dependent kinase-1. *Proc Natl Acad Sci U S A.* 2013;110:2569–2574. [PubMed: 23359693]
50. Reddy BV, Irvine KD. Regulation of hippo signaling by EGFR-MAPK signaling through Ajuba family proteins. *Dev Cell.* 2013;24:459–471. [PubMed: 23484853]
51. Ganem NJ, Cornils H, Chiu SY, et al. Cytokinesis failure triggers hippo tumor suppressor pathway activation. *Cell.* 2014;158:833–848. [PubMed: 25126788]
52. Sun G, Irvine KD. Ajuba family proteins link JNK to hippo signaling. *Sci Signal.* 2013;6:ra81. [PubMed: 24023255]
53. Denysenko T, Annovazzi L, Cassoni P, Melcarne A, Mellai M, Schiffer D. WNT/ β -catenin signaling pathway and downstream modulators in low- and high-grade Glioma. *Cancer Genomics Proteomics.* 2016;13:31–45. [PubMed: 26708597]
54. Tsutsumi R, Masoudi M, Takahashi A, et al. YAP and TAZ, hippo signaling targets, act as a rheostat for nuclear SHP2 function. *Dev Cell.* 2013;26:658–665. [PubMed: 24035415]
55. Varelas X, Miller BW, Sopko R, et al. The hippo pathway regulates Wnt/ β -catenin signaling. *Dev Cell.* 2010a;18:579–591. [PubMed: 20412773]
56. Kim W, Khan SK, Yang Y. Interacting network of hippo, Wnt/ β -catenin and Notch signaling represses liver tumor formation. *BMB Rep.* 2017;50:1–2. [PubMed: 27881216]
57. Tschaharganeh DF, Chen X, Latzko P, et al. Yes-associated protein up-regulates Jagged-1 and activates the notch pathway in human hepatocellular carcinoma. *Gastroenterology.* 2013;144:1530–1542 e1512. [PubMed: 23419361]
58. Chen R, Xie R, Meng Z, Ma S, Guan KL. STRIPAK integrates upstream signals to initiate the hippo kinase cascade. *Nat Cell Biol.* 2019;21:1565–1577. [PubMed: 31792377]

59. Couzens AL, Knight JD, Kean MJ, et al. Protein interaction network of the mammalian hippo pathway reveals mechanisms of kinase-phosphatase interactions. *Sci Signal*. 2013;6:rs15. [PubMed: 24255178]
60. Kim JW, Berrios C, Kim M, et al. STRIPAK directs PP2A activity toward MAP4K4 to promote oncogenic transformation of human cells. *Elife*. 2020;9.
61. Tang Y, Chen M, Zhou L, et al. Architecture, substructures, and dynamic assembly of STRIPAK complexes in hippo signaling. *Cell Discov*. 2019;5:3. [PubMed: 30622739]
62. Zheng Y, Liu B, Wang L, Lei H, Pulgar Prieto KD, Pan D. Homeostatic control of Hpo/MST kinase activity through autophosphorylation-dependent recruitment of the STRIPAK PP2A phosphatase complex. *Cell Rep*. 2017;21:3612–3623. [PubMed: 29262338]
63. Ren F, Zhang L, Jiang J. Hippo signaling regulates Yorkie nuclear localization and activity through 14-3-3 dependent and independent mechanisms. *Dev Biol*. 2010;337:303–312. [PubMed: 19900439]
64. Wada K, Itoga K, Okano T, Yonemura S, Sasaki H. Hippo pathway regulation by cell morphology and stress fibers. *Development*. 2011;138:3907–3914. [PubMed: 21831922]
65. Shreberk-Shaked M, Oren M. New insights into YAP/TAZ nucleocytoplasmic shuttling: new cancer therapeutic opportunities? *Mol Oncol*. 2019;13:1335–1341. [PubMed: 31050214]
66. Ege N, Dowbaj AM, Jiang M, et al. Quantitative analysis reveals that Actin and Src-family kinases regulate nuclear YAP1 and its export. *Cell Syst*. 2018;6:692–708 e613. [PubMed: 29909276]
67. Elosegui-Artola A, Andreu I, Beedle AEM, et al. Force triggers YAP nuclear entry by regulating transport across nuclear pores. *Cell*. 2017;171:1397–1410 e1314. [PubMed: 29107331]
68. Azad T, Nouri K, Janse van Rensburg HJ, et al. A gain-of-functional screen identifies the hippo pathway as a central mediator of receptor tyrosine kinases during tumorigenesis. *Oncogene*. 2020;39:334–355. [PubMed: 31477837]
69. Cho YS, Zhu J, Li S, Wang B, Han Y, Jiang J. Regulation of Yki/yap subcellular localization and Hpo signaling by a nuclear kinase PRP4K. *Nat Commun*. 2018;9:1657. [PubMed: 29695716]
70. Enzo E, Santinon G, Pocaterra A, et al. Aerobic glycolysis tunes YAP/TAZ transcriptional activity. *EMBO J*. 2015;34:1349–1370. [PubMed: 25796446]
71. Kedan A, Verma N, Saroha A, et al. PYK2 negatively regulates the hippo pathway in TNBC by stabilizing TAZ protein. *Cell Death Dis*. 2018;9:985. [PubMed: 30250159]
72. Mo JS, Meng Z, Kim YC, et al. Cellular energy stress induces AMPK-mediated regulation of YAP and the hippo pathway. *Nat Cell Biol*. 2015;17:500–510. [PubMed: 25751140]
73. Wang W, Xiao ZD, Li X, et al. AMPK modulates hippo pathway activity to regulate energy homeostasis. *Nat Cell Biol*. 2015;17:490–499. [PubMed: 25751139]
74. Michaloglou C, Lehmann W, Martin T, et al. The tyrosine phosphatase PTPN14 is a negative regulator of YAP activity. *PloS One*. 2013;8:e61916. [PubMed: 23613971]
75. Yang S, Zhang L, Liu M, et al. CDK1 phosphorylation of YAP promotes mitotic defects and cell motility and is essential for neoplastic transformation. *Cancer Res*. 2013;73:6722–6733. [PubMed: 24101154]
76. Aragona M, Panciera T, Manfrin A, et al. A mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by Actin-processing factors. *Cell*. 2013;154:1047–1059. [PubMed: 23954413]
77. Totaro A, Castellan M, Battilana G, et al. YAP/TAZ link cell mechanics to notch signalling to control epidermal stem cell fate. *Nat Commun*. 2017;8:15206. [PubMed: 28513598]
78. Reginensi A, Scott RP, Gregorieff A, et al. Yap- and Cdc42-dependent nephrogenesis and morphogenesis during mouse kidney development. *PLoS Genet*. 2013;9:e1003380. [PubMed: 23555292]
79. Lin C, Yao E, Zhang K, et al. YAP is essential for mechanical force production and epithelial cell proliferation during lung branching morphogenesis. *Elife*. 2017;6.
80. Porazinski S, Wang H, Asaoka Y, et al. YAP is essential for tissue tension to ensure vertebrate 3D body shape. *Nature*. 2015;521:217–221. [PubMed: 25778702]
81. Deng H, Wang W, Yu J, Zheng Y, Qing Y, Pan D. Spectrin regulates hippo signaling by modulating cortical actomyosin activity. *Elife*. 2015;4:e06567. [PubMed: 25826608]

82. Fletcher GC, Elbediwy A, Khanal I, Ribeiro PS, Tapon N, Thompson BJ. The Spectrin cytoskeleton regulates the hippo signalling pathway. *EMBO J.* 2015;34:940–954. [PubMed: 25712476]
83. Wong KK, Li W, An Y, et al. Beta-Spectrin regulates the hippo signaling pathway and modulates the basal Actin network. *J Biol Chem.* 2015;290:6397–6407. [PubMed: 25589787]
84. Furukawa KT, Yamashita K, Sakurai N, Ohno S. The epithelial circumferential Actin Belt regulates YAP/TAZ through Nucleocytoplasmic shuttling of Merlin. *Cell Rep.* 2017;20:1435–1447. [PubMed: 28793266]
85. Le Douarin NM, Smith J. Development of the peripheral nervous system from the neural crest. *Annu Rev Cell Biol.* 1988;4:375–404. [PubMed: 3058162]
86. Hindley CJ, Condurat AL, Menon V, et al. The hippo pathway member YAP enhances human neural crest cell fate and migration. *Sci Rep.* 2016;6:23208. [PubMed: 26980066]
87. Kumar D, Nitzan E, Kalcheim C. YAP promotes neural crest emigration through interactions with BMP and Wnt activities. *Cell Commun Signal.* 2019;17:69. [PubMed: 31228951]
88. Manderfield LJ, Aghajanian H, Engleka KA, et al. Hippo signaling is required for notch-dependent smooth muscle differentiation of neural crest. *Development.* 2015;142:2962–2971. [PubMed: 26253400]
89. Manderfield LJ, Engleka KA, Aghajanian H, et al. Pax3 and hippo signaling coordinate melanocyte gene expression in neural crest. *Cell Rep.* 2014;9:1885–1895. [PubMed: 25466249]
90. Sun Z, da Fontoura CSG, Moreno M, et al. FoxO6 regulates hippo signaling and growth of the craniofacial complex. *PLoS Genet.* 2018;14:e1007675. [PubMed: 30286078]
91. Wang J, Xiao Y, Hsu CW, et al. Yap and Taz play a crucial role in neural crest-derived craniofacial development. *Development.* 2016;143:504–515. [PubMed: 26718006]
92. Grove M, Kim H, Santerre M, et al. YAP/TAZ initiate and maintain Schwann cell myelination. *Elife.* 2017;6.
93. Serinagaoglu Y, Pare J, Giovannini M, Cao X. Nf2-yap signaling controls the expansion of DRG progenitors and glia during DRG development. *Dev Biol.* 2015;398:97–109. [PubMed: 25433207]
94. Frank E, Sanes JR. Lineage of neurons and glia in chick dorsal root ganglia: analysis in vivo with a recombinant retrovirus. *Development.* 1991;111:895–908. [PubMed: 1908772]
95. Serbedzija GN, Bronner-Fraser M, Fraser SE. Vital dye analysis of cranial neural crest cell migration in the mouse embryo. *Development.* 1992;116:297–307. [PubMed: 1283734]
96. Hanani M. Satellite glial cells in sensory ganglia: from form to function. *Brain Res Brain Res Rev.* 2005;48:457–476. [PubMed: 15914252]
97. Ma Q, Fode C, Guillemot F, Anderson DJ. Neurogenin1 and neurogenin2 control two distinct waves of neurogenesis in developing dorsal root ganglia. *Genes Dev.* 1999;13:1717–1728. [PubMed: 10398684]
98. Rifkin JT, Todd VJ, Anderson LW, Lefcort F. Dynamic expression of neurotrophin receptors during sensory neuron genesis and differentiation. *Dev Biol.* 2000;227:465–480. [PubMed: 11071767]
99. Woodhoo A, Sommer L. Development of the Schwann cell lineage: from the neural crest to the myelinated nerve. *Glia.* 2008;56:1481–1490. [PubMed: 18803317]
100. Koser DE, Thompson AJ, Foster SK, et al. Mechanosensing is critical for axon growth in the developing brain. *Nat Neurosci.* 2016;19:1592–1598. [PubMed: 27643431]
101. Le Douarin NM, Teillet MA. Experimental analysis of the migration and differentiation of neuroblasts of the autonomic nervous system and of neurectodermal mesenchymal derivatives, using a biological cell marking technique. *Dev Biol.* 1974;41:162–184. [PubMed: 4140118]
102. Maro GS, Vermeren M, Voiculescu O, et al. Neural crest boundary cap cells constitute a source of neuronal and glial cells of the PNS. *Nat Neurosci.* 2004;7:930–938. [PubMed: 15322547]
103. Zujovic V, Thibaud J, Bachelin C, et al. Boundary cap cells are peripheral nervous system stem cells that can be redirected into central nervous system lineages. *Proc Natl Acad Sci U S A.* 2011;108:10714–10719. [PubMed: 21670295]
104. Radomska KJ, Topilko P. Boundary cap cells in development and disease. *Curr Opin Neurobiol.* 2017;47:209–215. [PubMed: 29174469]

105. Smith CJ, Morris AD, Welsh TG, Kucenas S. Contact-mediated inhibition between oligodendrocyte progenitor cells and motor exit point glia establishes the spinal cord transition zone. *PLoS Biol.* 2014;12:e1001961. [PubMed: 25268888]
106. Fontenas L, Kucenas S. Motor exit point (MEP) glia: novel Myelinating glia that bridge CNS and PNS myelin. *Front Cell Neurosci.* 2018;12:333. [PubMed: 30356886]
107. Jessen KR, Brennan A, Morgan L, et al. The Schwann cell precursor and its fate: a study of cell death and differentiation during gliogenesis in rat embryonic nerves. *Neuron.* 1994;12:509–527. [PubMed: 8155318]
108. Michailov GV, Sereda MW, Brinkmann BG, et al. Axonal neuregulin-1 regulates myelin sheath thickness. *Science.* 2004;304:700–703. [PubMed: 15044753]
109. Taveggia C, Zanazzi G, Petrylak A, et al. Neuregulin-1 type III determines the ensheathment fate of axons. *Neuron.* 2005;47:681–694. [PubMed: 16129398]
110. Rasi K, Hurskainen M, Kallio M, et al. Lack of collagen XV impairs peripheral nerve maturation and, when combined with laminin-411 deficiency, leads to basement membrane abnormalities and sensorimotor dysfunction. *J Neurosci.* 2010;30:14490–14501. [PubMed: 20980607]
111. Yang D, Bierman J, Tarumi YS, et al. Coordinate control of axon defasciculation and myelination by laminin-2 and -8. *J Cell Biol.* 2005;168:655–666. [PubMed: 15699217]
112. Yu WM, Feltri ML, Wrabetz L, Strickland S, Chen ZL. Schwann cell-specific ablation of laminin gamma1 causes apoptosis and prevents proliferation. *J Neurosci.* 2005;25:4463–4472. [PubMed: 15872093]
113. Feltri ML, Graus Porta D, Previtali SC, et al. Conditional disruption of beta 1 integrin in Schwann cells impedes interactions with axons. *J Cell Biol.* 2002;156:199–209. [PubMed: 11777940]
114. Pellegatta M, De Arcangelis A, D'Urso A, et al. alpha6beta1 and alpha7beta1 integrins are required in Schwann cells to sort axons. *J Neurosci.* 2013;33:17995–18007. [PubMed: 24227711]
115. Petersen SC, Luo R, Liebscher I, et al. The adhesion GPCR GPR126 has distinct, domain-dependent functions in Schwann cell development mediated by interaction with laminin-211. *Neuron.* 2015;85:755–769. [PubMed: 25695270]
116. Benninger Y, Thurnherr T, Pereira JA, et al. Essential and distinct roles for cdc42 and rac1 in the regulation of Schwann cell biology during peripheral nervous system development. *J Cell Biol.* 2007;177:1051–1061. [PubMed: 17576798]
117. Grove M, Komiyama NH, Nave KA, Grant SG, Sherman DL, Brophy PJ. FAK is required for axonal sorting by Schwann cells. *J Cell Biol.* 2007;176:277–282. [PubMed: 17242067]
118. Guo X, Stafford LJ, Bryan B, et al. A Rac/Cdc42-specific exchange factor, GEFT, induces cell proliferation, transformation, and migration. *J Biol Chem.* 2003;278:13207–13215. [PubMed: 12547822]
119. Nodari A, Zambroni D, Quattrini A, et al. Beta1 integrin activates Rac1 in Schwann cells to generate radial lamellae during axonal sorting and myelination. *J Cell Biol.* 2007;177:1063–1075. [PubMed: 17576799]
120. Pereira JA, Benninger Y, Baumann R, et al. Integrin-linked kinase is required for radial sorting of axons and Schwann cell remyelination in the peripheral nervous system. *J Cell Biol.* 2009;185:147–161. [PubMed: 19349584]
121. Ghidinelli M, Poitelon Y, Shin YK, et al. Laminin 211 inhibits protein kinase A in Schwann cells to modulate neuregulin 1 type III-driven myelination. *PLoS Biol.* 2017;15:e2001408. [PubMed: 28636612]
122. Monk KR, Naylor SG, Glenn TD, et al. A G protein-coupled receptor is essential for Schwann cells to initiate myelination. *Science.* 2009;325:1402–1405. [PubMed: 19745155]
123. Feltri ML, Poitelon Y, Previtali SC. How Schwann cells Sort axons: new concepts. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry.* 2016;22:252–265.
124. Jessen KR, Mirsky R. Schwann cell precursors; multipotent glial cells in embryonic nerves. *Frontiers in Molecular Neuroscience.* 2019;12:69. [PubMed: 30971890]
125. Monk KR, Feltri ML, Taveggia C. New insights on Schwann cell development. *Glia.* 2015;63:1376–1393. [PubMed: 25921593]

126. Wilson ER, Della-Flora Nunes G, Weaver MR, Frick LR, Feltri ML. Schwann cell interactions during the development of the peripheral nervous system. *Developmental Neurobiology*. 2020. 10.1002/dneu.22744.
127. Deng Y, Wu LMN, Bai S, et al. A reciprocal regulatory loop between TAZ/YAP and G-protein Galphas regulates Schwann cell proliferation and myelination. *Nat Commun*. 2017;8:15161. [PubMed: 28443644]
128. Poitelon Y, Lopez-Anido C, Catignas K, et al. YAP and TAZ control peripheral myelination and the expression of laminin receptors in Schwann cells. *Nat Neurosci*. 2016;19:879–887. [PubMed: 27273766]
129. Rosso G, Liashkovich I, Gess B, Young P, Kun A, Shahin V. Unravelling crucial biomechanical resilience of myelinated peripheral nerve fibres provided by the Schwann cell basal lamina and PMP22. *Sci Rep*. 2014;4:7286. [PubMed: 25446378]
130. Urbanski MM, Kingsbury L, Moussouros D, et al. Myelinating glia differentiation is regulated by extracellular matrix elasticity. *Sci Rep*. 2016;6:33751. [PubMed: 27646171]
131. Guo L, Moon C, Niehaus K, Zheng Y, Ratner N. Rac1 controls Schwann cell myelination through cAMP and NF2/merlin. *J Neurosci*. 2012;32:17251–17261. [PubMed: 23197717]
132. Lopez-Fagundo C, Bar-Kochba E, Livi LL, Hoffman-Kim D, Franck C. Three-dimensional traction forces of Schwann cells on compliant substrates. *Journal of the Royal Society, Interface / the Royal Society*. 2014;11:20140247.
133. Lopez-Anido C, Poitelon Y, Gopinath C, et al. Tead1 regulates the expression of peripheral myelin protein 22 during Schwann cell development. *Hum Mol Genet*. 2016;25:3055–3069. [PubMed: 27288457]
134. Wu LMN, Deng Y, Wang J, et al. Programming of Schwann cells by Lats1/2-TAZ/YAP signaling drives malignant peripheral nerve sheath tumorigenesis. *Cancer Cell*. 2018;33:this issue:292–308.e7. [PubMed: 29438698]
135. Mindos T, Dun XP, North K, et al. Merlin controls the repair capacity of Schwann cells after injury by regulating hippo/YAP activity. *J Cell Biol*. 2017;216:495–510. [PubMed: 28137778]
136. He X, Zhang L, Queme LF, et al. A histone deacetylase 3-dependent pathway delimits peripheral myelin growth and functional regeneration. *Nat Med*. 2018;24:338–351. [PubMed: 29431744]
137. Lu Y, Wu T, Gutman O, et al. Phase separation of TAZ compartmentalizes the transcription machinery to promote gene expression. *Nat Cell Biol*. 2020;22:453–464. [PubMed: 32203417]
138. Fernandez-Valle C, Gorman D, Gomez AM, Bunge MB. Actin plays a role in both changes in cell shape and gene-expression associated with Schwann cell myelination. *J Neurosci*. 1997;17:241–250. [PubMed: 8987752]
139. Parrinello S, Napoli I, Ribeiro S, et al. EphB signaling directs peripheral nerve regeneration through Sox2-dependent Schwann cell sorting. *Cell*. 2010;143:145–155. [PubMed: 20869108]
140. Moleirinho S, Patrick C, Tilston-Lunel AM, et al. Willin, an upstream component of the hippo signaling pathway, orchestrates mammalian peripheral nerve fibroblasts. *PloS One*. 2013;8:e60028. [PubMed: 23593160]
141. Zhang N, Bai H, David KK, et al. The Merlin/NF2 tumor suppressor functions through the YAP oncoprotein to regulate tissue homeostasis in mammals. *Dev Cell*. 2010;19:27–38. [PubMed: 20643348]
142. Oh JE, Ohta T, Satomi K, et al. Alterations in the NF2-LATS1/LATS2/YAP pathway in Schwannomas. *J Neuropathol Exp Neurol*. 2015;74:952–959. [PubMed: 26360373]
143. Strowd RE. Available therapies for patients with Neurofibromatosis-related nervous system tumors. *Curr Treat Options Oncol*. 2020;21:81. [PubMed: 32767156]
144. Kim DH, Murovic JA, Tiel RL, Kline DG. Operative outcomes of 546 Louisiana State University health sciences center peripheral nerve tumors. *Neurosurg Clin N Am*. 2004;15:177–192. [PubMed: 15177317]
145. Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. *Lancet*. 2009;373:1974–1986. [PubMed: 19476995]
146. Evans DG, Huson SM, Donnai D, et al. A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity. *J Med Genet*. 1992;29:841–846. [PubMed: 1479598]

147. Brandt ZJ, North PN, Link BA. Somatic Mutations of *lats2* Cause Peripheral Nerve Sheath Tumors in Zebrafish. *Cells*. 2019;8(9):972. 10.3390/cells8090972.
148. Guerrant W, Kota S, Troutman S, et al. YAP mediates tumorigenesis in Neurofibromatosis type 2 by promoting cell survival and proliferation through a COX-2-EGFR signaling Axis. *Cancer Res*. 2016;76:3507–3519. [PubMed: 27216189]
149. Hoxha S, Shepard A, Troutman S, et al. YAP-mediated recruitment of YY1 and EZH2 represses transcription of key cell-cycle regulators. *Cancer Res*. 2020;80:2512–2522. [PubMed: 32409309]
150. Zhao F, Yang Z, Chen Y, et al. Deregulation of the hippo pathway promotes tumor cell proliferation through YAP activity in human sporadic vestibular Schwannoma. *World Neurosurg*. 2018;117:e269–e279. [PubMed: 29902598]
151. Chen Z, Li S, Mo J, et al. Schwannoma development is mediated by Hippo pathway dysregulation and modified by RAS/MAPK signaling. *JCI Insight*. 2020;5(20). 10.1172/jci.insight.141514.
152. Valeyrie-Allanore L, Ismaili N, Bastuji-Garin S, et al. Symptoms associated with malignancy of peripheral nerve sheath tumours: a retrospective study of 69 patients with neurofibromatosis 1. *Br J Dermatol*. 2005;153:79–82. [PubMed: 16029330]
153. Jessen WJ, Miller SJ, Jousma E, et al. MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. *J Clin Invest*. 2013;123:340–347. [PubMed: 23221341]
154. Kolberg M, Holand M, Lind GE, et al. Protein expression of BIRC5, TK1, and TOP2A in malignant peripheral nerve sheath tumours—a prognostic test after surgical resection. *Mol Oncol*. 2015;9:1129–1139. [PubMed: 25769404]
155. Coleman MP, Hoke A. Programmed axon degeneration: from mouse to mechanism to medicine. *Nat Rev Neurosci*. 2020;21:183–196. [PubMed: 32152523]
156. Arthur-Farraj PJ, Latouche M, Wilton DK, et al. C-Jun reprograms Schwann cells of injured nerves to generate a repair cell essential for regeneration. *Neuron*. 2012;75:633–647. [PubMed: 22920255]
157. Grove M, Lee H, Zhao H, Son YJ. Axon-dependent expression of YAP/TAZ mediates Schwann cell remyelination but not proliferation after nerve injury. *Elife*. 2020;9.
158. Jeanette H, Marziali LN, Bhatia U, et al. YAP and TAZ regulate Schwann cell proliferation and differentiation during peripheral nerve regeneration. *Glia*. 2020. 10.1002/glia.23949.
159. DiBonaventura MD, Sadosky A, Concialdi K, et al. The prevalence of probable neuropathic pain in the US: results from a multimodal general-population health survey. *J Pain Res*. 2017;10:2525–2538. [PubMed: 29138590]
160. Pinho-Ribeiro FA, Verri WA Jr, Chiu IM. Nociceptor sensory neuron-immune interactions in pain and inflammation. *Trends Immunol*. 2017;38:5–19. [PubMed: 27793571]
161. Lyu C, Lyu GW, Mulder J, et al. Expression and regulation of FRMD6 in mouse DRG neurons and spinal cord after nerve injury. *Sci Rep*. 2020;10:1880. [PubMed: 32024965]
162. Xu N, Wu MZ, Deng XT, et al. Inhibition of YAP/TAZ activity in spinal cord suppresses neuropathic pain. *J Neurosci*. 2016;36:10128–10140. [PubMed: 27683908]
163. Abdo H, Calvo-Enrique L, Lopez JM, et al. Specialized cutaneous Schwann cells initiate pain sensation. *Science*. 2019;365:695–699. [PubMed: 31416963]
164. Pathak MM, Nourse JL, Tran T, et al. Stretch-activated ion channel Piezo1 directs lineage choice in human neural stem cells. *Proc Natl Acad Sci U S A*. 2014;111:16148–16153. [PubMed: 25349416]
165. Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. *J Neurol Neurosurg Psychiatry*. 1997;62:310–318. [PubMed: 9120441]
166. Chance PF, Alderson MK, Leppig KA, et al. DNA deletion associated with hereditary neuropathy with liability to pressure palsies. *Cell*. 1993;72:143–151. [PubMed: 8422677]
167. Matsunami N, Smith B, Ballard L, et al. Peripheral myelin protein-22 gene maps in the duplication in chromosome 17p11.2 associated with Charcot-Marie-tooth 1A. *Nat Genet*. 1992;1:176–179. [PubMed: 1303231]
168. Patel PI, Roa BB, Welcher AA, et al. The gene for the peripheral myelin protein PMP-22 is a candidate for Charcot-Marie-tooth disease type 1A. *Nat Genet*. 1992;1:159–165. [PubMed: 1303228]

169. Timmerman V, Nelis E, Van Hul W, et al. The peripheral myelin protein gene PMP-22 is contained within the Charcot-Marie-Tooth disease type 1A duplication. *Nat Genet.* 1992;1:171–175. [PubMed: 1303230]
170. Valentijn LJ, Bolhuis PA, Zorn I, et al. The peripheral myelin gene PMP-22/GAS-3 is duplicated in Charcot-Marie-Tooth disease type 1A. *Nat Genet.* 1992;1:166–170. [PubMed: 1303229]
171. Li J. Genetic factors for nerve susceptibility to injuries - lessons from PMP22 deficiency. *Neural Regen Res.* 2014;9:1661–1664. [PubMed: 25374586]
172. Johnson R, Halder G. The two faces of hippo: targeting the hippo pathway for regenerative medicine and cancer treatment. *Nat Rev Drug Discov.* 2014;13:63–79. [PubMed: 24336504]
173. Pobbati AV, Hong W. A combat with the YAP/TAZ-TEAD oncoproteins for cancer therapy. *Theranostics.* 2020;10:3622–3635. [PubMed: 32206112]
174. Wu L, Yang X. Targeting the hippo pathway for breast cancer therapy. *Cancers.* 2018;10(11):422. 10.3390/cancers10110422.
175. Edwards DN, Ngwa VM, Wang S, et al. The receptor tyrosine kinase EphA2 promotes glutamine metabolism in tumors by activating the transcriptional coactivators YAP and TAZ. *Sci Signal.* 2017;10:eaa4667. [PubMed: 29208682]
176. Rosenbluh J, Nijhawan D, Cox AG, et al. Beta-catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis. *Cell.* 2012;151:1457–1473. [PubMed: 23245941]
177. Si Y, Ji X, Cao X, et al. Src inhibits the hippo tumor suppressor pathway through tyrosine phosphorylation of Lats1. *Cancer Res.* 2017;77:4868–4880. [PubMed: 28754671]
178. Bao Y, Nakagawa K, Yang Z, et al. A cell-based assay to screen stimulators of the hippo pathway reveals the inhibitory effect of dobutamine on the YAP-dependent gene transcription. *J Biochem.* 2011;150:199–208. [PubMed: 21586534]
179. Azad T, Janse van Rensburg HJ, Lightbody ED, et al. A LATS biosensor screen identifies VEGFR as a regulator of the hippo pathway in angiogenesis. *Nat Commun.* 2018;9:1061. [PubMed: 29535383]
180. Oku Y, Nishiya N, Shito T, et al. Small molecules inhibiting the nuclear localization of YAP/TAZ for chemotherapeutics and chemosensitizers against breast cancers. *FEBS Open Bio.* 2015;5:542–549.
181. Wang X, Freire Valls A, Schermann G, et al. YAP/TAZ orchestrate VEGF signaling during developmental angiogenesis. *Dev Cell.* 2017;42:462–478 e467. [PubMed: 28867486]
182. Wennmann DO, Vollenbröker B, Eckart AK, et al. The Hippo pathway is controlled by Angiotensin II signaling and its reactivation induces apoptosis in podocytes. *Cell Death & Disease.* 2014;5(11):e1519–e1519. 10.1038/cddis.2014.476. [PubMed: 25393475]
183. Liu-Chittenden Y, Huang B, Shim JS, et al. Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP. *Genes Dev.* 2012;26:1300–1305. [PubMed: 22677547]
184. Dasari VR, Mazack V, Feng W, Nash J, Carey DJ, Gogoi R. Verteporfin exhibits YAP-independent anti-proliferative and cytotoxic effects in endometrial cancer cells. *Oncotarget.* 2017;8:28628–28640. [PubMed: 28404908]
185. Zhang H, Ramakrishnan SK, Triner D, et al. Tumor-selective proteotoxicity of verteporfin inhibits colon cancer progression independently of YAP1. *Sci Signal.* 2015;8:ra98. [PubMed: 26443705]
186. Elzinga K, Tyreman N, Ladak A, Savaryn B, Olson J, Gordon T. Brief electrical stimulation improves nerve regeneration after delayed repair in Sprague Dawley rats. *Exp Neurol.* 2015;269:142–153. [PubMed: 25842267]
187. Rusovan A, Kanje M, Mild KH. The stimulatory effect of magnetic fields on regeneration of the rat sciatic nerve is frequency dependent. *Exp Neurol.* 1992;117:81–84. [PubMed: 1618289]
188. Sene GA, Sousa FF, Fazan VS, Barbieri CH. Effects of laser therapy in peripheral nerve regeneration. *Acta Ortop Bras.* 2013;21:266–270. [PubMed: 24453680]
189. Daeschler SC, Harhaus L, Schoenle P, Boecker A, Kneser U, Bergmeister KD. Ultrasound and shock-wave stimulation to promote axonal regeneration following nerve surgery: a systematic review and meta-analysis of preclinical studies. *Sci Rep.* 2018;8:3168. [PubMed: 29453349]

190. Li H, Chen C, Wang D. Lowfrequency ultrasound and microbubbles combined with simvastatin promote the apoptosis of MCF7 cells by affecting the LATS1/YAP/RHAMM pathway. *Mol Med Rep.* 2018;18:2724–2732. [PubMed: 30015955]
191. Puts R, Rikeit P, Ruschke K, Knaus P, Schreivogel S, Raum K. Functional regulation of YAP mechanosensitive transcriptional coactivator by focused low-intensity pulsed ultrasound (FLIPUS) enhances proliferation of murine mesenchymal precursors. *PloS One.* 2018;13:e0206041. [PubMed: 30365513]
192. Xu XM, Xu TM, Wei YB, et al. Low-intensity pulsed ultrasound treatment accelerates angiogenesis by activating YAP/TAZ in human umbilical vein endothelial cells. *Ultrasound Med Biol.* 2018;44:2655–2661. [PubMed: 30205992]
193. Ren C, Chen X, Du N, et al. Low-intensity pulsed ultrasound promotes Schwann cell viability and proliferation via the GSK-3 β /beta-catenin signaling pathway. *Int J Biol Sci.* 2018;14:497–507. [PubMed: 29805301]
194. Zhang H, Lin X, Wan H, Li JH, Li JM. Effect of low-intensity pulsed ultrasound on the expression of neurotrophin-3 and brain-derived neurotrophic factor in cultured Schwann cells. *Microsurgery.* 2009;29:479–485. [PubMed: 19308950]
195. Belin S, Zuloaga KL, Poitelon Y. Influence of mechanical stimuli on Schwann cell biology. *Front Cell Neurosci.* 2017;11:347. [PubMed: 29209171]
196. Colciago A, Melfi S, Giannotti G, et al. Tumor suppressor Nf2/merlin drives Schwann cell changes following electromagnetic field exposure through hippo-dependent mechanisms. *Cell Death Discov.* 2015;1:15021. [PubMed: 27551454]
197. Chen Q, Zhang N, Xie R, et al. Homeostatic control of hippo signaling activity revealed by an endogenous activating mutation in YAP. *Genes Dev.* 2015;29:1285–1297. [PubMed: 26109051]
198. Heng BC, Zhang X, Aubel D, et al. Role of YAP/TAZ in cell lineage fate determination and related signaling pathways. *Front Cell Dev Biol.* 2020;8:735. [PubMed: 32850847]
199. Dasgupta I, McCollum D. Control of cellular responses to mechanical cues through YAP/TAZ regulation. *J Biol Chem.* 2019;294:17693–17706. [PubMed: 31594864]
200. Sophie Belin, Jacob Herron, VerPlank Jordan JS, Park Yungki, Feltri Laura M., Poitelon Yannick. Corrigendum: YAP and TAZ Regulate Cc2d1b and Pur β in Schwann Cells. *Frontiers in Molecular Neuroscience.* 2019;12. 10.3389/fnmol.2019.00256.

FIGURE 1.

Core components of the Hippo pathway. The Hippo pathway control the cytoplasmic-nuclear shuttling of YAP/TAZ. A, When the Hippo pathway is active (ON), LATS1/LATS2 kinases phosphorylate YAP/TAZ, causing either their cytoplasmic retention or degradation. NF2 contributes to the Hippo pathway activation. B, When the Hippo pathway is inactive (OFF), YAP and TAZ are not phosphorylated and shuttle into the nucleus to regulate gene expression. Mechanical stimuli and Actin dynamics can regulate LATS1/LATS2 kinases

FIGURE 2.

Non-comprehensive, schematic representation of peripheral nerve development (green background) and pathology (blue background). The PNS is formed from the soma and axons of sensory and autonomic neurons, and from the axons of motor neurons. These axons are ensheathed by glial cells and surrounded by blood vessels, endoneurial fibroblasts, perineurial and epineurial cells. Many of these cell types derive from the neural crest. Schwann cells are the major type of ensheathing glia. Yet, the PNS also includes region-specific ensheathing glia: PNS ganglia are associated with satellite cells and axons at the sensory terminals are surrounded by nociceptive glial cells. Magenta notes indicate the steps where an involvement of the Hippo pathway or YAP/TAZ have been described. Ax, axon; BL, basal lamina; CM, compact myelin

FIGURE 3.

Schematic representing the different approaches to pharmacologically target the Hippo pathway. Group I drugs enhance phosphorylation of YAP/TAZ. Group II drugs directly modify the YAP/TAZ-TEAD interaction. Group III drugs target the genes regulated by YAP/TAZ-TEAD

TABLE 1

Examples of FDA-approved drugs targeting the Hippo pathway

Group	Drug Name	Mechanism of Action	Effect on Hippo pathway	Reference
I	dasatinib	Src family tyrosin kinase inhibitor	activates LATS1/2	(175,32,176,177)
I	dobutamine	β 1-adrenergic receptor agonist	Increase YAP/TAZ phosphorylation	178
I	pazopanib	c-KIT, FGF PDGF, VEGF, receptors inhibitor	LATS1/2 activation	(179,180,181)
I	losartan	Angiotensin II receptor inhibitor	Activates LATS1/1	182
II	verteporfin	YAP ligand	inhibits YAP/TAZ-TEAD interaction	183
III	celecoxib	COX-2 inhibitor	-	148