Hippo signaling: bridging the gap between cancer and neurodegenerative disorders

Abstract
During development, regulation of organ size requires a balance between cell proliferation, growth and cell death. Dysregulation of these fundamental processes can cause a variety of diseases. Excessive cell proliferation results in cancer whereas excessive cell death results in neurodegenerative disorders. Many signaling pathways known-to-date have a role in growth regulation. Among them, evolutionarily conserved Hippo signaling pathway is unique as it controls both cell proliferation and cell death by a variety of mechanisms during organ sculpture and development. Neurodegeneration, a complex process of progressive death of neuronal population, results in fatal disorders with no available cure to date. During normal development, cell death is required for sculpting of an organ. However, aberrant cell death in neuronal cell population can result in neurodegenerative disorders. Hippo pathway has gathered major attention for its role in growth regulation and cancer, however, other functions like its role in neurodegeneration are also emerging rapidly. This review highlights the role of Hippo signaling in cell death and neurodegenerative diseases and provide the information on the chemical inhibitors employed to block Hippo pathway. Understanding Hippo mediated cell death mechanisms will aid in development of reliable and effective therapeutic strategies in future.

Key Words: animal models; cell death mechanisms; cell-signaling; chemical inhibitors; Drosophila eye; Hippo pathway; neurodegeneration; neurological diseases; therapeutic targets

Introduction
A fundamental area in biology is to study growth regulation and organ size. Animal organ size complies with a complex set of biological constraints that ensures survival. During organogenesis, patterning and growth are tightly regulated to determine the correct size. Growth regulation determines the number of cells in organ(s) of a multi-cellular organism by balancing the cell biological processes like cell polarity, cell proliferation and cell death (Dong et al., 2007; Penzo-Mendez and Stanger, 2015; Eder et al., 2017). Broadly speaking, growth properties of a developing field can be regulated by cell number alterations or by changes in cell size. Several highly conserved growth regulatory pathways are involved in growth regulation and organ size homeostasis such as insulin signaling pathway, target of rapamycin (TOR), and Hippo signaling pathway. Insulin signaling is involved in maintaining carbohydrate metabolism while interacting with other conserved signaling pathways like TOR, AMP-activated protein kinase (AMPK) and phosphatidylinositol 3-kinase (PI3K) pathways (Nijhout, 2003; Badisco et al., 2013). TOR signaling controls organ size growth by increasing the cell size; whereas Hippo signaling pathway determines organ size by regulating the cell number. To obtain an ideal organ size, optimum levels of Hippo signaling is required during organogenesis (Camargo et al., 2007; Dong et al., 2007; Tumaneng et al., 2012). Downregulation of Hippo signaling causes over proliferation, which results in cancer, whereas upregulation of Hippo signaling triggers cell death and apoptosis resulting in incomplete or reduced organs or cellular dysfunctions. This growth regulatory Hippo pathway is highly conserved from fruit flies to humans and has been known to play a crucial role in growth, cell proliferation and apoptosis (Kango-Singh and Singh, 2009; Zhao et al., 2011; Verghese et al., 2012b; Halder and Camargo, 2013; Han, 2019; Moya and Halder, 2019). The purpose of this review is to highlight the role of signaling pathway in two distinct disease like cancer and neurodegenerative disorders.

Discovery of Hippo Pathway
The Hippo pathway, which was initially discovered in the Drosophila melanogaster (a.k.a fruit fly) model, and has been a subject of extensive investigation both in Drosophila as well as mammals in the last two decades. Drosophila, with its arsenal of powerful genetic manipulation tools, allows for cost-effective and large scale screens equipped to answer scientific questions immediately. Drosophila with a shorter life cycle, strong reproductive ability, and genetic legacy of more than a century of this model system, has proved to be a

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highly versatile and tractable model for genetic screens. The conservation of genetic machinery from fruit flies to human makes Drosophila an ideal human disease model (Bier, 2005; Singh and Irvine, 2012; Yeates et al., 2019). Therefore, it not only serves as a model for genetic research but also for a wide array of studies including investigations of basic cellular and molecular mechanisms of human disease. To identify genes involved in growth regulation, an EMS mutagenesis screen was conducted in Drosophila eye using eyeless-FLP/FRT system that resulted in identification of members of Hippo signaling pathway. The rationale was to identify the genetic mosaic clones, which exhibit phenotypes affecting cell proliferation, cell death and overall organ size in the adult fly eye.

The adult compound eye of Drosophila develops from an epithelial bilayer structure housed inside the larva, which has blue print for the adult eye and the head structures, and is referred to as the larval eye-imaginal disc. During late second instar and early third instar of larval development, a synchronous wave of differentiation emerges from the posterior margin and moves anteriorly, which results in differentiation of retinal precursor cells to the retina neurons.

The first growth regulation component of the Hippo signaling pathway was reported from the fly model and later it was confirmed that the Hippo pathway is evolutionarily conserved from flies to humans. Hippo pathway, a kinase cascade, also known as Salvador/Warts/Hippo (SWH) pathway, gets its name, “Hippo” from the characteristic overgrowth phenotype of adult structures shown in the pathway component mutants (Justice et al., 1995; Xu et al., 1995; Harvey et al., 2003; Jia et al., 2003; Pantalacci et al., 2003; Udan et al., 2003; Wu et al., 2003; Kango-Singh and Singh, 2009). In 2002, two drosophila lab identified a novel mutation called salvador (sav, also referred to as Shar-pei) that encodes a WW45 domain protein which exhibits over proliferation phenotypes in the Drosophila eye (Kango-Singh et al., 2002; Tapon et al., 2002; Huang et al., 2005; Kango-Singh and Singh, 2009; Zhao et al., 2011; Verghese et al., 2012a). Later, mutants for other components like hippo (hpo, a mammalian Ste20-like kinases in mammals), warts (wts, a serine/threonine kinase) that exhibit similar bigger eyes due to increased number of inter-ommatidial cells in the pupal retinae, were identified (Udan et al., 2003; Wu et al., 2003). The kinases Hippo (MST1/2 in mammals), Warts (Wts or LATSI/2 in mammals) and transcriptional co-activator Yki (YAP/TAZ in mammals), form the core components of Hippo signaling pathway (Huang et al., 2005; figure 1).

There are several upstream components, which regulate Hippo pathway by influencing the cell polarity, cell junctions, and stress induced responses (Meng et al., 2016). Activation of Hpo, upon phosphorylation by its upstream regulators, results in phosphorylation of Sav, which leads to formation of Hippo-Sav complex. This complex activates its downstream components Warts and Mats (Mob as a tumor suppressor, mammalian homolog Mob) via phosphorylation and forms Wts-Mats complex. The Wts-Mats complex further phosphorylates the transcriptional co-activator Yorkie (Yki or YAP/TAZ in mammals), which binds to the 14-3-3 adaptor proteins, gets restricted to the cytoplasm, and gets degraded (Huang et al., 2005; Zhao et al., 2007; Oh and Irvine, 2008; Kango-Singh and Singh, 2009; Snigdha et al., 2019). However, when Hippo is inactivated, Yki is not phosphorylated; therefore, Yki translocates into the nucleus and binds to a transcription factor Scalloped (Sd, mammalian homolog TEA-domain-containing (TEAD) and induces transcription of its downstream targets. The various downstream targets of Yki are Cyclin E (Cyc-E) required for cell proliferation and cell cycle progression, Myc required for growth, Drosophila associated inhibitor of apoptosis 1 (Diap1), Bantam microRNA important for cell survival (Jia et al., 2003; Wu et al., 2003, 2008; Huang et al., 2005; Nolo et al., 2006; Thompson and Cohen, 2006; Peng et al., 2009; Neto-Silva et al., 2010; Ziosi et al., 2010), Wingless (Wg), Drosophila homolog of Wnt (in mammals), and ligand for evolutionarily conserved Wg/Wnt signaling pathway (Singh et al., 2002; Wittkorn et al., 2015) and Homothorax (Hth), a MEIS class of transcription factor, act as the negative regulators of eye formation in the Drosophila eye (Pai et al., 1998; Singh et al., 2011). Downregulation of Hippo pathway causes uncontrolled growth due to increased level of Yki homolog YAP/TAZ results in human cancers and tumors (Harvey and Tapon, 2007) whereas activation of Hippo signaling triggers cell death (apoptosis) (Udan et al., 2003; Verghese et al., 2012a). As such, Hippo pathway has multiple functions, and coordinates a balance between growth, cell survival and death, which is required for organ formation with balanced size and shape (Kango-Singh and Singh, 2009; Han, 2019), and has implications in cancers, cell death, or neurodegeneration.

Multiple Roles of Hippo Signaling Pathway

Apart from its role in growth regulation and organ size control (Xu et al., 1995; Jia et al., 2003; Pantalacci et al., 2003; Udan et al., 2003; Wu et al., 2003; Kango-Singh and Singh, 2009; Han, 2019), Hippo pathway and its downstream targets have other functions in cell proliferation, apoptosis, cell differentiation, cell competition, cell contact inhibition, epithelial-mesenchymal transition (EMT), innate immunity, regeneration and repair (Mehta and Singh, 2019; Moya and Halder, 2019; figure 2). Downstream targets of Hippo pathway are crucial for various cellular processes like (a) cell proliferation, cell cycle progression (Cyclin E), (b) inhibition of cell death (Diap1),
Role of Hippo in Cell Death and Neurodegenerative Diseases

Role of Hippo in cell death

Neurodegeneration is characterized by excessive cell death of functional neurons (Singh, 2012). Aberrant activation of Hippo signaling causes cell death, making it a potential candidate that can link cancer with neurodegeneration. Several in vitro and in vivo models including Drosophila melanogaster (fruit fly), Mus musculus (mouse), Danio rerio (zebrafish), are being used to study the role of Hippo pathway in cell death and neurodegenerative diseases. Hippo signaling has been used to study growth, cell death and to identify potential targets which can block or ameliorate the onset of neurodegenerative diseases (Table 1) (Udan et al., 2003; Wu et al., 2003; Lehtinen et al., 2006; Kango-Singh and Singh, 2009; Lee et al., 2013; Sanphui and Biswas, 2013; Wei et al., 2013; Sarkar et al., 2016, 2018; Mueller et al., 2018; Deshpande et al., 2019; Gogia et al., 2020b; Irwin et al., 2020). These models aid in understanding molecular pathogenesis, mechanism of action, progression and therapeutics for neurodegenerative diseases due to conservation of basic genetic machinery. Hippo pathway causes cell death by a variety of mechanisms that include:

(a) Inactivation of Yki. Yeast two hybrid screening techniques were employed to identify the downstream targets of partners of Wts, which resulted in identification of Yki/YAP (Yorkshire) as the binding partner of Wts, and as the link between Hpo signaling activation and its transcriptional control. Genetic epistasis experiments revealed antagonistic interaction between yki and previously identified components of Hippo pathway such as hpo, sav and wts. Furthermore, Hippo pathway negatively regulates Yki activity. LOF of yki resulted in downregulation of Dap1 levels and showed severe growth defects (Huang et al., 2005; Han, 2019).

(b) Upregulation of wg/WNT, the downstream target of Hippo pathway. Wg, a ligand of Wingless/Wnt signaling, regulates the expression of Homothorax (Hth), and it acts as a negative regulator of retinal fate. Hyperactivation of Yki by misexpression of yki16 in the developing fly eye causes ectopic induction of Wg. This ectopic upregulation of Wg (Singh et al., 2002, 2006) causes induction of Hth, suppresses progression of Morphogenetic Furrow (MF) and retinal differentiation (Pai et al., 1998; Singh et al., 2002, 2006, 2011, 2019; Wittkorn et al., 2015) (Figure 3).

(c) Activation of caspases. In Drosophila model, dronc (Drosophila caspase-9 homologue) acts as a transcriptional target of Hippo pathway and regulates cell proliferation and cell death during development (Verghese et al., 2012a). Hyperactivation of Hippo pathway in the fly eye causes induction of Drosophila effector caspases Drice and Dronc, which result in increased cell death (Verghese et al., 2012a). The molecular mechanism underlying Hpo-mediated Dronc regulation is not fully understood.

(d) Activation of evolutionarily conserved c-Jun-amino terminal (NH2)-Kinase (JNK) signaling. Hippo signaling has been shown to play role(s) in neurodegeneration (Azuma et al., 2018; Gogia et al., 2020b; Irwin et al., 2020). Fly model has allowed researchers to exploit genetic tools like GAL4/UAS system to misexpress target gene(s) of interest along the spatial-temporal axes in specific tissues of interest (Brand and Perrimon, 1993). Genetic screens conducted in flies have shown Hippo as a genetic modifier of neurodegeneration as seen in amyloid-beta 42 (Aβ42) mediated neurodegeneration observed in Alzheimer’s disease (AD) and FUS accumulation mediated neurodegeneration as reported in amyotrophic lateral sclerosis (ALS) (Gogia et al., 2020b; Irwin et al., 2020) (Figure 3). Hippo pathway causes cell death by activation of JNK signaling. Interestingly, in AD model, it has been seen that JNK signaling and Hippo signaling are involved in positive feedback loop to trigger neurodegeneration (Irwin et al., 2020).

(e) Oxidative stress mediated activation of MST1-FOXO signaling. Oxidative stress regulates cell survival and homeostasis by unknown mechanisms. Activation of MST1 (by oxidative stress) induces cell death in primary mammalian neurons. If MST1 phosphorylates FOXO transcription factors, which disrupts its interaction with 14-3-3 protein and thereby facilitates translocation of FOXO transcription factor into the nucleus resulting in transcription of pro-apoptotic genes that trigger neuronal cell death (Lehtinen et al., 2006; Figure 3).

Role of Hippo in neurodegenerative diseases

- AD is an age related progressive neurodegenerative disorder with no cure to date (Tare et al., 2011; Sarkar et al., 2016, 2018). It is caused by many factors such as (i) accumulation of extracellular Aβ plaques, (ii) aggregation of intracellular neurofibrillary tau tangles, (iii) oxidative stress due to mitochondrial dysfunction, and (iv) genetic factors (Crews...
### Hippo target genes

| Genes          | Diseases | Role in neurodegenerative disorders                                                                 | Model organism                                      | References                  |
|----------------|----------|----------------------------------------------------------------------------------------------------|----------------------------------------------------|-----------------------------|
| MST1/2 (Hpo)   | AD       | Hippo is a genetic modifier of Aβ<sub>1-42</sub> mediated neurodegeneration                      | Drosophila neuronal culture, rat transgenic mouse model | Irwin et al. (2020)         |
|                |          | MST1 activation leads to FOXO nuclear translocation and transcription of apoptosis-related genes | transgenic mouse model                              | Sanphui and Biswas (2013)   |
|                |          | Inhibition of HDAC3 blocks c-AbI/MST1/YAP signaling ameliorates AD                               | APP/PS1 mouse                                      | Yu et al. (2018)            |
|                | ALS      | Hippo is a genetic modifier of FUS mediated neurodegeneration                                       | Drosophila                                         | Gogia et al. (2020)         |
|                |          | Hpo/ MST is a modifier of motor neuron cell death induced by knockdown of Caz/ FUS               | Drosophila                                         | Azuma et al. (2018)         |
|                |          | MST induces p38MAPK, caspases, and impairment of autophagy that results in motor neuron cell death. | SOD1 mouse model                                   | Lee et al. (2013)           |
|                | HD       | Activation of MST1 and downregulation of nuclear YAP lead to transcriptional deregulation in HD models | Mouse model, neuronal stem cells, human post-mortem cortex samples | Mueller et al. (2018)       |
|                | Skeletal muscle atrophy | MST1 kinase regulates atrophy in fast-dominant skeletal muscle models. | Transgenic mouse model                             | Wei et al. (2013)           |
|                | RD       | MST2 regulates caspase-mediated photoreceptor cell death during retinal detachment.              | Transgenic mouse model                             | Matsumoto et al. (2014)     |
|                | Charcot-Marie-Tooth disease | Hpo acts as a modifier of Charcot-Marie-Tooth disease caused by L01p mutation in factor induced gene 4.  | Drosophila                                         | Kushimura et al. (2018)     |
| Intracerebral hemorrhage | Increased MST1 phosphorylation induces secondary brain injury resulting in intracerebral hemorrhage | Rat                                                | Zhang et al. (2019)         |
| Cerebral ischemia/reperfusion injury | Src-MST1-Ikb signaling in stroke-induced microglial activation which may contribute to neuronal cell death | Microglial cell culture, primary neuronal cell culture, mouse model | Zhao et al. (2016)          |
| LATS (Wts)     | HD       | Activation of LATS (without Polo like kinase 1, Pik1) triggers TRIAD form of cell death           | HD patients’ cortex samples, transgenic mouse model | Yamanishi et al. (2017); Mao et al. (2016) |
|                | AD       | APP-Mint3-TAZ/YAP transcriptionally active triple protein complex regulates amyloid precursor proteins and Aβ production | Cell culture                                       | Swistowski et al. (2009)   |
|                | ALS      | Decreased YAPDCS levels and increased p-p73 are associated with progression in ALS model          | Transgenic mouse model                             | Morimoto et al. (2009)      |
|                | HD       | Decreased YAP nuclear localization and increased YAP phosphorylation was associated with transcriptional deregulation in HD models. | Transgenic mouse model, neuronal stem cells, human post-mortem cortex samples | Mueller et al. (2018)       |
|                |          | Activation of LATS, downregulation of Pik1, YAP/YAPαDC5 triggers TRIAD form of cell death         | HD patients’ cortex samples, transgenic mouse models | Yamanishi et al. (2017)     |
|                |          | Downregulation of YAP triggers TRIAD cell death in HD                                             | Primary neuronal cell culture, Drosophila, transgenic mouse model, HD patients’ brain samples | Hoshino et al. (2006)       |
| Alexander disease | Increased Yki levels and activity | Ischemia/reperfusion injury causes decreased YAP and TAZ activity | Drosophila                                         | Wang et al. (2018)          |
| Cerebral ischemia/reperfusion injury | Ischemia/reperfusion injury causes decreased YAP and TAZ activity | Rat                                                | Gong et al. (2019)          |
| Skeletal muscle atrophy, disruption of NMJ, neuromuscular disorders | Increased YAP activity and nuclear localization is a mediator of size in adult skeletal muscle fibres | Mouse model                                       | Watt et al. (2015)          |
| Neuronal cell death | YAP in neocortical neuron survival and astrocytes differentiation and proliferation | Transgenic mouse model, neuronal cell culture | Huang et al. (2016)         |
| Polyglutamine (PolyQ) diseases | Yki is a genetic modifier of polyglutamine (PolyQ-mediated neurodegeneration | Drosophila                                          | Dubey & Tapadia, (2017)    |
| RD              | Activation of YAP/TEAD in reactive Müller cells                                                  | Mouse model                                        | Hamon et al. (2017)         |
| Sveinsson’s chorioretinal atrophy and congenital retinal coloboma. | LOF of YAP/TAZ results in loss of retinal pigment epithelium, and has implications in congenital ocular defects, retinal coloboma, SCRA | Transgenic mouse model | Zebrabsh | Miesfeld et al. (2015) |
| TEAD (Scalloped) | SCRA    | TEAD1 mutation in disease pathogenesis                                                             | Human clinical tissues                              | Fossdal et al. (2004)       |
| Neurupathies    | HDAC3 activates myelination inhibitory programs (inhibition of myelin growth by TEAD4)          | Cell culture                                       | Kitagawa (2007)             |
|                | F-actin  | Loss of actin capping protein causes degeneration of Drosophila retina via misregulation of Hippo pathway and regulation of F-actin | Drosophila                                         | Bräs-Pereira et al. (2011) |
| Crumbs (Crb)   | AD       | Gain-of-function of apical-basal polarity gene crumbs (crb) enhances Aβ<sub>1-42</sub>-mediated neurodegeneration. | Drosophila                                         | Steffensmeier et al. (2013) |
| Leber congenital amaurosis | Loss of CRB2 in the developing retina results in retinal disorganization and subsequent degeneration | Transgenic mouse mouse | Alves et al. (2013)         |
| Retinitis pigmentosa | Heterozygous mutations in CRB1/crb causes photoreceptor degeneration, retinitis pigmentosa | Human RP patient samples | den Hollander et al. (1999) |
| Fat            | Dentatorubral-pallidolusian atrophy | PolyQ atrophin represses fat gene transcription, which results in progressive neuronal and autophagic degeneration | Drosophila                                         | Napoli et al. (2011)       |
|                |          | Transcriptional repression of fat and downregulation of Hippo pathway mediates neurodegeneration. | Drosophila                                         | Calamita and Fanto (2011)   |
| KIBRA          | AD       | KIBRA is associated with normal episodic memory and Alzheimer’s disease.                         | AD patients tissue samples                          | Corneveaux et al. (2010)   |
|                | Other genes | KIBRA polymorphisms associated with AD risk                                                      | AD patients                                         | Rodriguez et al. (2009)    |
| Teashirt (Tsk) | AD       | Teashirt acts as a suppressor of Aβ<sub>1-42</sub> mediated neurodegeneration                  | Drosophila                                         | Moran et al. (2013)        |
| CBP            | AD       | CBP is a genetic modifier of Aβ<sub>1-42</sub> mediated neurodegeneration.                     | Drosophila                                         | Cutler et al. (2015)       |

Table shows the components of Hippo pathway in mammals as well as their respective orthologs in Drosophila. The table summarizes studies conducted in several in vitro or in vivo models and shows involvement or association of genes or components of Hippo pathway with neurodegenerative diseases. AD; Alzheimer’s disease; ALS: amyotrophic lateral sclerosis; CBP: CREB binding protein; FOXO: Forkhead Box; HD: Huntington’s disease; HDAC3: histone deacetylase 3; LAT5: large tumor suppressor; LOF: Loss-of-function; MST: Mammalian STE20-like kinase-1; RD: retinal degeneration; SCRA: Sveinsson’s chorioretinal atrophy; TAZ: transcriptional coactivator with PDZ-binding motif; TRIAD: transcriptional repression induced atypical cell death; YAP: yes associated protein.
and Masliah, 2010; O’Brien and Wong, 2011; Selkoe and Hardy, 2016; Yeates et al., 2019). AD model in flies allows misexpression of human-AB\textsubscript{\textbeta} in the retinal neurons and helps in understanding the role of Hippo in cell death and neurodegeneration (Figure 4) (Tare et al., 2011; Moran et al., 2013; Steffensmeier et al., 2013; Cutler et al., 2015; Sarkar et al., 2016, 2018; Irwin et al., 2020). Other AD models in fly model allows ectopic of human AB\textsubscript{\textbeta} expression in other neuronal population(s) of the nervous system. Studies conducted using one of those fly models have shown that accumulation of AB\textsubscript{\textbeta} activates the Hippo pathway that further activates JNK pathway by a positive feedback loop mechanism to induce cell death (Figure 4; Irwin et al., 2020). These fly models identified other genetic modifiers like homeotic gene teashirt (tsh) as a suppressor (Moran et al., 2013), and crumbs (crb) with a neuroprotective function in AB\textsubscript{\textbeta} mediated neurodegeneration (Steffensmeier et al., 2013). Prostate derived sterile 20 like kinases (PSKs/TAOKs), an upstream regulator of Hippo signaling cascade, has been reported in the pathogenesis of AD. Activation of PSKs, phosphorylates Tau, results in Alzheimer’s pathology as observed in in vitro cell culture models (Tavares et al., 2013; Table 1). In AD, Hippo mediated neurodegeneration is triggered by dysregulation of MST-FOXO3a pathway, which in turn activates downstream apoptosis regulator Bcl-2 (Figure 5) (Sanphui and Biswas, 2013; Fallahi et al., 2016). Hippo pathway is modulated by inhibition of Histone deacetylases (HDAC-3), which are abundantly expressed in the brain, and has neurotoxic effects. Inhibition of HDAC-3 Tyrsozo-protein kinase ABL (c-Abl), p-MST, p-YAP, reduces oxidative stress and cell death in transgenic mice model of AD (APPsw/PS1dE9) (Figure 5 and Table 1; Yu et al., 2018). Some other Hippo pathway components that play a role in AD are listed in Table 1.

### ALS

ALS, a progressive neurodegenerative disorder, which involves death of upper and lower motor neurons in the brain and spinal cord. More than 30 genes including human-Fused in Sarcoma, FUS (Cabeza in Drosophila) and Cu/Zn superoxide dismutase (SOD1) are known to be associated with ALS pathogenesis (Rosen et al., 1993; Rutherford et al., 2008; Kwiatkowski et al., 2009). Misexpression of human FUS or mutant FUS in the fly eye causes degeneration of photoreceptor neurons and recapitulates neuropathological features similar to ALS (Lanson et al., 2011; Gogia et al., 2020b) (Figure 4). Hippo has been identified as a genetic modifier of FUS mediated neurodegeneration (Azuma et al., 2018; Gogia et al., 2020b). In fly model of ALS, accumulation of FUS leads to the activation of Hippo, which induces JNK pathway and triggers neuronal cell death (Gogia et al., 2020b) (Figures 3 and 4). Similarly, SOD1 (G93A) mouse model of ALS also identified MST1 (Hpo) as a key modulator of neurodegeneration and shows that modulation of levels of MST1 (Hpo), p38, MAPK and caspase-9, 3 and other autophagy markers, affects neuronal death (Figure 5) (Lee et al., 2013). Thus, ectopic Hippo pathway induction triggers neurodegeneration in ALS.

### Polyglutamine diseases

Polyglutamine diseases are caused by expansion of Cytosine-Adenine-Guanine (CAG) repeats encoding a polyQ (polyglutamine) tract in the respective proteins. This leads to aggregation of insoluble ubiquitinated proteins in different neuronal cell populations of the brain and spinal cord which triggers neuronal death (Paulson and Fischbeck, 1996; McGurk et al., 2015). Hippo pathway and its targets have been extensively studied to decipher the molecular pathogenesis in polyglutamine diseases. Studies conducted in Dentatorubral pallidolysian atrophy (DRPLA) fly model has shown that presence of extra CAG repeats in atrophin-1 (at-1) gene suppresses the transcription of tumor suppressor gene fat (ft), an upstream regulator of Hippo pathway, which results in progressive neurodegeneration by regulating autophagy (Calamita and Fanto, 2011; Napoletano et al., 2011). A mouse model reported MST1 as a key player in enhancing fast skeletal muscle atrophy. It reports that increased levels of MST1 in fast skeletal muscles, increases phosphorylation of FOXO3a (a major mediator of muscle atrophy), which leads to its translocation into the nucleus resulting in skeletal muscle atrophy (Figure 5; Wei et al., 2013). Additionally, Yki/ YAP was identified as a genetic modifier of polyglutamine mediated neurodegeneration (Figure 5; Dubey and Tapadia, 2018). It is required to maintain both basal skeletal myofiber mass and size of adult skeletal muscles fibers through its interaction with TEAD. Increased TEAD activity during injury or degeneration of muscle fibers mitigates muscle degeneration (Watt et al., 2015). As seen in denervation induced model of skeletal muscle atrophy, increased YAP nuclear localization regulates muscle mass and growth (Watt et al., 2015).

### Huntington’s disease (HD)

HD, an autosomal dominant neurodegenerative disorder, is caused by CAG repeat(s) expansion. Accumulation of mutant Htt protein triggers cell death. Studies conducted in mouse model of HD (CAG knock-in HdhQ111/Q111) indicated the role of Hippo pathway in HD (Mueller et al., 2018). In HD, the mutant Htt interacts with YAP and disrupts formation of TEAD/YAP complex, which triggers necrotic cell death known as transcriptional repression induced atypical cell death of neuron (TRIAD) (Mao et al., 2016; Yamanishi et al., 2017). TRIAD is mainly regulated by YAP and Hippo pathway in HD models (Hoshino et al., 2006; Yamanishi et al., 2017). Increased levels of MST1 and decreased levels of nuclear YAP are associated with TRIAD as seen in post-mortem HD cortex and HD mouse brain (Mueller et al., 2018). Activation of LATS1/Wts, suppression of cell cycle regulator PK1 (mediates balance between TEAD/YAP-dependent necrosis and p73/YAP-dependent apoptosis), and reduced expression of YAP/ YAPAC isoform in human HD brains, supports occurrence of TRIAD (Yamanishi et al., 2017). Thus, targeting TEAD/YAP transcription based necrosis activity of Hippo pathway can be effectively used for development of therapeutic targets of HD (Mao et al., 2016).

### Parkinson’s disease (PD)

PD, a progressive neurodegenerative disease, which exhibits symptoms of memory loss and movement related disorder. PD is characterized by formation of intracytoplasmic Lewy body (LB) inclusion structures, accumulation of a-synuclein in Lewy bodies and loss of dopaminergic neurons of substantia nigra, which result in neuronal death (Feany and Bender, 2000). Mutations in genes including Synuclein alpha (SNA), leucine-rich repeat kinase 2 (LRKK2), PTEN Induced Kinase 1 (PINK1) and others cause PD (Forno, 1996; Hardy et al., 2006). PINK1, is a mitochondrial serine/threonine kinase, which plays a crucial role in viral infection. Upon viral infection, PINK1 inhibits the formation of YAP1/IRF3 complex, and positively regulates retinoic-acid-inducible gene-I (RIG-I) which triggers innate antiviral immune response (Figure 5; Zhou et al., 2019).

### Role of Hippo in Other Neurodegenerative Diseases

#### Retinal degeneration (RD)

Retinal degeneration (RD) is caused by deterioration of the retina due to progressive death of photoreceptor cells (Wert et al., 2014). Several Hippo pathway members have known roles and involved in retinal degeneration as listed in Table 1. Sodium hyaluronate induced retinal detachment model in MST knock out mice, shows MST-2 as key regulator of caspase-dependent death of photoreceptor cells resulting in loss of vision (Matsumoto et al., 2014). Studies conducted in RD mouse model have shown that Mueller’s glia gets highly activated upon loss of photoreceptor cells and that increases YAP and TEAD1 mRNA and protein levels (Hamon et al., 2017) (Table 1). Mutations in apical-basal polarity gene Crb (Crb2 KO mouse using Cre/loxP technology) exhibits Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) disease, which

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Table 1

| Name | Description |
|------|-------------|
| Crb | Apical-basal polarity gene |
| YAP | Transcriptional repressor |
| TSH | Homeotic gene |
| CRB | Apical-basal polarity gene |
| FOXO3a | Transcription factor |

Table 2

| Gene | Function |
|------|----------|
| Crb | Regulates cell polarity |
| YAP | Regulates cell survival |
| TSH | Regulates cell differentiation |
| FOXO3a | Regulates cell death |
| CRB | Regulates cell proliferation |
Sveinsson’s chorioretinal atrophy (SCRA) is an eye disease marked by bilateral chorioretinal degeneration. The disease exhibit characteristic progressive degeneration phenotype during late retinal development (den Hollander et al., 1999; Alves et al., 2013). In RD, the Hippo pathway and actin Capping protein inhibits the accumulation of F-actin. In Drosophila model, deregulation of Hippo pathway is associated with the loss of Capping protein and retinal degeneration of the adult fly (Brás-Pereira et al., 2011) (Table 1).

- Sveinsson’s chorioretinal atrophy (SCRA) is an eye disease marked by bilateral chorioretinal degeneration. The disease is caused by missense mutation in gene coding for TEAD1. Missense mutation in human TEAD1 reduces its ability to bind to YAP/TAZ and results in SCRA pathogenesis as seen in mice model (Kitagawa, 2007). A previous study conducted in human cell lines show that mutation in TEAD1 gene affects binding site of a retinal co-factor of TEAD1 and causes SCRA (Figure 5; Fossdal et al., 2004). YAP/TAZ-TEAD activity has also been found to be hyperactivated in patients with strong neurodegenerative phenotypes. (Hpo)/MST1/2, Warts (Wts)/LATS1/2, and downregulation of Yorkie (Yki)/YAP and Scalloped (Sd)/TEAD cause(s) various neurodegenerative disorders. The red arrows mark the association of Hippo target(s) with specific neurodegenerative disorders. AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease; PD: Parkinson’s disease; SMA: spinal muscular atrophy.

**Hippo Pathway Members as Putative Therapeutic Targets**

Neurodegenerative disorders are heterogeneous group of disorders characterized by reduced size of brain, which results in loss of cognitive and/or motor function(s). These neurodegenerative disorders are associated with lots of morbidity and puts an enormous burden on the society. Thus, there is a desperate need for development of reliable therapeutic strategies. One of the challenges is the lack of validated therapeutic target(s). Cellular therapies offer great promise in this aspect, however, they face obstacles like dealing with neurons that are post-mitotic in nature, and do not possess regenerative potential. An alternative solution for neurodegeneration is to screen for agents that block or prevent neuronal cell death. Blocking cell death machinery is known to have adverse effects, and therefore there is a need for other possible targets. Hippo pathway has been observed to be hyperactivated in patients with strong neurodegenerative disorders. This raises an important question of whether Hippo pathway or its targets can be utilized as the potential therapeutic targets to control progression of neurodegenerative disorders. Therefore, chemical inhibitors designed to modulate Hippo pathway or its target(s) that can block or delay neurodegeneration via inhibiting Hippo pathway directly or indirectly may serve as effective and reliable therapeutics in future (Schmidt-Erfurth and Hasan, 2000; Oku et al., 2015; Qu et al., 2018). Several chemical inhibitors have been identified to modulate Hippo signaling levels in cancer. However, these drugs could also potentially be repurposed to treat neurodegenerative disease as loss-of-function of Hippo signaling causes over proliferation, which result in cancers while gain-of-function of Hippo signaling results in cell death and neurodegeneration (Figure 6) as observed in AD, ALS and other neurodegenerative diseases.
Thus these chemical inhibitors of Hippo signaling can be a valuable resource for downregulating Hippo signaling, which can block neurodegeneration.

Hippo pathway can be inhibited by using these chemical inhibitors (Schmidt-Erfurth and Hasan, 2000; Oku et al., 2015; Qu et al., 2018). The chemical inhibitors that target various components of Hippo pathway and are effective in treating growth related or neurodegenerative diseases with their mechanism of action are summarized in Table 2. Currently, there are three possible approaches for directly inhibiting Hippo pathway, viz., 1. Inhibition of Hpo/MST1/2 kinase (Fan et al., 2016; Qu et al., 2018), 2. Alteration of Yki/YAP localization (Barsyte-Lovejoy et al., 2014), and 3. Inhibition of Yki-Sd/YAP-TEAD interaction (Schmidt-Erfurth and Hasan, 2000; Jiao et al., 2014; Zhang et al., 2014; Nouri et al., 2019).

Alternatively, several small molecule inhibitors have been reported which target(s) other pathway components that interact with Hippo pathway (Oku et al., 2015) for example kinase inhibitors, which target Src family kinase, EGFR, MEK which interact with Hippo signaling (Lin et al., 2015; Oku et al., 2015). Table 2| Chemical inhibitors of Hippo target genes may serve as putative therapeutic targets

| Inhibitor | Target/mechanism of action | Diseases | Model system | References |
|-----------|-----------------------------|----------|--------------|------------|
| XMU-MP-1 | MST1/2 inhibitor, blocks kinase activity and in turn activates downstream YAP | Repair and regeneration in liver injury | Mouse | Fan et al. (2016) |
| YAP-TEAD inhibitor 1 (peptide 17) | YAP-TEAD inhibitor blocks YAP-TEAD complex formation | Hepatocellular carcinoma | Mouse and cell line (BEL-7404) | Zhang et al. (2014) |
| Verteporfin | YAP-TEAD inhibitor, photodynamic agent | Age-related macular degeneration, neovascularization | Schmidt-Erfurth and Hasan (2000); Al-Moujahed et al. (2017) |
| Super-TDU | YAP-TEAD inhibitor | Cancer | Cell lines (H1299 and MDA-MB-231) | Jiao et al. (2014) |
| CA3 (CIL56) | YAP nuclear translocation affected | HD | Mouse | Song et al. (2018) |
| (R)-PFI 2 hydrochloride | YAP nuclear translocation affected | HD | Mouse | Barsyte-Lovejoy et al. (2014) |
| Sphingosine-1-phosphate (S1P) | YAP nuclear translocation affected | Sphingosine-1-phosphate (S1P) | Mouse | Mao et al. (2016); Mueller et al. (2018) |
| LPA- synthesized from phosphatidic acid or lysophosphatidyl choline | YAP nuclear translocation affected | LPA - synthesized from phosphatidic acid or lysophosphatidyl choline | iPS cell culture | Mao et al. (2016) |
| dCTB | YAP nuclear translocation affected | dCTB | Rat | Xu et al. (2016) |
| Digitoxin | YAP nuclear translocation affected | Digitoxin | Congestive cardiac insufficiency, heart failure | Sun et al. (2012); Xu et al. (2016); Huang et al. (2017) |
| Flufenamic acid | YAP nuclear translocation affected | Flufenamic acid | NSAIAD | Pobbi et al. (2015) |
| CGP3466B | YAP nuclear translocation affected | CGP3466B | Traumatic brain injury | Liang et al. (2017) |
| Desatinib | BCR ABL inhibitor | Desatinib | ALL/CML | Rosenbluh et al. (2012); Taccioli et al. (2015) |
| Doxetinib | B1 adrenergic receptor agonist | Doxetinib | Cardiac decompensation, coronary artery disease | Bao et al. (2011) |
| Dimethylfumarate | Nrf2 cysteine covalent modification | Dimethylfumarate | Relapsing remitting multiple sclerosis | Toyama et al. (2018) |
| Erlotinib | EGFR inhibitor | Erlotinib | NSCLC, metastatic pancreatic cancer | Hsu et al. (2016) |
| Fluvastatin | HMGI-CoA reductase | Fluvastatin | Atherosclerosis, hypercholesterolemia | Sorrentino et al. (2014); Oku et al. (2015) |
| Gefitinib | EGFR inhibitor | Gefitinib | Metastatic non-small cell lung cancer | Xu et al. (2017); Lee et al. (2019) |
| Losmapimod | p38 MAPK inhibitor | Losmapimod | Type II diabetes | Yeung et al. (2018) |
| Melatonin | MT1/2 receptors agonist | Melatonin | Sleeplessness | Lo Sardo et al. (2017); Zhao et al. (2018) |
| Metformin | AMPK activator; mitochondrial complex I inhibitor | Metformin | Type II diabetes | Wang and Wang (2016) |
| Pazopanib | c-KIT, FGFR, PDGFR, VEGFR receptors inhibitor | Pazopanib | Advanced renal carcinoma, advanced soft tissue carcinoma | Davidson and Secord (2014); Oku et al. (2015) |
| Trametinib | MEK1/2 inhibitor | Trametinib | Metastatic melanoma | Lin et al. (2015) |

This table lists the chemical inhibitors which target the different members of the Hippo pathway. It is split into two sections – direct (upper part) and indirect inhibitors (lower part). Albin: Ablaseon murine leukemia; AMPK: 5’ adenosine monophosphate-activated protein kinase; BCR: breakpoint cluster region protein; BCR-ABL: Philadelphia chromosome; EGFR: epidermal growth factor receptor; FGF: fibroblast growth factors; HD: Huntington’s disease; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; Hpo/MST1/2: hippo; MAPK: mitogen-activated protein kinase; MEK1/2: mitogen-activated protein kinase kinase 1/2; PDGF: platelet-derived growth factor; TEAD: TEA domain protein; VEGF: vascular endothelial growth factor; YAP: yes associated protein.
al., 2015; Hsu et al., 2016; Wang et al., 2016; Xu et al., 2017; Yeung et al., 2018; Lee et al., 2019) (Table 2). Other examples include inhibitors against Melatonin signaling, Wnt pathway, G-protein coupled receptors, mevalonate pathway which can also inhibit Hippo pathway (Bao et al., 2011; Rosenbluh et al., 2012; Davidson and Secord, 2014; Sorrentino et al., 2014; Oku et al., 2015; Taccioli et al., 2015; Lo Sardo et al., 2017; Toyama et al., 2018; Zhao et al., 2018) (Table 2). Many natural products have also been tested and found effective in alleviating diseases such as AD (Deshpande et al., 2019). A soy protein Lunasin, acts as a neuroprotective agent that can block AP2, mediated neurodegeneration in AD by downregulated JNK signaling (Sarkar et al., 2018; Deshpande et al., 2019). JNK and Hippo signaling act in a positive feedback loop mechanism (Irwin et al., 2020). Thus, the role of natural product(s) as putative therapeutic targets also holds immense potential in finding cures for neurodegenerative disorders.

The rationale of this kind of studies is to extend the information from the bench to the bedside. Understanding the molecular genetic mechanisms of a disease will allow us to identify the members of signaling pathways which exhibit aberrant signaling in a disease. Our understanding is further expanded from the chemical screens results, which will help in identifying chemical inhibitors that may block function of the signaling pathway members, for example, Hippo signaling in AD. These studies will have significant bearing on finding cures since potential therapeutic targets can be first tested in animal models (pre-clinical), followed by patient cell lines and then expanded to clinical trials. This bench to bedside modular approach to finding therapeutic targets holds immense potential as it cuts down the time and excess expenditure.

Conclusion

Although the relationship between cancer and neurodegenerative disorders is complicated but there are some common connecting links. Interestingly, Hippo signaling pathway can link the two important maladies like cancer and neurodegenerative disorders, which represent opposite ends of a spectrum. On one end of the spectrum is abnormal cell proliferation observed in cancer and on the other end there is abnormal cell death, the hallmark of neurodegenerative disorders. This further resonates with the existing notion that those who suffer with cancer generally have a reduced risk of developing a neurodegenerative disorder(s). Furthermore, patients undergoing chemotherapy regimen for cancer have also demonstrated cognitive impairment.

Since Hippo pathway has been discovered, extensive research has been conducted to study the role of Hippo pathway in development, growth, diseases and in other different contexts. Thus, Hippo exerts profound effects on cellular homeostasis. We understand that activation of Hippo signaling causes cytoplasmic sequestration of Yki/YAP/TAZ, which results in restricted growth response and apoptosis. Alternatively, through non-canonical pathway, YAP interacts with p73 inside the nucleus to trigger apoptosis. More components of Hippo pathway, regulatory mechanism and its relatedness to diseases still need to be elucidated. Our current understanding about the exact regulation and molecular mechanism of proper functioning of Hippo pathway associated with the neurodegenerative disorders is far from complete.

Multiple chemical inhibitors that block function of various components of the Hippo signaling pathway have been identified. Interestingly, majority of these studies emphasize on regulating the cell proliferation aspect of the Hippo signaling pathway. However, with emerging role of Hippo in neurodegenerative disorders, all these candidates can be tested for their efficacy in neurodegenerative disorders. These strategies will help in the development of effective and reliable therapeutic targets with the potential to block, suppress, or delay the onset of diseases.

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