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Journal of Cellular Immunology Review Article

The Hippo Pathway, Immunity, and Cancer: An update

Helena J. Janse van Rensburg[1#*], Zaid Taha[2#]

[1]Department of Medicine, University of Toronto, Toronto, Ontario, M5S 3H2, Canada

[2]The Ottawa Hospital Research Institute, Ottawa, Ontario, K1H 8L6, Canada

[#]Both authors contributed equally to this work

*Correspondence should be addressed to Helena J. Janse van Rensburg; ellen.jansevanrensburg@mail.utoronto.ca

Received date: July 15, 2020 , **Accepted date:** August 26, 2020

Abstract

The Hippo pathway has well-established roles in physiology and pathology. However, functions for the Hippo pathway in modulating interactions with the immune system have only recently been elucidated. In this review, we provide a brief update on our previous summary of the field. More specifically, we highlight literature that demonstrates a role for the Hippo pathway in modulating the anti-tumour immune response, primarily through acting on PD-L1. We continue to discuss Hippo pathway involvement in modulating inflammation, both sterile and in the context of pathogenic infection. We further review emerging evidence implicating Hippo pathway proteins in immune-related processes across species. Finally, we provide an update into the vital immune cell-intrinsic roles of the Hippo pathway core components and draw attention to opportunities for future study.

Keywords: Hippo pathway, Cancer, Immunology, Immunotherapy, Inflammation, MST1/2, LATS1/2, YAP, TAZ, PD-L1

Abbreviations: AKT: Protein kinase B; ALK: Anaplastic Lymphoma Kinase; AMP: Antimicrobial Peptide; BIK1: Botrytis-induced Kinase 1; CagA: Cytotoxicity-associated immunodominant antigen; CorA: Magnesium transport protein CorA; CYR61: Cysteine-rich angiogenic inducer 61; DAZAP2: DAZ-associated Protein 2; DCLK1: Doublecortin-Like Kinase 1; EMT: Epithelial-to-mesenchymal Transition; ETS1: Protein C-ets-1; FOXP3: Forkhead box protein P3; HPV: Human Papillomavirus; HSCs: Hepatic Stellate Cells; IκB: NFκB inhibitor; IFN: Interferon; IL: Interleukin; IRAK1: Interleukin-1 Receptor-associated Kinase 1; IRI: Ischemia-reperfusion Injury; ISLR: Immunoglobulin Superfamily containing Leucine-rich Repeat protein; JAK: Janus Kinase 1; LATS1/2: Large Tumour Suppressor Kinases ½; MAP4K4: Mitogen-activated Protein Kinase Kinase Kinase Kinase 4; miR-130a: MicroRNA-130a; MFN2: Mitofusin-2; MnMOB1: *Macrobrachium nipponense* homolog of MOB1; MOB1: MOB kinase activator 1; MST1/2: Mammalian Ste20-like kinases ½; NFκB: Nuclear Factor κB; NrxIV: Neurexin 4; PAMP: Pathogen-associated Molecular Pattern; PD-1: Programmed Cell Death 1; PD-L1: Programmed Cell Death 1 Ligand 1; PDGF: Platelet-derived Growth Factor; PI3K: Phosphatidylinositol 4,5-bisphosphate 3-kinase; ROS: Reactive Oxygen Species; SeNPs: Selenium Nanoparticles; SPON2: Spondin-2; STAT: Signal Transducer and Transcription Activator; TCTP: Translationally-controlled Tumour Protein; TEADs: TEA Domain family members; TNFα: Tumour Necrosis Factor α; TRAF6: TNF Receptor-associated Factor 6; VGLL4: Transcription cofactor vestigial-like protein 4; Yki: Yorkie

Introduction

Signaling pathways form the fundamental basis of physiology and pathology. The Hippo signaling pathway plays physiologic roles in organ size control as well as tissue regeneration/repair, while aberrant Hippo signaling has been implicated in fibrotic disease and various types of cancer [1]. It is well-established that the Hippo pathway core components (mammalian Ste20-like kinases 1/2 (MST1/2), large tumour suppressor kinases 1/2 (LATS1/2), yes-associated protein (YAP) and WW domain-containing transcription regulator 1 (WWTR1 aka. TAZ) regulate cell proliferation, motility, epithelial-mesenchymal transition, and cell "stemness" among other phenotypes [2-4]. In contrast, the finding that these proteins are involved in modulating immune responses marks a fairly recent

development in this field. This is a topic that we have previously reviewed in depth elsewhere [5]. However, since the publication of our previous review paper, the pace of advancement in this area has continued to hasten, necessitating a brief "update". Here, we highlight some of the most notable findings from the last two years in the study of the Hippo signaling pathway and its role in immunity.

The Hippo Pathway Modulates the Anti-cancer Immune Response through PD-L1

Building upon literature defining the Hippo components as tumour suppressors and oncogenes in cancer, some of the earliest papers investigating the interaction between the Hippo pathway and the immune system offered an extension of the YAP/TAZ oncogenic functions into immune evasion. These findings uncovered a role for tumour cell-intrinsic Hippo pathway activity in shaping the anti-cancer immune response. Indeed, we and others identified programmed cell death 1 ligand 1 (PD-L1) as a Hippo pathway target gene in human cancer cells [6-10]. More recently, additional regulators of PD-L1 expression have been characterized that modify PD-L1 expression indirectly by acting on the Hippo pathway. In a kinome-wide screen for regulators of LATS1/2, Nouri et al. found that the receptor tyrosine kinase anaplastic lymphoma kinase (ALK) suppresses LATS1/2 activity, thereby promoting YAP nuclear localization, transcriptional co-activation of PD-L1, and T cell apoptosis in co-culture experiments [11]. Similarly, Zhang et al. recently reported that metformin treatment inhibits YAP and downregulates PD-L1 expression in colorectal cancer cell lines [12]. Doublecortin-like kinase 1 (DCLK1), a protein kinase induced by interleukin-17 (IL-17) in pancreatic cancer, has also been shown to enhance PD-L1 expression through YAP, while treatment with the YAP-TEA domain family members (TEADs) inhibitor verteporfin suppressed this effect [13]. Finally, two small molecule immune checkpoint inhibitors, TPFS-201 and TPFS-202, were recently found to downregulate PD-L1 expression at the transcriptional level potentially through the Hippo pathway [14]. Interestingly, after observing downregulation of *PD-L1* mRNA by TPFS compounds in human but not mouse cell lines, Zhang et al. hypothesized that known species-specific regulation of PD-L1 by Hippo signaling might be involved [6]. Deletion of a TEAD-response element in the human *PD-L1* promoter suppressed downregulation of PD-L1 by TPFS-202 supporting this model. Thus, the Hippo pathway facilitates regulation of PD-L1 by multiple other signaling proteins and may offer therapeutic opportunities for indirect inhibition of PD-L1 using repurposed or novel agents.

While these studies all support a role for YAP/TAZ in upregulating PD-L1 expression, Wu et al. have recently discovered some nuance in this interaction [15]. While characterizing transcription cofactor vestigial-like protein 4 (VGLL4) as a positive transcriptional regulator of PD-L1 in response to interferon γ (IFNγ), the authors tested the role of YAP in this interaction, as YAP has been shown to negatively regulate VGLL4 through microRNA-130a (miR-130a) [16]. Interestingly, the authors found that wild-type YAP or constitutively active YAP-5SA overexpression led to decreased VGLL4 levels and suppressed IFNγ-induced PD-L1 upregulation. They observed a similar effect with overexpression of a miR-130a mimic. Despite suppressing IFNγ-inducible PD-L1 expression, the authors confirmed that overexpression of YAP-5SA enhanced basal *PD-L1* mRNA levels in A549 lung cancer cells, consistent with previous studies. Finally, the authors unexpectedly found that YAP also suppresses inducible PD-L1 upregulation in response to tumour necrosis factor α (TNFα) treatment. Thus, it is possible that the Hippo pathway effectors act as positive or negative regulators of PD-L1 depending on the specific transcriptional factors contributing to its expression, and, perhaps, that this interaction may change depending on the larger context of the tumour microenvironment in which this regulation is occurring.

When compared to the literature characterizing the relationship between the Hippo pathway and PD-L1, admittedly less work has been undertaken investigating potential interactions between programmed cell death 1 (PD-1), the receptor for PD-L1, and the Hippo pathway. Pu et al. recently set out to explore this topic in pancreatic cancer [17]. The authors identified a correlation between high cancer cell-intrinsic PD-1 expression and shorter overall survival in a tissue microarray. Overexpression of PD-1 in the MIA-PaCa-2 pancreatic cancer cell line enhanced cell proliferation, clone formation, and xenograft tumour formation *in vivo*, while knockdown of PD-1 in BxPC-3 cells had the opposite effects on these phenotypes. The authors used RNA sequencing to explore the molecular mechanisms underlying these effects and identified the Hippo pathway as being regulated by PD-1. Using immunoprecipitation-LC-MS/MS, they determined that PD-1 interacts directly with the Hippo pathway adaptor protein MOB kinase activator 1 (MOB1). Overall, the authors proposed a model in which PD-1 directly binds to MOB1, leading to reduced LATS1 activity and enhanced YAP transcriptional co-activation of downstream gene targets. Notably, PD-L1 was highly expressed by the cancer cell lines studied and blockade of the PD-1/PD-L1 interaction with antibodies disrupted the effect of PD-1 on MOB1, LATS1 and YAP. These findings provide compelling new insight into the importance of the Hippo pathway in modulating PD-1/PD-L1 signaling and point to complexity in the molecular network in which these pathways interact.

The Hippo Pathway and Inflammation

Interestingly, the interaction between Hippo signaling and immune processes is not a unidirectional relationship. Rather, Hippo signaling may be modulated by physiological and pathological processes involved in inflammation and resolution. Under normal circumstances, there is basal signaling through the Hippo pathway to maintain tissue homeostasis. While normally transient and aimed at tissue repair, persistent activation of inflammatory programs can stray from regeneration towards malignant capacity. In this section we summarize recent work highlighting the involvement of Hippo signaling in tissue inflammation.

Gut epithelial injury and repair

Kwon et al. have recently demonstrated the role of Yorkie (Yki) in the process of intestinal repair and regeneration following epithelial damage [18]. Using pathogenic bacteria, bleomycin, or dextran sulphate sodium treatments, the authors were able to gain insight into the intricacies of the process of intestinal repair in *Drosophila*. It was discovered that Hippo signaling is modulated following midgut epithelial injury and inflammation, leading to an upregulation of translationally-controlled tumour protein (TCTP), a downstream target of Yki required in the process of resolution. Similar findings by Xu et al. and Romera-Hernandez et al. echo the sensitivity of Hippo signaling to inflammation, though the intricacies of these mechanisms appear to differ, likely owing to the differences in investigational design and the models used [19,20]. Utilizing *in vitro* and *in vivo* murine models, Romera-Hernandez and colleagues reveal that intestinal epithelial crypt cell damage may be repaired by a newly understood mechanism involving Group 3 innate lymphoid cells, whose cytokine secretion profiles suppresses Hippo signaling through SRC family kinases, thereby activating YAP1 [20]. Xu and colleagues establish a parallel mechanism in intestinal regeneration and tumorigenesis in murine models and human patient samples, whereby inflammation triggers the oncogenic transcription factor protein C-ets-1 (ETS1) in stromal cells [19]. A downstream signaling cascade induces the secretion of immunoglobulin superfamily containing leucine-rich repeat protein (ISLR) whose inhibitory effects upon Hippo signaling in neighbouring epithelial cells leads to YAP activation, cell proliferation, and subsequent tissue regeneration or tumorigenesis. Importantly, these findings highlight the fine line of physiology *vs.* pathology that Hippo signaling may play in the context of inflammation; its regenerative role may very well overshoot and result in neoplasia, as such mechanistic findings made by multiple groups have been correlated to patient irritable bowel syndrome samples, minor gut inflammatory injury, and colorectal adenocarcinomas [19,21].

Inflammation and fibrosis

As discussed in our prior review, Hippo signaling has several implications in the pathogenesis of tissue fibrosis [5]. More recent evidence further supports this involvement in the context of alveolar regeneration, and possible subsequent fibrosis, following lung inflammation. In a murine model challenged with *Streptococcus pneumoniae*, mice expressing lower levels of YAP/TAZ exhibited reduced levels of alveolar epithelial type II cells, prolonged inflammatory responses, and development of fibrotic tissue [22]. Several groups have suggested that the alleviation of the inflammatory response and subsequent fibrotic scarring is, in part, due to the ability of YAP/TAZ to upregulate NFκB inhibitor (IκB), which would ultimately suppress nuclear factor κB (NFκB)-induced inflammation [22,23]. Similar observations pointing to the anti-inflammatory and anti-fibrotic nature of YAP/TAZ have been made in the context of hepatic ischemia-reperfusion injury (IRI) by Liu et al. [24]. In this work, the authors assess the impact of sterile liver inflammation on murine *in vivo* and *in vitro* hepatocyte culture following induced IRI or pharmacologic activation or inhibition of YAP, respectively. In addition, 60 patient biopsies from orthotopic liver transplantations were assessed following a 2-13 hour period of induced ischemia-reperfusion. The sum of these investigations demonstrated that YAP activation prevented hypoxia-reoxygenation stress, enhanced anti-oxidative damage gene expression, and preserved the histology and hepatocellular function of patient biopsies.

Further work has uncovered a contrasting role for YAP/TAZ in pancreatic acinar cells. Liu et al. have shown that disrupting Hippo signaling induced pancreatic acinar cells to secrete several pro-inflammatory factors, which activated the surrounding stroma to enable proliferation and consequent metaplasia [25]. The suppression of Hippo signaling did not induce cell-autonomous proliferative effects, rather, it primed the acinar cells to vicinal proliferative stimuli.

The anti-inflammatory role of Hippo signaling includes the heart. For example, Ouyang et al. indirectly suggested a similar anti-inflammatory role of YAP by demonstrating an alleviation of viral myocarditis-induced inflammation and fibrosis following melatonin-induced MST1 inhibition [26]. The work of several other groups highlighting the regulation of Hippo signaling in cardiac tissue regeneration has been recently reviewed [27].

Although several studies suggest an anti-inflammatory and pro-resolution role for YAP/TAZ, other literature suggests that the opposite may also be true. For example, Yu *et al.* have identified a pro-inflammatory function of YAP/TAZ in hepatic fibrosis. In a murine model of

hepatic injury induced by carbon tetrachloride, levels of activated YAP were significantly elevated in fibrotic tissue [28]. Given that the role of hepatic stellate cells (HSCs) in liver fibrosis is well understood, it was found that the genetic or pharmacologic inhibition of YAP led to led to the suppression of HSC proliferation, activation, and migration of HSCs, ultimately reverting the pro-fibrotic phenotype. Mooring and colleagues make similar observations, though their findings are less focused on stromal HSCs, and more focused on cell-intrinsic YAP signaling [29]. In similar mouse models of carbon tetrachloride-induced hepatic damage, the authors found that hepatocytes exposed to oxidative stress resulted in the secretion of a number of fibrosis-promoting compounds, including collagen, platelet-derived growth factor (PDGF), and TNFα. Interestingly, YAP-expressing hepatocytes uniquely secreted cysteine-rich angiogenic inducer 61 (CYR61), which was found to be a key chemokine controlling liver fibrosis in both preclinical models as well as patient samples of high-grade non-alcoholic steatohepatitis. Additionally, Hagenbeek and colleagues have identified a previously uncharacterized link between TAZ upregulation in patient liver samples and substantial proinflammatory myeloid cell infiltration [30]. It was revealed for the first time that TAZ-hyperactive liver tumours express a distinct transcriptional signature from YAP-hyperactive liver tumours, the latter of which is less associated with a proinflammatory cytokine secretion profile.

Neuronal inflammation

Inflammation is often a major driving factor in the etiology of neurodegenerative disease. Thus, it is rather unsurprising that Hippo signaling has been implicated in neuronal inflammation and neurodegeneration. Recently, Hou et al. have shown that the ability of mitofusin-2 (MFN2), a member of the GTPase family of proteins, to regulate or alleviate ER stress may attenuate inflammation-mediated neuronal dysfunction [31]. The intricacies of this mechanism converged upon the induction of YAP by MFN2, enabling the activation of anti-oxidative and anti-inflammatory programs. Furthermore, inflammation following IRI as a result of cerebrovascular events has been recently experimentally targeted by selenium nanoparticles (SeNPs) [32]. It was found that *in vitro* treatment of rat or human cells with SeNPs led to elevated mRNA levels of YAP1, which is associated with reduced neuronal susceptibility to reactive oxygen species. It is most interesting to see the expression signatures of Hippo pathway components being used in this study as a surrogate biomarker for a treatment efficacy. Further literature, over the past decade, on the role of Hippo signaling in neuroinflammation and neurodegenerative diseases may be found reviewed by Cheng *et al.* [33].

Due to the complexity of Hippo signaling and its many intricacies, there is a large number of discrepancies in the literature surrounding its role as a pro- or anti-inflammatory pathway. Naturally, a primary objective of Hippo signaling is regulating and maintaining tissue integrity and homeostasis. Therefore, depending upon the investigational design, the models used, the induction of disease or injury, and the consideration of cell autonomous *vs.* stromal effects, the contributions of Hippo signaling to tissue inflammation appear to vary. It is important to note that much of the literature utilizes induced models of tissue injury, such as sterile inflammation by IRI. On the other hand, models of pathogen-induced injury are also frequently employed, though these may have multiple immune impacts which may not be entirely accounted for in the mechanisms being studied. These nuances may, in part, explain conflicting findings within the field and should be carefully considered when interpreting the literature.

The Hippo Pathway and Host-pathogen Immune Conflict

As a modulator of tissue homeostasis, Hippo signaling has been found to contribute towards the clearance of pathogenic infections. Fang et al. have recently put forth evidence of an alternative TAZ splice variant hypothesized to fine tune the cellular antiviral response [34]. This C-terminus truncated TAZ variant was shown to be induced by IFN type I in a negative feedback fashion to downregulate Janus kinase 1 (JAK)/signal transducer and transcription activator (STAT) signaling and prevent hyperactivation and autoimmunity. In addition to its role in regulating antiviral and antimicrobial responses, a subset of investigated pathogens have been shown to modulate Hippo signaling to promote their replication and survival [5]. For example, human papillomavirus (HPV) infections have been shown to alter LATS phosphorylation status, ultimately promoting cutaneous squamous cell carcinomas, especially in immunocompromised populations [35]. Furthermore, cervical cancers attributable to HPV infections express distinct genetic and epigenetic signatures that frequently involve alterations to Hippo component expression that Yang et al. have proposed may hold value for cervical cancer risk stratification [36]. As well, He et al. have shown that YAP1 hyperactivation in murine cervical epithelium represents a novel unconventional mechanism that increases susceptibility to high-grade HPV infection, persistence, and consequent carcinogenesis [37].

Interestingly, recent evidence suggests novel functions of Hippo pertaining to the biology of the re-emerging Zika virus [38,39]. Through gene silencing, Garcia et al. demonstrated that Zika virus replication in human fetal retinal pigment epithelial cells requires YAP/TAZ activation

[38]. *In vivo* investigation further demonstrated that Zika virus infection upregulates levels of phospho-Ser127-YAP in retinal and brain tissue, implying the potential hijacking of Hippo signaling by Zika virus. Indeed, whole genome DNA methylation profiling by a different group, using human neural progenitor cells, demonstrated that Zika virus infection alters DNA methylation status of several genes belonging to the Hippo pathway, including *WWTR1* (TAZ) [39]. Other groups have made similar observations detailing unique genetic or epigenetic signatures that involve distinct alterations to Hippo genes, following infection with hepatitis C virus [40], HPV [36], bluetongue virus [41], *Mycobacterium tuberculosis* [42], or Influenza A subtype H7N9 [43].

In addition to the participation of Hippo signaling in the host response to pathogenic infection, emerging evidence suggests that this signaling pathway may contrarily be hijacked by Ebola virus [44], Marburg virus [45], hepatitis C virus [46], *Legionella pneumophila* [47], *Toxoplasma gondii* [48], and as previously discussed, Zika virus [38], to promote pathogen replication and virulence. Consequences of pathogen-induced dysregulation of Hippo signaling included immune suppression, persistent inflammation, persistent infection, and neoplastic transformation.

Notably, there is a growing body of literature on the specific involvement of Hippo signaling in the context of *Helicobacter pylori* infection. In response to *H. pylori* infection of the gastric mucosa, it was found that induced nuclear translocation of YAP/TAZ activate multiple inflammatory programs through IL-1β, which ultimately contributes towards the gastric epithelial-to-mesenchymal transition (EMT) phenotype [49]. This mechanism has subsequently been shown to operate in both murine and human samples and was dependent upon LATS2 [50]. The inhibitory function of LATS2 upon YAP1 restricted *H. pylori*-induced EMT progression and retained the epithelial phenotype of the gastric mucosa. Furthermore, oncogenic *H. pylori* cytotoxicity-associated immunodominant antigen (CagA) protein (established to play a role in the etiology of gastric carcinogenesis) has been recently highlighted to engage the Hippo pathway, specifically YAP/TAZ, as part of its mechanism of EMT induction [50-53].

It is clear that the Hippo pathway, as a downstream regulator of tissue integrity and homeostasis, plays a role in the host-pathogen conflict response. Whether the involvement of Hippo is host-protective or pathogen-protective appears to be context-specific. Multiple inflammatory immune responses trigger or are triggered by Hippo signaling, while on the other hand pathogens such as Marburg virus [45] or *L. pneumophila* [47], seize control over intricate molecular mechanisms to promote their virulence. Currently, the clinical relevance of the noted involvement of Hippo signaling in the aforementioned pathological events is unclear and warrants further investigation, which may reveal opportunities for novel clinical approaches for the prevention and management of these infectious diseases.

The Hippo Pathway and the Immune System Across Species

While the vast majority of the aforementioned studies utilized human cell lines, murine models or *Drosophila* to study the Hippo pathway in immunity, studies investigating this relationship in other species are also of particular interest. Considering our previously reported observation that TAZ immune-related transcriptional targets differ between human and mice, we have speculated that there are likely to be varying functions for the Hippo pathway across different species [6]. Interesting new functions for Hippo pathway homologs have been described in recent years. Hippo pathway components have been identified among differentially-expressed genes in a screen for genes uniquely regulated by H7N9 influenza A virus infection in chick embryo fibroblasts but not in human A549 lung cancer cells infected with the same virus or in chick embryo fibroblasts infected with other avian influenza subtypes [43]. Yang et al. have identified a mediating function for the Hippo pathway downstream of DAZ-associated protein 2 (DAZAP2) in the immune response to *S. aureus* and *V. parahemolyticus* infection in the Chinese mitten crab (*Eriocheir sinensis*) [54]. While exploring the mechanisms underlying enhanced susceptibility to infection in *DAZAP2*-knockdown crabs, the authors performed a yeast-2-hybrid screen and discovered DAZAP2 directly binds to the Salvador Hippo pathway adaptor protein. The authors further showed that DAZAP2 stimulates Hippo pathway activity and that knockdown of Hippo suppressed antimicrobial peptide (AMP) expression through Yki and Cactus. A similar role has been described for the Hippo pathway adaptor protein MOB1 homolog (MnMOB1) in the oriental river prawn (*Macrobrachium nipponense*) [55]. MnMOB1was upregulated in response to bacterial challenge while MnMOB1 knockdown suppressed bacterial challenge-induced upregulation of AMPs. Although the Hippo pathway has already been implicated in nucleic acid sensing within the zebrafish immune response [56], Flinn *et al.* have identified a potential immune-related role for Yap in this species in regulating macrophage abundance in the response to cardiac cryoinjury [57]. Finally, the Hippo/STE20 homolog mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4) has been found to modulate immune responses in the plant genus *Arabidopsis* [58]. Loss of MAP4K4 rendered plants susceptible to *Pseudomonas syringae* infection despite protective pre-treatment with flagellin. Mechanistically, the authors of this study showed that MAP4K4 directly binds to,

phosphorylates, and stabilizes botrytis-induced kinase 1 (BIK1) thereby enhancing pathogen-associated molecular pattern (PAMP)-triggered reactive oxygen species (ROS) production. While certainly interesting, more work will be needed to understand the significance of these findings, and to place them in greater context. As many of these studies focus on single Hippo pathway components, further study will be necessary to clarify whether these phenotypes are mediated by canonical or non-canonical Hippo signaling in each of the respective organisms.

Immune Cell-intrinsic Hippo Signaling

The role of MST1 (*STK4)* in immune cell development, mobility, invasion, and functionality has been documented and comprehensively reviewed [5,59-63]. There is also wealth of clinical evidence citing distinct clinical presentation of patients with congenital mutations in this gene. Nonetheless new studies continue to offer novel insights into previously uncharacterized roles for both canonical and non-canonical Hippo signaling in host immunity.

More recently, Huang et al. emphasize the potential of targeting the Hippo pathway for pregnancy-related complications by reviewing the dialogue between Hippo signaling, immunity, and maternal-fetal interface [64]. More specifically, Liu et al. have demonstrated the importance of MST1/2 at the level of maternal-fetal immunity in the context of pre-eclampsia [65]. The authors revealed a striking positive correlation between 14 severe pre-eclampsia placentas and their high levels of MST1/2 mRNA and protein, and low levels of YAP/TAZ, findings which were similarly observed by Sun and colleagues [66].

In *Drosophila*, Khadilkar and Tanentzapf have shown that septate junctions are key driving factors in hematopoiesis, and cellular immunity following infection [67]. It was found that components of these septate junctions, Magnesium transport protein CorA (CorA) and Neurexin 4 (NrxIV), promote Hippo signalling to regulate immune cell differentiation. Stoner and colleagues similarly reveal the importance of MST1 through the molecular dissection of myelodysplastic syndrome and myeloproliferative neoplasm [68]. In these haematologic neoplasms as well as in murine models, the clinically prominent del(20q) was shown to downregulate *STK4* and yielded uncontrolled inflammation and disease progression through the interleukin-1 receptor-associated kinase 1 (IRAK1)-TNF receptor-associated factor 6 (TRAF6)-NFkB axis [68,69].

MST1 continues to be shown as a requirement for the complete development and maturation of B lymphocytes and was recently shown to be necessary for trafficking and homing of follicular B cells [70]. Bagherzadeh Yazdchi et al. moreover reveal that MST1 is required for long-term humoral immunity [71]. Authors showed that MST1-deficient mice yielded hyperactive germinal centers and overproduced plasma cells, although the resultant high levels of IgG1 were found to be of poor affinity. These data suggest for the first time that MST1 plays a critical role in ensuring the rigor of affinity maturation, implying that MST1-deficient patients may not benefit from the full extent of vaccines.

In T lymphocytes, it was revealed that MST1 acts as part of the apoptotic signaling cascade [72]. Authors utilized Jurkat T cells and demonstrated that through specific pharmacologic inhibition of phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (AKT) signaling, MST1 activation facilitated the executioner caspase cascade. These findings suggest that MST1 may play a role in the physiological negative selection of auto-reactive T lymphocytes, as well as a potential role in the therapy of lymphoid malignancies. Very interestingly, Stampoulouglou et al. have characterized a novel suppressive role of YAP1 upon T lymphocyte function [73]. This immunosuppressive effect, previously thought only to be due to the relationship between YAP1 – Forkhead box protein P3 (FOXP3) [74] or IL-2 - STAT5 [75] in T_{reg} function, appears to arise from a $CD4^+$ or $CD8^+$ T cell intrinsic negative feedback loop. The authors discovered that YAP1 is upregulated in T cells isolated from murine spleens following activation of CD4 or CD8 clusters, leading to reduced viability, differentiation, and function. Most importantly, YAP1 appeared to act as a global regulator of T cell activity in the tumour microenvironment, positively correlated with tumour volume in multiple syngeneic tumour models, and exhibited an inverse relationship with overall tumour infiltrating lymphocyte count. These findings were echoed by survival data procured from The Cancer Genome Atlas [73]. It is curious that Li and colleagues determined that macrophage-intrinsic levels of YAP1 promote polarization towards the anti-inflammatory and suppressive M2 phenotype [76]. Although the relationship between YAP1 and macrophage M2 polarization was discovered in the context of liver injury, it would be reasonable to hypothesize that a similar mechanism may also be operative alongside YAP1-high lymphocytes [73], all of which would contribute towards an immunosuppressive tumour microenvironment.

In addition to the lymphocyte-intrinsic role of the Hippo pathway in modulating immune responses, tumour-intrinsic Hippo signaling has been shown to recruit tumour associated macrophages. Matricellular protein Spondin-2 (SPON2) plays a key role in the facilitation of immune interfaces [77]. SPON2 has been shown to upregulate F-actin within hepatocellular carcinoma cells, which leads to activation of Hippo signalling through mechanotransduction, and downstream recruitment

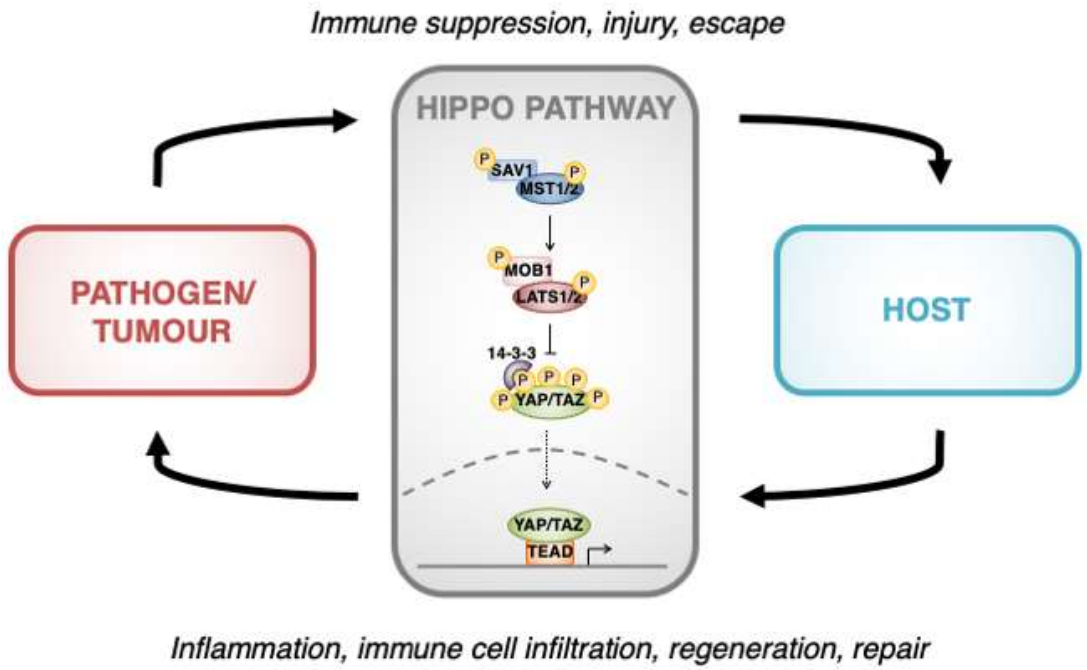

Figure 1: The Hippo pathway mediates interactions between host and pathogens/tumours across species by modulating immune responses. In the context of pathogenic infection or tumourigenesis, Hippo signaling determines pathogen/tumour cell survival in a host by affecting immune suppression and inflammation. In turn, Hippo signaling functions within immune and other cell types to affect the immune response against these pathological stressors.

of pro-inflammatory M1-polarized macrophages. In *Drosophila*, the Taiman protein engages with Yki to promote proliferation and invasion of tumour cells into adjacent tissue [78]. Interestingly, this inter-tissue invasion is mediated in part by Yki-induced secretion of innate immunity ligands that prompt apoptosis in vicinal cells. This finding demonstrates that aberrant Hippo signaling may be hijacked not only for its proliferative potential, but also for its ability to confer competitive cell killing by inducing pro-apoptotic secretory programs. Finally, at the intersection between innate and adaptive immunity, MST1/2 have been shown to play a critical role in the development, maturation, and function of $CD8\alpha^+$ dendritic cells [79]. These dendritic cells are especially specific towards antigen presentation for $CD8^+$ T lymphocytes and are therefore crucial for cell-mediated responses to non-self-immune challenges. Du et al. characterize the molecular pathways underlying $CD8\alpha^+$ dendritic cell function. Through computational algorithms and gene ablation studies, it was found that MST1/2 kinases play a dual role in $CD8\alpha^+$ dendritic cell development through orchestrating metabolism as well as cytokine secretion and NFkB inflammatory signaling. Thus, endogenous Hippo proteins function within multiple immune cell types, likely playing multi-directional roles in regulating immune processes.

Conclusion

Recent years have brought enticing new insights into our understanding of the various functions of the Hippo pathway in immune responses across development, pathologies, and species. Further advancement and clarification should be expected from this field in the years to come. In this review, we have highlighted key findings from the last two years and suggest interested readers explore in-depth reviews on specific topics for further study [60,62,63,80-84].

Conflicts of Interest

The authors have no conflicts of interest to declare.

Acknowledgments/Funding Statement

This work was supported by a generous contribution from Dr. Chandrakant Tayade and the MD/PhD Program at Queen's University in Kingston, Ontario.

Authorship Statement

Z.T. and H.J.J.V.R. contributed equally to researching, writing, and editing this work.

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