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Forum

Hippo Signaling in the Immune System

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Hippo signaling has a pivotal role in organ size control, tissue regeneration, and cancer. Recent studies have demonstrated critical functions of Hippo signaling in cancer immunity, innate immune responses against pathogens, and autoimmune diseases, refreshing our understanding of the implications of this pathway in the context of disease and therapy design.

Hippo Signaling in Cancer Immunity

The Hippo pathway has evolutionarily conserved roles in limiting the size of organs [1]. It is a kinase cascade regulating transcriptional complexes in response to various upstream signals (Box 1). At the cellular level, the Hippo pathway inhibits cell proliferation and stemness, while promoting apoptosis in a cell autonomous manner. In mice, dysregulation of the Hippo pathway causes a marked increase in cell number and, thus, robust enlargement of organs and initiation of tumorigenesis.

Recent reports demonstrated critical roles of the Hippo pathway in cancer immunity. Contrary to its tumor-suppressor function, loss of *LATS1/2* was found to inhibit subcutaneous xenograft tumor growth in syngeneic mice by enhancing antitumor immunity [2]. *LATS1/2* knockout (KO) induces a type-I interferon response noncell autonomously in a manner dependent on the Toll-like receptor (TLR)-MYD88/TRIF pathway via secretion of nucleic acid-rich extracellular vesicles. By contrast, *LATS1/2* KO, *MST1/2* KO, as well as expression of active YAP in murine hepatocytes *in vivo*, recruit type II macrophages through the induction of cytokines CCL2 and CSF1, leading to the establishment of an immunosuppressive microenvironment (Figure 1A) [3,4]. Knockdown of CCL2 and CSF1 blocks macrophage recruitment and diminishes liver tumorigenesis due to clearance of YAP-active tumor-initiating cells by immunosurveillance [3]. These findings indicate that functions of the Hippo pathway in tumorigenesis are not confined to tumor cells, but instead involve modulation of the tumor immune microenvironment.

However, it is still unclear how seemingly opposite effects of *LATS1/2* KO in promoting or repressing cancer immunosurveillance can be reconciled. Oncogenic driving forces of distinct tumors might tip the balance between the tumor-promoting and tumor-suppressive effects of *LATS1/2* KO. In tumors driven by YAP activation, the profound cell autonomous effect together with anti-immunosurveillance functions might strongly promote tumorigenesis. However, in cancers driven by other growth-promoting pathways, the immune-stimulating functions of *LATS1/2* ablation might elicit an overall tumor-suppressive effect. In addition, the composition of immune cells and factors in a tissue context could be a determining factor in the immune response induced by *LATS1/2* KO. Thus, the experimental models used to study the Hippo pathway in cancer immunity could be critical.

Hippo Signaling in Innate Immunity

Innate immunity is the nonspecific first line of defense against foreign pathogens. While seemingly unrelated to growth control, innate immunity was recently reported as being regulated by the Hippo pathway. It was found that canonical Hippo signaling is activated upon infection in fat bodies, the *Drosophila* immune organ producing antimicrobial peptides, by the Toll-Myd88-Pelle (IRAK1 homolog) pathway due to inhibition of the Hippo phosphatase STRIPAK PP2A complex [5]. Thus, the antimicrobial response is enhanced through decreased expression of *Cactus* (the *IκB* homolog), a Yki target gene (Figure 1B). In mouse macrophages, infection by *Mycobacterium tuberculosis* also activates MST1/2 phosphorylation in a TLR2-IRAK1/4-dependent manner [6]. However, in this case, MST1/2 promotes innate immunity response independently of the canonical Hippo pathway downstream effectors by directly activating IRF3 (Figure 1B). Furthermore, Mst1/2 in myeloid cells could also promote direct killing of phagocytosed bacteria by inducing juxtaposition of phagosomes with reactive oxygen species (ROS)-producing mitochondria through Rac activation (Figure 1B) [7]. Taken together, the above studies reveal critical roles of the Hippo pathway in antibacterial immunity through several different mechanisms. How these mechanisms coordinate in different contexts still waits to be determined. Recent reports also demonstrated roles of YAP/TAZ in antagonizing the antiviral response through direct binding of IRF3 or TBK1 [8,9]. Thus, further clarification of the physiological roles and mechanisms of Hippo signaling in antiviral immunity is needed.

Hippo Signaling in Autoimmunity

An imbalance of T cell subsets, such as immunosuppressive regulatory T cells (T_{reg}) and inflammatory T_H17, has a key role in autoimmune diseases. Recently, investigations found that TAZ but not YAP enhances T_H17 differentiation but attenuates T_{reg} differentiation [10]. Mechanistically, TAZ coactivates the T_H17-defining transcription factor RORγt while

Box 1. The Hippo Pathway

The Hippo pathway is regulated by signals such as mechanical stress, G-protein-coupled receptor signaling, and cellular energy status (Figure I). When the Hippo pathway is active, MST1/2 (homologs of *Drosophila hippo*) phosphorylate SAV1, MOB1A/B, and LATS1/2 (*warts* homologs), which result in LATS1/2 kinase activation. Recent findings indicate that MAP4K family kinases could act in parallel to MST1/2 to activate LATS1/2. LATS1/2 then phosphorylate YAP/TAZ (*yorkie* homologs), thus causing their cytoplasmic retention mediated by scaffold protein 14-3-3, and degradation mediated by E3 ligase $SCF^{\beta\text{-}TRCP}$. When the Hippo pathway is inactivated, YAP/TAZ translocate to cell nuclei and physically bind to transcription factors, such as TEAD1/2/3/4 (homologs of *Drosophila* Scalloped), and other transcription factors containing PPXY motifs, to promote gene transcription.

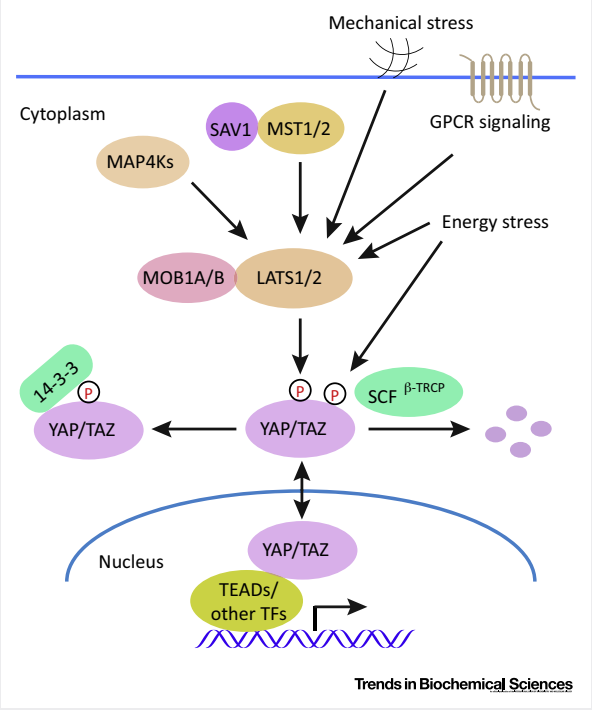

Figure I. Organization of the Hippo Pathway.

promoting the degradation of the T_{reg}-defining transcription factor Foxp3 (Figure 1B). As a result, KO of TAZ in T cells ameliorates T_H17-mediated autoimmune diseases in mouse models. MST1/2 are known to regulate T cell functions, for example, the MST1 mutation in humans was found to cause a primary immunodeficiency syndrome with a progressive loss of naïve T cells, recurrent bacterial and viral infections, and autoimmune manifestations [11,12]. Importantly, *TAZ* KO attenuates the ability of *MST1*-deficient T cells to induce intestinal inflammation [10]. Therefore, deregulation of TAZ could underlie autoimmune manifestations caused by MST1 deficiency. In addition, the function of TAZ in directing T cell differentiation is independent of TEADs, which are canonical Hippo pathway transcription factors. Instead, expression of TEAD1 sequesters TAZ away from RORγt, thus repressing T_H17 differentiation [10]. Furthermore, the proliferation of T cells is not affected by TAZ KO [10]. Therefore, the Hippo pathway regulates T cell differentiation through a transcriptional program distinct from that in growth control, which might be determined by the expression levels of target transcription factors.

Implications in Therapy Design

The inhibitory effect of LATS1/2 on antitumor immunity, along with its tumor-suppressive roles, emphasizes the context-dependent mechanisms of the Hippo pathway in cancer immunity. Further insights into secretory and non-cell autonomous effects of LATS1/2 in cancer immunity may enable a selective therapeutic approach. Similarly, while YAP activation has a robust oncogenic role, its function in inducing cancer immunity also suggests the need for careful monitoring of the tumor immune microenvironment upon application of YAP inhibitors to avoid unexpected complications.

An additional consideration is that the Hippo pathway functions not only in cancer cells, but also in immune cells. Therefore, mechanisms of the Hippo pathway in innate immunity may also have a role in cancer immunity. Indeed, it was found that inflammatory conditions repress the expression of *MST1* in liver macrophages, promoting inflammation, fibrosis, and tumorigenesis [13]. Furthermore, although discussed only in the context of autoimmunity [10], the function of TAZ in directing T cell differentiation may also have a role in shaping the tumor microenvironment. Therefore, the effect of a proposed therapy on different cell types in the tumor microenvironment should be considered. A particular opportunity to enhance effectiveness and to avoid potential adverse effects lies in the differential involvement of YAP, TAZ, and their binding transcription factors in growth control and certain types of immune reactions, for instance, TAZ-TEAD in cancer stem cells and TAZ-RORγt in T cell differentiation [10].

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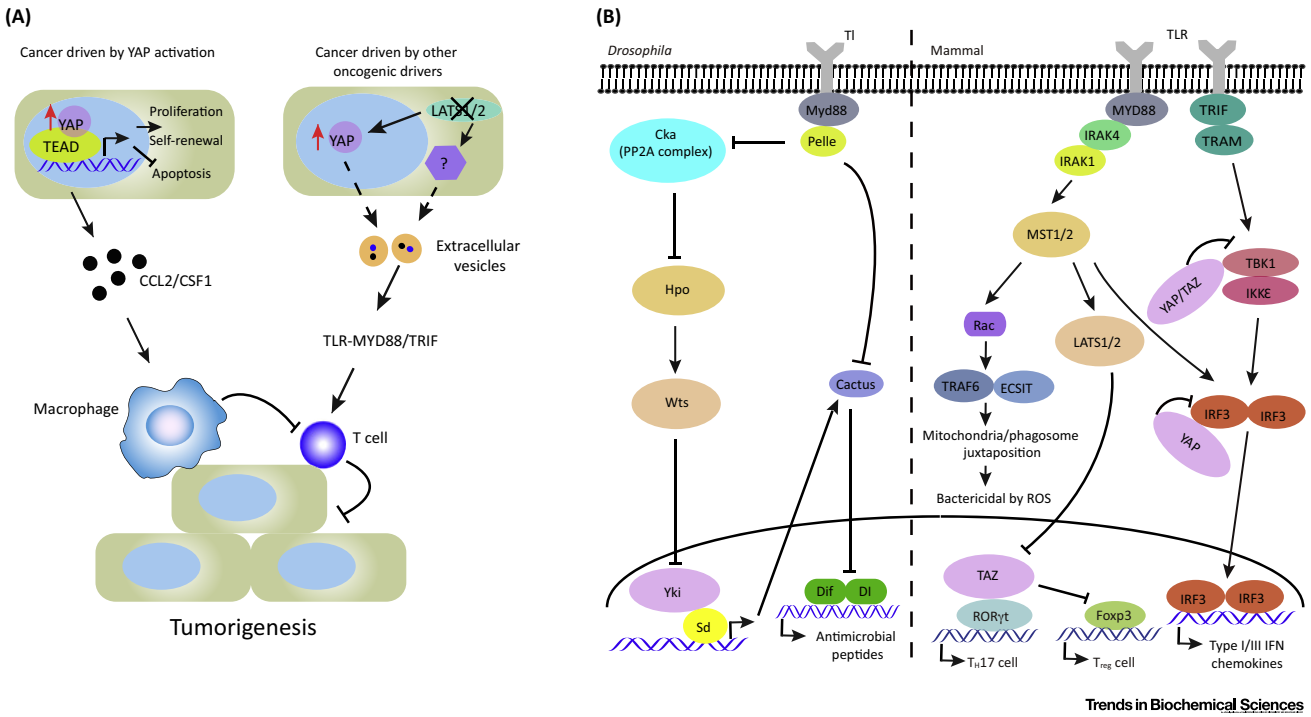

Figure 1. Roles of the Hippo Pathway in the Immune System. (A) The Hippo pathway in cancer immunity. The Hippo pathway regulates tumorigenesis through modulating immunity by regulating secreted cytokines or extracellular vesicles. Arrows indicate activation and blunted ends indicate inhibition. (B) Mechanisms of the Hippo pathway in innate immunity and autoimmunity. Components of the Hippo pathway and immune signaling are shown and reported regulating mechanisms are illustrated. Corresponding proteins in *Drosophila* and in mammals are indicated in the same color.

Concluding Remarks

Recent studies have revealed a new paradigm of Hippo signaling in the immune system. These findings remind us that the Hippo pathway is not only a developmental pathway, but also has specific functions in differentiated tissues. Of particular interest is whether Hippo signaling could coordinate growth with specific cellular functions in response to physiological conditions.

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