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Mechanosensation to inflammation: Roles for YAP/TAZ in innate immune cells

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Abstract

Innate immune cells are responsible for eliminating foreign infectious agents and cell debris, and their ability to perceive, respond and integrate biochemical and mechanical cues from their microenvironment eventually determines their behavior. In response to tissue injury, pathogen invasion, or a biomaterial implant, immune cells activate many inflammatory pathways to initiate inflammation in the tissue. In addition to the common inflammatory pathways, recent studies have demonstrated the role of mechanosensitive proteins YAP/TAZ in inflammation and immunity. Here, we review the current knowledge of the transcriptional co-activators YAP/TAZ in controlling inflammation and immunity in innate immune cells. Further, we discuss their role in inflammatory diseases, wound healing, and tissue regeneration, and how they can integrate mechanical cues with biochemical signaling during disease progression. Finally, we comment on possible approaches that can be exploited to harness the therapeutic potential of YAP/TAZ in inflammatory diseases.

1. Introduction

Cells in living organisms experience a multitude of biophysical and biochemical cues from the surrounding cells and the extracellular matrix, which together influence their behavior. To proliferate, differentiate, and regenerate, cells must integrate and respond to these cues emerging from the immediate milieu. Further, dysregulated coordination between

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cells and their microenvironment has been shown to drive multiple diseases, including atherosclerosis, fibrosis, and cancer [1,2]. Over the years, biochemical signals such as cytokines, chemokines, and growth factors that govern various immune cell functions have been relatively well studied, often overlooking the contributions of biophysical cues [3]. Emerging evidence underpins the significance of mechanical signals as fundamental regulators of cell behavior [1,4], yet, how these mechanical cues are perceived and relayed at the molecular level to regulate gene expression, and their distinct roles in immune cells, still remains elusive. The two related and conserved transcriptional regulators, Yes-associated protein (YAP) and its paralog transcriptional co-activator with PDZ-binding motif (TAZ), have been shown to be involved in sensing the microenvironmental landscape, and modulating cell function [1]. These transcriptional co-activators were primarily identified as genes that promote cell proliferation, differentiation, and survival to stress upon nuclear translocation [5]. However, recent works show that they also have an essential role in innate immunity and inflammatory diseases [6-14]. In this review, we will describe our current understanding of YAP/TAZ functions in innate immune cells in response to biomechanical perturbations during physiological and pathological conditions.

The Hippo pathway is a kinase cascade that was first identified in *Drosophila* and is highly conserved in mammals. This evolutionarily conserved pathway controls tissue growth and organ size by suppressing cell proliferation and promoting cell death, and is therefore often referred to as a tumor suppressor pathway [1]. The core Hippo pathway consists of an upstream *Hippo (Hpo)*/mammalian STE20-like serine/threonine kinases (MST1/2) that phosphorylate and activate downstream kinase *Warts (Wts)*/Large tumor suppressor kinase (LATS1/2). Further, LATS1/2 kinases phosphorylate transcriptional co-activators *Yorkie (Yki)*/YAP/TAZ to inhibit their nuclear translocation. When the Hippo pathway is active, this inhibitory phosphorylation by LATS1/2 leads to the cytoplasmic retention of YAP/TAZ by 14-3-3 for proteasomal degradation [15]. On the other hand, when the Hippo pathway is inactive, YAP/TAZ accumulate in the nucleus and bind the transcription factors TEA domain, *Scalloped (Sd)* orthologs (TEAD 1-4) to transcribe many genes involved in cell proliferation and survival [2,16,17]. The canonical Hippo signaling pathway is thought to primarily inhibit YAP/TAZ activation, suppressing proliferation and assisting apoptosis during tissue homeostasis [18] (Figure 1). However, recent studies have revealed additional kinases and posttranslational modifications independent of the canonical Hippo pathway that can also regulate YAP and TAZ [9,19,20] (in-depth review by Cho and Jiang [21]). Thus, YAP/TAZ are regulated by Hippo kinase-dependent and independent pathways, which together determine their subcellular localization and stability, and effects on cell behavior.

The role of YAP and TAZ in sensing mechanical cues has been studied extensively across different cell types and tissues. Although immune cells function within dynamic mechanical niches and experience varied stiffness, shear flow, and dynamic cell-cell interactions, their general non-adherent nature and inherent structural plasticity have led them to be relatively understudied in the context of mechanobiology [22]. Early studies found that YAP was not detected in peripheral blood leukocytes [23], and its expression was low in variety of immune cells including THP-1 monocytes and peritoneal macrophages compared to HEK293 and mouse embryonic fibroblasts [24,25], contesting its significance and functionality in immune cells. YAP expression in monocytes and macrophages is up to

10-fold lower than non-immune cells like fibroblasts, endothelial cells, and epithelial cells (Figure 1A) [26]. Interestingly however, we have shown that YAP, but not TAZ, expression increases upon differentiation from monocytes to adherent macrophages [11] (Figure 1B). Moreover, recent discoveries have demonstrated context-dependent YAP/TAZ functions in immune cells controlling inflammation and immunity [11]. It was found that Hippo signaling and the innate immune system cross talk and result in antiviral and antibacterial activity. In addition, YAP and TAZ are abnormally regulated in many inflammatory diseases, wound healing, and tissue regeneration [11,13]. Despite these recent insights, the importance of cues from the mechanical niche in which innate immune cells reside and differentiate is still understated.

Mechanical cues control the YAP/TAZ activity through both Hippo-dependent and –independent pathways. Cells perceive ECM stiffness and shear forces through integrins, the engagement and activation of which promote focal adhesion assembly. ECM rigidity is relayed by the Ras-related GTPase RAP2, which is activated at low stiffness and binds to mitogen activated protein kinases (MAPKs) and ARHGAP29, activating LATS1/2 and inhibiting YAP/TAZ [27]. Further downstream is Rho-ROCK signaling, the activation of which induces F-actin polymerization and acto-myosin contractility, leading to YAP/TAZ nuclear translocation [28,29]. In response to mechanical stimuli, the cytoskeleton remodels leading to changes in F-actin levels, which can modulate YAP/TAZ activity [30-34]. Disassembly of F-actin activates LATS1/2 and promotes YAP phosphorylation. In addition, MAPKs, PKA (Protein kinase A), and TAO (thousand and one) kinases can activate LATS1/2, but their regulation by F-actin remains unclear [28,31,35-37]. Furthermore, angiomotins (AMOTs) bind F-actin [38] and regulate Hippo signaling. When F-actin levels are low, AMOT binds to MST1/2 and LATS1/2 and activates these kinases to sequester YAP in the cytoplasm [39,40]. Neurofibromatosis (NF2), has been shown to be controlled by mechanical stimuli and AMOTs, and also regulates Hippo-pathway. AMOT binds to NF2 to activate LATS1/2 or directly to YAP in a Hippo-independent manner and inhibits nuclear translocation [41]. However, F-actin assembly caused by mechanical stimuli promotes AMOT binding to actin, rendering MST1 and LATS1/2 inactive, therefore facilitating nuclear translocation of YAP. In addition, signaling components of focal adhesions, including focal adhesion kinase (FAK) and Src are required for YAP/TAZ activity, and Src has been shown to phosphorylate YAP directly [42,43] or activate YAP indirectly by phosphorylating LATS1 [44]. However, it is still unclear if direct phosphorylation of YAP/TAZ by Src impacts its activity or indirectly through the cytoskeleton. In addition, the co-receptor for inflammatory IL-6 cytokines, gp130, associates with Src kinase, phosphorylates YAP and promotes its nuclear translocation in epithelial cells [45] (Figure 2). Src kinase has also been shown to promote inflammation in macrophages [46], but its regulation of YAP in this cell type has not yet been demonstrated.

In addition to forces at focal adhesions, tension sensing at the adherens junction component of cell-cell contacts can regulate YAP/TAZ. Under conditions of high tension (low cell density), α and β-catenin bind to the actin stress fibers, LIMD1 (LIM Domain containing 1) and vinculin proteins. The LIMD1 promotes LATS1/2 recruitment to junctions, and vinculin recruits TRIP6 (thyroid hormone receptor interactor 6), which inhibits LATS1/2 activation leading to the nuclear translocation of YAP/TAZ [28]. On the other hand, high cell densities

(reduced tension) leads to loss of actin stress fibers inhibiting recruitment of LIMD1, vinculin, TRIP6, and LATS1/2 at the junction to suppress YAP/TAZ nuclear translocation [28]. Additionally, the circumferential actin belt contraction due to high cell density in a certain type of cells underlying the adherens junctions can regulate YAP/TAZ activity independent of the Hippo pathway [47]. Mechanistically, high cell density dissociates NF2 from adherens junctions that physically bind to YAP/TAZ to suppress YAP/TAZ nuclear localization. Nonetheless, while upstream regulators of YAP/TAZ by mechanical stimuli are better characterized in other cell types in comparison to immune cells, it is possible that upstream regulators in immune cells may function similarly to other cell types.

Here, we review the current understanding of YAP/TAZ in innate immune cell function, inflammation, and immunity. We discuss the potential role of biophysical cues that influence YAP/TAZ in innate immune cells. We then describe the role of YAP and TAZ in inflammatory diseases, wound healing, and tissue regeneration. We propose a physical basis of these disease conditions caused by changes in tissue structure and remodeling, which might contribute to perturbed mechanochemical signaling. Finally, we comment on the therapeutic potential of controlling and potentially coopting YAP/TAZ in inflammatory diseases.

2. YAP/TAZ regulate immune cell function and inflammation

2.1 YAP/TAZ in differentiation and polarization of innate immune cells.

It was postulated early on that Hippo signaling might be involved in the regulation of hematopoietic stem cells that give rise to myeloid and lymphoid lineage, given its known role in expansion of undifferentiated progenitor cells, stem cell self-renewal and differentiation, and organ size in various tissues [48-50]. However, ectopic expression of YAP did not influence hematopoietic stem cell function in physiological or hematopoietic stress situations [51]. Recently it was demonstrated that YAP regulates differentiation and activity of osteoclasts, specialized cells derived from monocyte/macrophage hematopoietic lineage formed at or near the bone surface [52,53]. Zhao *et al.* demonstrated that short hairpin RNA-mediated YAP knockdown in bone marrow-derived macrophages (BMDMs) and inhibiting YAP-TEAD association with the small molecule verteporfin, both prevented the formation of multinucleated osteoclasts [52]. Despite the relatively low expression of YAP in leukocytes [23], our group and others have shown that YAP plays critical roles in macrophage function. YAP expression appears to not only increase with differentiation of peripheral blood mononuclear cells (PBMC) derived monocytes to macrophages [11], but also macrophages undergoing proinflammatory [11] and reparative programs [12]. Additionally in dendritic cells, the Hippo kinases MST1/2 selectively drive antigen presentation to CD8+ T cells by integrating metabolic activity and cytokine signaling [54]. These examples highlight the interplay between Hippo signaling and innate immune cell differentiation, signaling, metabolic reprogramming, and phenotype specific function.

The few studies examining the role of YAP/TAZ in macrophage polarization have yielded somewhat varied results. In one study, YAP promoted proinflammatory classically activation of (M1) peritoneal and bone marrow derived macrophages, and YAP deficiency enhanced their pro-healing alternative (M2) activation, suggesting that YAP regulates the balance

between M1 and M2 activation [13]. However, in another study, the YAP inhibitor (verteporfin) attenuated M2 polarization of RAW 264.7 cells [55]. Similarly, TAZ ablation reduced macrophage M2 polarization in a kidney fibrosis model [55]. Taken together, the role of YAP/TAZ in differentiation and polarization of immune cells is still emerging, and more work is warranted to define the specific roles of YAP/TAZ in hematopoietic stem cell lineage determination, differentiation of myeloid cells, macrophage polarization, and function. Considering most studies examining the role of YAP/TAZ in immune cell function have been performed on standard tissue culture plastic substrate, it is likely that mechanical signals presented by the culture environment can influence the experimental conclusions. Furthermore, observed discrepancies in YAP/TAZ expression may be attributed to different tissue or cell sources, as well as the differentiation methods used to obtain macrophages.

2.2 The Hippo pathway in inflammation and immunity

Innate immune cells express pattern recognition receptors (PRRs) as a surveillance system to respond to pathogen-associated molecular patterns (PAMPs) or host-derived damage-associated molecular patterns (DAMPs). Signaling from PRR-caused expression of transcription factors leads to expression of genes needed to eliminate host debris and foreign infectious agents, and initiation of inflammation [56]. Common inflammatory pathways triggered by the innate immune cells include nuclear factor kappa B (NF-κB), MAPK, and janus kinase/signal transducers and activators of transcription (JAK-STAT) pathways [57]. However, recent evidence also suggests that the Hippo pathway is connected to innate and adaptive responses [11,15,58,59]. One of the earliest evidence of YAP's involvement in immunity came from *Drosophila*, where the YAP homolog *Yki* was shown to directly regulate the IκB homolog, *Cactus*, to control antimicrobial response. Exogenous overexpression of *Yki* in fat bodies, the *Drosophila* immune organ, enhanced *Cactus* transcripts and reduced production of antimicrobial peptides leading to susceptibility to Gram-positive bacteria [60]. Upon infection by gram-positive bacteria, TLR signaling causes nuclear to cytoplasmic translocation of *Yki*, resulting in *Cactus* downregulation, and reliving the NF-κB family transcription factors *Dorsal (Dl)* and Dorsal-related immune factor (*Dif*) from its inhibitory influence [60].

The role of YAP in macrophage inflammation has been demonstrated by a few recent studies. We showed that YAP/TAZ knockdown in human monocyte-derived macrophages significantly reduced TNF-α secretion in response to lipopolysaccharide (LPS) [11]. Consistent with this observation, deletion of YAP in mouse myeloid cells led to suppression of lipopolysaccharide (LPS)-induced systemic inflammation [61]. In Kupffer cells (KCs), LPS stimulation induced the accumulation of YAP, enhanced hepatic inflammation and production of proinflammatory cytokines, which was suppressed by knocking out YAP [14]. YAP is mostly localized to the nucleus in cells cultured on stiffer substrates irrespective of the biochemical microenvironment, although some studies showed that the inflammatory cytokine, IL-1β [11], and TLR4 agonist, LPS [11] can enhance nuclear localization of YAP in macrophages cultured on tissue culture plastic. The effects of various inflammation associated biochemical stimulations on YAP/TAZ expression are summarized in Table 1. In addition, culture on stiffer substrates enhanced inflammatory mediators such as IL-1β, IL-6, TNF-α, TLR4 [62], which also promote YAP nuclear localization leading to positive

feedback and increased inflammation. In contrast, when macrophages are cultured on soft substrates, YAP is mostly cytoplasmic and stimulation with LPS does not enhance its nuclear translocation [11], but overexpressing the phosphorylation resistant YAP (YAP-5SA) cultured on soft substrate significantly enhanced LPS-induced inflammatory responses. Similarly, pharmacological inhibition of TAZ, or deficiency suppressed stiffness-induced inflammatory cytokine production in bone marrow-derived dendritic cells [63]. Thus, nuclear YAP enhances inflammatory activation of innate immune cells, and mechanical cues and the ability of the cells to sense it tune their functional outcome.

In addition to their roles in transcriptional regulation, the Hippo pathway effectors YAP/TAZ also directly regulate innate immune responses in the cytoplasm and the notion that YAP/TAZ are functional only in the nucleus is beginning to fade. Evidence of YAP/TAZ physically binding to transcription factors and kinases in the cytoplasm to regulate immune response is emerging. It was demonstrated that YAP negatively regulates antiviral immune response, and its deficiency in PEMs and BMDMs increased antiviral response [64]. Macrophages isolated from myeloid YAP-deficient mice showed higher expression of interferon beta 1 (*Ifnb1*), and downstream chemokine-encoding genes, upon stimulation with virus/RNA mimics. Therefore, myeloid YAP deficiency protected mice against viral infection. Mechanistically, YAP in the cytoplasm inhibited dimerization of the transcription factor IRF3 and its translocation to the nucleus. However, these *in vitro* experiments were performed on tissue culture plastic, which potentially has a profound influencing on the findings. Independent of YAP, another upstream Hippo pathway kinase, MST1, suppressed cytosolic RNA/DNA sensing by directly binding and phosphorylating IRF3 and suppressing anti-viral immunity [65]. Similarly, in another study, YAP/TAZ associated directly and suppressed TBK1/IKKε kinases, key components needed to dampen the antiviral response. Further, knockdown of YAP/TAZ enhanced antiviral response [25]. This study showed the role of Hippo signaling in determining nucleic acid sensing and innate antiviral immunity through YAP/TAZ-mediated TBK1 blockade. Considering that the classic functions of YAP/TAZ are related to cell survival [2] and sensing the mechanical environment, it will be interesting to better understand how the biophysical environment regulates responses to viral RNA/DNA. It is possible that the higher amount of phosphorylated or inactive cytoplasmic YAP in soft environments [11] might be unable to suppress TBK1 activation [25] or inhibit IRF3 dimerization [64] and therefore enhance antiviral response. On the contrary, cells in a soft environment might be sensitive to the viral RNA/DNA because of lower phosphorylated level of TBK1 [66] and phosphorylated NF-κB [11] adding more complexity to antiviral immunity involving YAP, and possibly TAZ, regulation.

2.3 Epigenetic and chromatin regulatory roles of YAP/TAZ

YAP/TAZ are also known to orchestrate transcriptional control by integrating epigenetic regulators in the nucleus to steer chromatin accessibility. While many of such studies exploring YAP/TAZ exist in the context of tumorigenesis, not much is known on the epigenetic influences of YAP/TAZ with innate immunity and inflammation. Interestingly, several of the epigenetic enzymes that have been implicated in tumorigenesis studies are also involved in inflammation and immunity. In this subsection, we would like to shed light on YAP/TAZ and their associations with inflammatory epigenetic proteins such

as histone acetyltransferase (HAT) p300 and the histone acetylation reader BRD4 and speculate on the importance of these associations in contexts relevant to our review. The inflammatory transcriptional activity of YAP/TAZ likely involves association with inflammatory transcriptional factors and epigenetic determinants such as BRD4 and p300.

Histone acetylation is generally associated with regions of chromatin “open” for transcription. Enhancers occupied by YAP/TAZ are usually acetylated at histone 3 lysine 27 (H3K27Ac), a modification facilitated by p300/CBP HAT activity [67,68]. In agreement, p300 has been found enriched at enhancers that are associated with YAP binding [68], and it has also been found physically associated with YAP/TAZ-TEAD complex [69]. Interestingly, the association of YAP/TAZ with p300 was found to be biomechanically influenced. Cell crowding, which leads to YAP cytoplasmic localization in some cells, also diminished the p300 and H3K27Ac occupancy on YAP target gene enhancers in cancer cells [68]. Furthermore, silencing YAP results in reduced p300 association and H3K27Ac marks on enhancers of target genes, illustrating potential non-redundant roles of YAP in p300 recruitment to gene enhancers [68]. Thus, association with p300 confers YAP/TAZ the ability to target histone acetylation towards distal regulatory elements and activate nearby genes. Interestingly, the nuclear localization signal on p300 enhances TAZ nuclear import by associating with it in the cytoplasm [70]. p300 is a proinflammatory HAT that cooperates with NF-κB to drive proinflammatory gene programs, and the genetic and pharmacological inhibition of p300 leads to the suppression of inflammatory transcription [71]. Macrophages cultured on soft fibrin substrates express lower H3 acetylation and reduced YAP nuclear translocation than stiff controls, and further studies are required to study if macrophage mechanosensation can modulate epigenetic modifications through YAP [11]. Drawing from these reports, we posit that p300 is recruited by YAP/TAZ containing complexes to enhance its nuclear import and remodel the chromatin to permit inflammatory transcription in conjunction with proinflammatory transcriptional factors.

BRD4, an important histone acetylation reader (including H3K27Ac marks) and epigenetic mediator of inflammation [72], has also been found to be associated with YAP/TAZ-TEAD complex in cancer cells [69]. BRD4 is a cofactor required for YAP/TAZ-mediated sustained oncogene transcription in cancer, as evidenced by the dynamics of YAP/TAZ and its engagement with BRD4 at promoters and distal enhancers. It was also found that BRD4 is recruited to the chromatin by YAP/TAZ in MDA-MB-231 cells [69]. In the absence of YAP/TAZ, even overexpressed BRD4 could not upregulate YAP/TAZ target genes, including those involved in cell proliferation and survival [69]. While these findings highlight the interdependence between YAP/TAZ and BRD4 proteins in orchestrating the epigenetic regulation of cell proliferation and pro-cancer behaviors, a similar nexus in immune cells driving inflammation has not yet been shown. Given the prominent proinflammatory roles of BRD4 and YAP/TAZ in the nucleus, studies that explore this nexus from the context of innate immunity and inflammation are highly warranted.

3. Roles of macrophage YAP/TAZ in inflammatory diseases and tissue regeneration

3.1 Macrophage YAP/TAZ aggravate inflammation and contribute to inflammatory diseases.

A large and growing body of studies has recognized that pathological YAP/TAZ activation in cancer and inflammatory diseases promotes inflammation indirectly by stimulating chemokine production (like CCL2 and CXCL1) and driving macrophage recruitment [6,7,73]. Moreover, YAP/TAZ upregulation or hyperactivation through greater nuclear translocation is a recurring event in such diseases, underscoring the possibility of inherent mechanochemical signaling [8,11,14]. Congruently, recent studies have pinned the progression of inflammatory diseases on YAP/TAZ transcriptional activity in innate immune cells. In this section, we explore current reports on direct inflammatory influences stemming from YAP/TAZ transcriptional activity in macrophages and underscore their relevance in inflammatory diseases besides cancer (Figure 3). We also examine the roles of aberrant biomechanical cues that may potentiate inflammation through YAP/TAZ activation.

3.1.1 Atherosclerosis—Atherosclerosis is a progressive vascular disease characterized by fatty plaque buildup in the intima, monocyte/macrophage recruitment, and chronic local inflammation. Atheroprone regions of vessels experience disturbed flow and oscillatory shear forces that elicit vascular inflammation and proliferation [74]. In addition, it has been hypothesized that increased macrophage infiltration and matrix degradation in the disease causes the loss of elastic laminae, resulting in up to 100% thicker and 50% stiffer vascular walls that is observed in diseased aorta [75]. *En face* analysis of atheroprone areas of murine endothelium reveals increased YAP/TAZ nuclear localization and target gene expression compared to athero-protective areas [76]. Accordingly, YAP and TAZ have been described to play mechanosensing roles in atherosclerosis.

YAP/TAZ in macrophages and endothelial cells are both essential in atherogenesis. In endothelial cells, YAP/TAZ nuclear translocation increases in disturbed flow, promoting higher proliferative and proinflammatory gene expression [73,76]. YAP/TAZ inhibition in endothelial cells stifles inflammation, leukocyte attachment, and infiltration, and is atheroprotective in $Apoe^{-/-}$ mice fed atherogenic high fat diet (HFD) [73,76,77]. A recent study directly implicates macrophage YAP in inflammation associated with atherosclerosis [11]. TRAF6, a component of IL-1β signaling, is responsible for the Lys63 ubiquitination and stabilization of YAP, causing its dissociation from AMOT, an interaction that otherwise sequesters YAP in the cytoplasm. This leads to increased YAP localization in the nucleus, where it induces proinflammatory gene expression, exacerbating atherosclerosis in the process [11]. In addition, active YAP brings about an increase in macrophage migration through upregulated chemokines, contributing to enhanced monocyte/macrophage infiltration in the plaque produced in hypercholesteremic $Apoe^{-/-}$ mice whose macrophages overexpress YAP [11]. Overall, these results highlight YAP as an attractive target to curb atherogenesis. Further studies are required to examine how synergistic biophysical cues such as disturbed flow and vascular stiffening regulate YAP/TAZ in macrophage-mediated inflammation in atherosclerosis.

3.1.2 Nonalcoholic steatohepatitis—Nonalcoholic steatohepatitis (NASH) is a critical liver disease that has its origins in obesity-induced fatty liver (steatosis). NASH manifests as liver inflammation, fibrosis, and hepatocellular damage that progresses to scarring (cirrhosis) when left unchecked. Liver stiffness measurements are used to diagnose fibrosis and scarring, and the median stiffness quadruples between normal and cirrhotic subjects (6.3 kPa vs. 27.4 kPa) [78]. Triggered by metabolic syndrome and obesity, dysbiosis in the gut microbiota and intestinal permeability is believed to leak microbial products and cell wall components into circulation and drive inflammation by activating hepatic stellate cells and KCs [79,80]. *In vivo* studies show that the intestinal microbiota contributes to all three components of NASH: hepatic steatosis, inflammation, and fibrosis [80].

YAP and TAZ are both upregulated in NASH and have been implicated in its pathogenesis, vis-à-vis inflammation in hepatocytes and macrophages [8,81]. Hyperactive TAZ in the liver causes inflammation by promoting proinflammatory cytokines and myeloid cell infiltration [7]. In NASH, TAZ upregulation in hepatocytes induces Indian hedgehog (*Ihh*) expression, which subsequently activates fibrogenic genes in hepatic stellate cells [8]. Hepatocyte-specific TAZ silencing using AAV-mediated shRNA delivery reversed inflammation, fibrosis, and hepatocellular death [8]. In agreement, YAP knockout in KCs protects mice fed HFD from hepatic inflammation and progression to NASH [14]. Additionally, constitutive YAP activation through 5SA-YAP expression in KCs enhanced proinflammatory cytokines such as MCP-1, TNF-α, and IL-6. The study shows an increase in YAP enrichment at promoters of inflammatory cytokine genes upon inflammatory stimulation. It also proposes that LPS-induced inflammatory signaling promotes YAP nuclear translocation through histone deacetylase (HDAC) mediated MST1 degradation. LPS induced KC activation resulted in YAP upregulation in a toll-like receptor 4 (TLR4) and activator protein 1 (AP-1) dependent manner, implicating inflammatory signaling in YAP upregulation. These results highlight the critical role of YAP in sustaining hepatic inflammation associated with obesity.

Interestingly, YAP deletion in macrophages did not suppress fibrosis or the expression of fibrogenic genes in NASH [14]. Possibly, these could be under the control of TAZ, as has been reported in hepatocytes [8]. It is noteworthy that macrophage-specific TAZ knockout exhibits reduced fibrosis and collagen deposition in models of renal fibrosis induced by unilateral ureter obstruction and ischemic/reperfusion injury [55]. In addition, the influences of pathological fibrosis and consequent ECM stiffening on cellular mechanotransduction and YAP/TAZ activation in macrophages is yet to be examined. In this regard, it may be posited that YAP/TAZ activation in KCs can drive chronic inflammation by promoting fibrosis, and further studies are warranted to reveal the possible distinctive influences of YAP and TAZ in KCs.

3.2 Macrophage YAP/TAZ hamper tissue repair and regeneration

In several diseases, chronic inflammation impairs healing through delayed tissue regeneration. Alternatively activated macrophages (M2) drive tissue repair by producing pro-healing growth factors and cytokines. YAP/TAZ activity generally promotes tissue regeneration by pro-proliferative gene expression in non-immune cells. In contrast, YAP/TAZ activities in macrophages sustain disease and hamper healing through sustained

inflammation. We underscore a few examples where macrophage YAP/TAZ are responsible for curbing M2 activation and suppressing disease resolution (Figure 4), while the non-immune cells may contribute to tissue regeneration or fibrosis owing to pro-proliferative or pro-fibrotic transcription mediated by YAP/TAZ activation. This highlights the complexity of YAP/TAZ roles in inflammatory diseases and warrants studies that dissect the contrasting contributions of YAP/TAZ in a cell-specific manner, as well as therapeutics that targets YAP/TAZ in specific subsets of cells.

3.2.1 Dermal wound healing—Given the prominent roles of YAP/TAZ in keratinocyte proliferation, differentiation, and homeostasis [82], it is expectable that dermal wound healing processes require YAP and TAZ. The topical application of YAP/TAZ silencing RNA in a murine full thickness excision wound model resulted in delayed wound healing, amidst reduced TGF-β1 signaling that manifests as downregulated Smad-2, p21, and Smad-7 expression [83]. YAP/TAZ silencing also causes reduced connective tissue growth factor (CTGF) expression, contributing to the delayed healing [83]. Significantly, YAP/TAZ have been found to be active (nuclear) in the wounded dermis that is actively healing. In contrast, YAP/TAZ are both cytoplasmic and nuclear in uninjured tissue, suggesting a lower level of activity [83]. Skin scar tissue can present with viscoelastic and nanomechanical properties very distinct from healthy intact tissue. For instance, skin stiffness climbs from 1-20 kPa in healthy cases to ~50 kPa during the final stages of re-epithelialization, and eventually to ~80 kPa during fibrosis [84]. In addition to skin compliance, the dynamic mechanical forces associated with the different phases of dermal wound healing and ECM remodeling may also influence YAP/TAZ nucleocytoplasmic localization contributing to cellular mechanosensing and adaptation, making it especially important to understand the influence of YAP/TAZ in macrophages participating in wound healing.

Macrophage function is a major determinant of wound healing outcomes and fibrosis of the skin. We found that full thickness wounds in mice that were treated with Tegaderm (a stiff dressing), fibrin gel application led to a reduction in final scar size [11]. While there was no difference in macrophage infiltration between the fibrin and Tegaderm treated wounds, macrophages in contact with fibrin exhibited significantly reduced iNOS and YAP expression [11]. These results demonstrate the importance of modulating YAP activation in macrophages to reduce inflammation. In addition, a recent study described the role of YAP in wound fibroblasts during dermal scarring. YAP activity was involved in the activation of *En1*, a gene implicated in scarring and fibrosis [85]. Fibroblast-specific silencing of YAP and verteporfin treatment positively affected dermal regeneration by suppressing fibrosis and promoting secondary skin elements [85]. Taking note that this study did not focus on macrophages or inflammation, detailed investigations on the effects of macrophage-specific YAP/TAZ knockout on chronic wounds (such as diabetic wounds), dermal fibrosis, and infectious inflammatory wounds are warranted.

3.2.2 Inflammatory bowel disease—Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory conditions of the gastrointestinal tract comprising Crohn's disease (CD) and ulcerative colitis (UC). IBD represents a state of failed intestinal homeostasis illustrated by elevated mucosal ECM breakdown and altered microbiome that

is associated with a slower rate of epithelial regeneration amidst sustained inflammation. In addition, IBD complications such as intestinal fibrosis is preceded by an increase in stiffness of between 55-65% (~900-1100 Pa vs. ~500-700 Pa in healthy), which also correlates with increased local inflammation [86]. Curbing inflammation can assist in epithelial restitution, thereby alleviating the condition. Even under physiological conditions, intestinal tissue regeneration is vigorous. Regeneration-associated dynamic ECM remodeling triggers extracellular biomechanical forces that activate YAP/TAZ through focal adhesion kinase/Src kinase-mediated actin polymerization [87,88]. YAP/TAZ are required and sufficient to induce epithelial reprogramming in dextran sulfate sodium (DSS)-induced colitis, where they act as mechanosensors that promote cellular proliferation [87]. Inactivation of YAP/TAZ in the intestinal epithelium can prevent repair, as is evident by diminished marker of intestinal healing, *Sca-1* [87]. Similar results were captured in an earlier study that found YAP dispensable for normal intestinal homeostasis but critical for recovery after DSS-induced colitis [89]. Interestingly, the study also showed that the dysregulation of the Hippo pathway by knockout of *Sav1* causes YAP hyperactivation and accelerated polyp formation in mice administered DSS [89]. This highlights a need for exquisite control over YAP/TAZ signaling to avoid unintended consequences physiologically.

As effector cells of innate immunity, macrophages help maintain intestinal homeostasis. IBD resolution is driven by M2 polarized macrophages that suppress inflammation and support healing. A recent study showed that myeloid-specific YAP knockout attenuates inflammation and promotes recovery following DSS-induced colitis [13]. YAP expression has been shown to be influenced by the polarization state of macrophages. LPS-induced higher YAP expression, while IL-4/IL-13 induced YAP downregulation in macrophages. Interestingly, YAP also tunes the equilibrium between M1 and M2 polarization of macrophages [13]. Macrophage YAP activation in IBD triggers IL-6 production and associated inflammation. Furthermore, YAP inhibits M2 activation by upregulating p53, causing a disequilibrium in the M1/M2 balance. Subsequently, macrophage YAP activation triggers a dysregulation of the gut microbiome. Myeloid-specific YAP knockout helped DSS-treated mice maintain a higher proportion of beneficial *Bacteriodetes, Lactobacillus*, and *Bifidobacteria*, in addition to suppressing potentially harmful microbes such as *Prevotellaceae* [13]. These results reveal the extent to which macrophage YAP enables the various pathological processes associated with IBD, making it an appealing target for therapy.

3.2.3 Cardiac regeneration—Cardiac development in mice fetus requires YAP, as the loss of YAP results in lethal myocardial hypoplasia amidst decreased cardiomyocyte (CM) proliferation [90]. YAP knockdown also impedes regeneration and promotes fibrosis in murine neonatal heart post-myocardial infarction (MI) [91]. YAP/TAZ are active in developing cardiac tissue, but this declines with age [90]. As a result, murine postnatal (adult) hearts exhibit a limited ability for regeneration. Cardiac regeneration is accompanied with biomechanical forces arising from extensive ECM remodeling and architectural changes. In addition, fibrosis during post-MI regeneration results in scar tissue that is 4-fold stiffer (55 kPa vs. 18 kPa in healthy) and exhibits impaired muscle distensibility and

function [92]. Accordingly, it has been examined if YAP activation can be therapeutically modulated to induce myocardial regeneration.

The roles of YAP/TAZ in cardiac regeneration are cell-type specific. Transgenic mice having a cardiac-specific S112A-Yap mutation that heightens Yap activity exhibit enhanced CM proliferation, cardiac recovery, and survival post-MI [91]. A similar enhanced survival and recovery post-MI can be therapeutically induced by adeno-associated virus (AAV) mediated cardiac-specific YAP activation that stimulates CM proliferation, upregulates cell cycle genes, and promotes a less mature cardiac gene signature [93]. Interestingly, YAP forms functional complexes with FoxO1 in CMs, enabling the transcription of antioxidant enzymes (catalase and manganese superoxide dismutase) that protects from stress-induced cell death and injury from ischemia/reperfusion [94]. Conversely, in macrophages and fibroblasts, YAP/TAZ activation stimulates inflammatory and fibrotic programs, respectively, thereby curbing cardiac regeneration after injuries like MI. Post-MI, cardiac fibroblasts experience higher YAP activation that promotes fibrosis through the expression of pro-fibrotic IL33 [95]. This agrees with the observation that soft substrates prevent pro-fibrotic fibroblast programs and enhance cardiac reprogramming by attenuating integrin, Rho/ROCK, actomyosin, and subsequent YAP/TAZ signaling [96]. A fibroblast-specific loss of YAP/TAZ also causes reduced proinflammatory activation, and chemokine-mediated recruitment of macrophages. YAP/TAZ activation in macrophages and the accompanying inflammation impairs reparative responses [12]. YAP activation causes inflammatory IL6 production while suppressing M2-marker Arg1 expression, indicating a disequilibrium in the M1/M2 balance. YAP/TAZ genetic deletion allows for reduced fibrosis, and improved angiogenesis and survival in mice following MI-associated injury [12]. These results highlight the cell type-specific impacts of YAP/TAZ transcriptional programs, justifying the need for YAP/TAZ targeted therapy to be aimed at specific cell populations.

3.2.4 Pulmonary recovery—Lung regeneration after pulmonary injury requires alveolar epithelial type I cells that line the alveoli to be replaced by progenitor alveolar epithelial type II cells. Pulmonary regeneration, such as after bleomycin-induced injury, requires TAZ activation for cellular differentiation and proliferation [97]. Interestingly, the mechanical tension arising from regenerative processes activates YAP through F-actin/JNK and MAPK signaling, causing enhanced alveolar stem cell proliferation and restoration [98]. The activation of YAP in lung fibroblast induces upregulation of CTGF and type I collagen, resulting in a fibrotic response [99,100]. In agreement, higher expression of TAZ has been observed in the fibroblastic foci of lungs from patients with idiopathic pulmonary fibrosis [100]. The upregulation of pro-fibrotic YAP/TAZ targets in fibroblasts are believed to increase the ECM stiffness and sustain YAP/TAZ activation in a feedback loop that underlies pulmonary fibrosis [101]. Such fibrotic diseases can result in ~30 fold stiffer lungs compared to healthy tissue (20-100 kPa vs. 1-5 kPa) [102]. These results demonstrate a context-specific contribution of YAP/TAZ to pulmonary disease and recovery.

The prolonged use of mechanical ventilation in patients is associated with an immense risk of lung inflammation and injury. Recovery requires an M2 pro-healing activation of macrophages. It was recently reported that YAP activation in alveolar macrophages causes inflammatory production of TNF-α, IL-6, and IL-1β [10]. Macrophage YAP deficiency

attenuates inflammation and accelerates recovery by boosting M2 polarization, while overexpression of YAP catalyzes inflammatory slowdown of regeneration [10]. These results once again highlight the pro-M1 macrophage bias of YAP/YAZ transcriptional activity, resulting in sustained inflammation and sluggish tissue restoration.

4. Discussion

The role of transcriptional co-activators YAP/TAZ in tissue growth and homeostasis has been long explored, but the ability of YAP/TAZ in influencing cell immunity and inflammation is only recently becoming more perspicuous. Considering their transcriptional function to enhance inflammation by expressing target inflammatory genes and non-transcriptional activity to control immunity, YAP and TAZ are good candidate genes for therapeutic intervention to combat various diseases and disorders. Interestingly, studies until now have made it clear that YAP and TAZ are spatiotemporally distinct, have tissue-specific roles, and function in a context-dependent manner. Therefore, targeting YAP and TAZ similarly in every tissue may not be the best approach to confront all pathophysiological conditions. Some of the possible approaches to target YAP/TAZ in the cells include, but not limited to, pharmacological regulation, genetic manipulation, and biomaterial-based interventions.

Pharmacological regulation of YAP/TAZ aims to curb aberrant biomechanically activated transcriptional programs. The positive feedback loop involving pathological tissue stiffening, increased intracellular tension, YAP/TAZ nuclear translocation, and consequential pro-fibrotic transcriptional expression leading to fibrosis is one such example of the cell-ECM dynamic reciprocity underlying several diseases. Verteporfin is an FDA approved drug (trademark Visudyne®) used as a photosensitizer in photodynamic therapy for choroidal blood vessel ablation in age-related macular degeneration. Its function as a YAP/TAZ inhibitor is light-independent, wherein it targets YAP/TAZ-TEAD complex formation to inhibit their downstream gene transcription [103]. The effectiveness of verteporfin has been demonstrated in several fibrotic diseases including that of the liver, lung and skin [85,104,105]. Dimethyl fumarate (DMF, Tecfidera®) is another molecule that has been shown to be effective in treating systemic sclerosis, a fibrotic disease characterized by vascular, immune, and fibrotic changes in multiple organs [106]. DMF diminished the nuclear localization of YAP/TAZ and caused anti-fibrotic effects via inhibition of PI3-K/Akt1 pathway. FDA-approved statins are also promising as they are known to target YAP/TAZ nuclear localization through inhibition of the Rho, and the mevalonate pathways [107,108]. Apart from drugs, a peptide mimic of VGLL4 has been demonstrated to rein in YAP/TAZ activation in cancer by competitive binding to TEADs [109]. Such peptide mimics of binding domains of VGLL4, ARID1A [110] or YAP can disrupt YAP/TAZ-TEAD interactions and have the potential to treat inflammatory diseases (listed in [111]). However, the broad ranging inhibition of YAP/TAZ may also have detrimental effects in many pathologies owning to YAP/TAZ roles in healing-associated cellular proliferation. Genetic therapies may instead be employed to control YAP/TAZ expression levels and activation in a targeted, cell type specific and context-dependent manner.

YAP gene therapy using adeno-associated virus (AAV) has been demonstrated to improve cardiac recovery after myocardial infarction in mice [93]. The study used a cardiac-specific inducible system to activate YAP in cardiomyocytes, aiding in proliferation of cells, and accelerated recovery as registered by improved cardiac function and survival. AAV-mediated therapeutics can target certain tissues owing to capsid serotype driven tropism, and therapeutic genes can be expressed in specific cell types by placing them under the control of cell-type-specific regulatory elements [112]. Such targeted and inducible systems can be used to selectively switch on YAP/TAZ activity at those phases of recovery requiring proliferation of specific subsets of cells. Interestingly, there has been a recent study that engineered mechanoresponsive cellular systems that exploit YAP/TAZ as biosensors to activate drugs selectively. Here, cytosine deaminase (CD) was exogenously induced by a YAP/TAZ-responsive element in mesenchymal stem cells (MSCs), allowing these cells to produce the enzyme when sensing stiffer microenvironments that converts the prodrug 5-fluorocytosine to the active drug form 5-fluorouracil [113]. While such systems were developed for cancer treatment (reviewed in [114]), we posit that similar systems may be designed to fastidiously target stiffer microenvironments with anti-inflammatory or pro-healing therapeutics using YAP/TAZ as a mechanosensor.

Biomaterial design can also benefit from leveraging the modulation of immune cells through mechanosensitive factors like YAP and TAZ. Biomaterial implantation induces inflammatory and fibrotic reaction through the foreign body reaction (FBR). During this process, immune cells, including macrophages are recruited to the implant site. Since macrophages are among the first inflammatory immune cells that are recruited to the implant/ wound site, it is beneficial to suppress their inflammatory activation by modifying the properties of the biomaterials/implants. Along the same lines we found that treating wounds with softer fibrin hydrogels reduced scar size and suppressed YAP expression in macrophages in a full-thickness wound model [11]. Further, we demonstrated that in the tissue surrounding a stiff hydrogel implant, macrophages had higher expression of iNOS and YAP. This study suggested that it might be possible to control YAP/TAZ nucleocytoplasmic shuttling by manipulating biomaterial properties, thereby controlling inflammation. Another promising strategy to modulate macrophage inflammatory activation is by changing their cell shape, and possibly other immune cells by altering the surface properties of the biomaterial. It has been demonstrated that by modifying surface topography of the material (biomimetic multi-scale wrinkles, micro-and nanopatterned groves) [115,116], porosity [117] or micropatterning technique [118], it is possible to change the cell shape and polarize the macrophage towards alternatively activated phenotype. Interestingly, these shape change associated inflammatory downregulation have been shown to happen through modulation of Src, a kinase that is known to be upstream of YAP/TAZ [46]. More studies are warranted to pinpoint the role of cell shape in regulating YAP/TAZ in innate immune cells. Overall, YAP/TAZ can be a strong determinant of inflammatory behavior of innate immune cells that can be controlled by rational biomaterial design.

While several studies observe increased macrophage M1 activation, inflammation, intracellular calcium signaling and phagocytosis in macrophages on stiffer substrates [11,62,119-124], a few studies contradict the pro-inflammatory effects of stiffer substrates by observing higher inflammasome activation and IL-1β production on compliant surfaces

[125-127]. Some of these differences may be due to different *in vitro* experimental conditions (such as cell types and origin, ECM types, substrate chemistry/architecture, 2D vs 3D culture, cell density and time of adhesion). Interestingly, cytoplasmic YAP/TAZ have been implicated in inflammasome stabilization [61]. YAP/TAZ largely remains cytoplasmic in cells adhered to softer surfaces, explaining the observed greater inflammasome activation on compliant substrates. YAP/TAZ can play multifaceted roles depending on their location – pro-inflammatory transcriptional roles in the nucleus, while working towards inflammasome activation/stabilization [61] and anti-viral response suppression [64-66] in the cytoplasm. These findings warrant a holistic study of YAP/TAZ effects on macrophage mediated inflammation and disease progression, with a focus on the effects of differential YAP/TAZ activation, temporal localization (shuttling) and expression.

Finally, one of the significant challenges in targeting YAP/TAZ for therapeutics is the cell-specific expression and context-dependent function. As we described in Section 3, suppressing YAP/TAZ can have either beneficial or undesirable pathophysiological outcomes depending on the cell type being targeted. Briefly, YAP/TAZ are inflammatory not only in immune cells, but also in cell types such as endothelial cells and hepatocytes that propagate inflammatory programs. In structural cells such as epithelial cells and fibroblasts, YAP/TAZ activation has either been shown to promote healing through proliferation or responsible for abnormalities such as fibrosis. This underlines the necessity to manipulate YAP/TAZ in a cell-specific and temporal manner for desired therapeutic outcomes in mechano-inflammatory pathologies. Cell and gene therapy could help customize YAP/TAZ-targeted therapeutics to affect only the cell populations of interest in a disease-specific manner. Further understanding of YAP/TAZ roles in mechanosensory immune cells would assist in tailoring such therapeutic regimens and biomaterials and promote better health outcomes.

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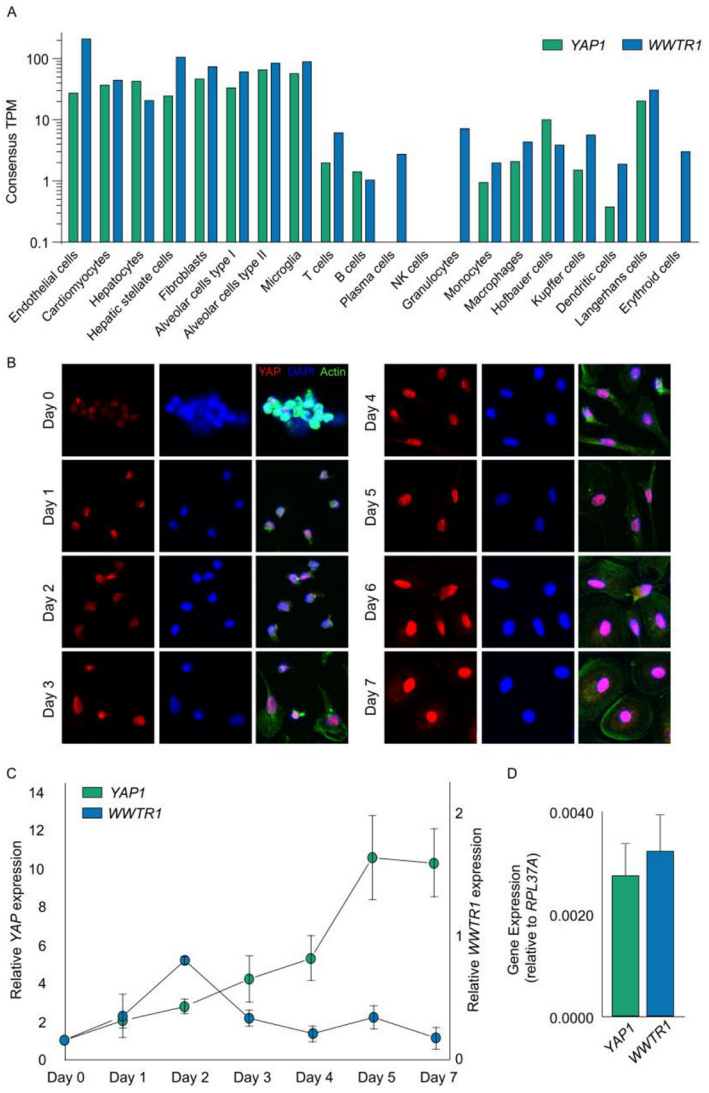

Fig 1. Expression of YAP, but not TAZ, increases during monocyte-macrophage differentiation.

(A) Data from the Human Protein Atlas [26] shows YAP (*YAP1*) and TAZ (*WWTR1*) gene expression in cell types of interest, (B) YAP expression increases during monocyte-to-macrophage PBMC differentiation, (C) YAP but not TAZ gene expression increases with monocyte-to-macrophage differentiation, (D) YAP and TAZ genes are substantially expressed in macrophages. Panels B, C, D adapted from [11] with permission.

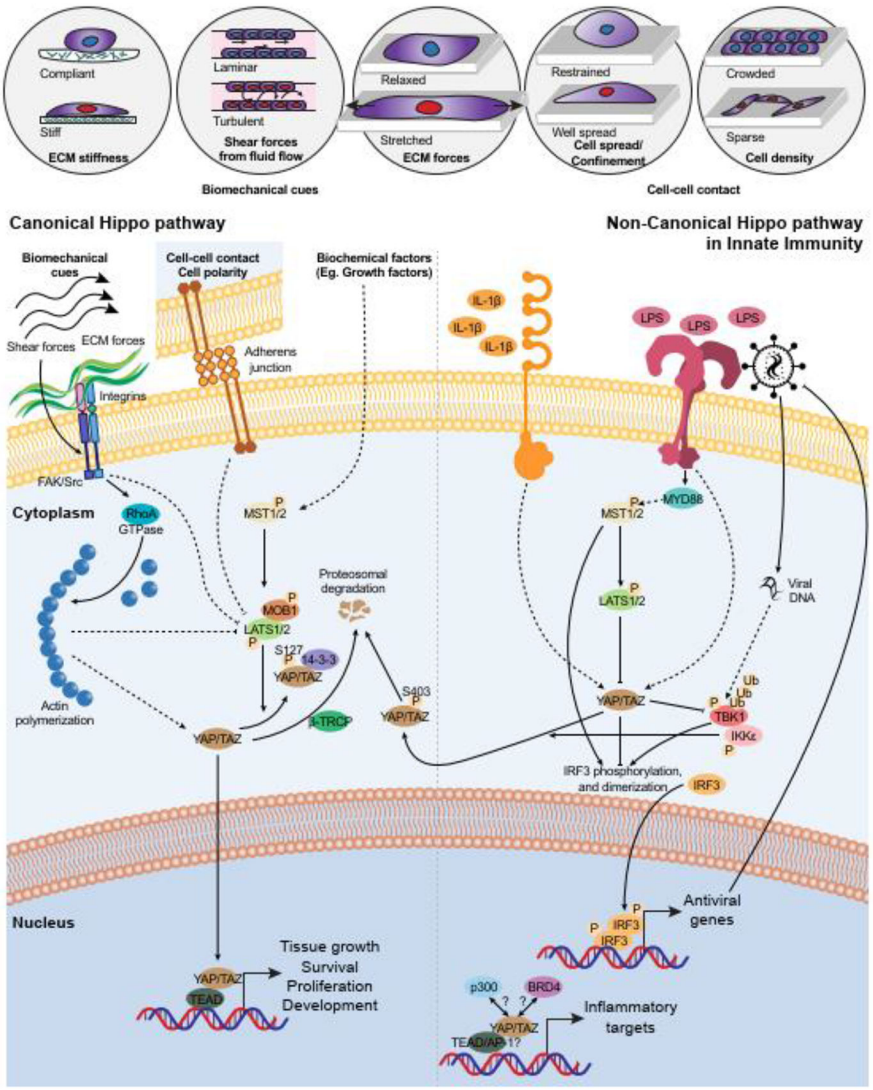

Fig 2. The canonical and non-canonical Hippo pathways modulate innate immunity and inflammation.

YAP/TAZ regulation is mechanically controlled through biophysical cues such as stiffness, shear flow, ECM forces, and cell density. Canonical regulation of YAP/TAZ occurs through upstream Hippo components/regulators that integrate biochemical and biomechanical cues to exert locational control over YAP/TAZ. YAP/TAZ transcriptional activity in the nucleus relates to increased tissue growth, survival, proliferation and development. In innate immune cells, YAP and TAZ localization is also influenced by bacterial and viral response pathways. In addition, cytoplasmic YAP/TAZ suppresses activation of the anti-viral transcriptional factor IRF3.

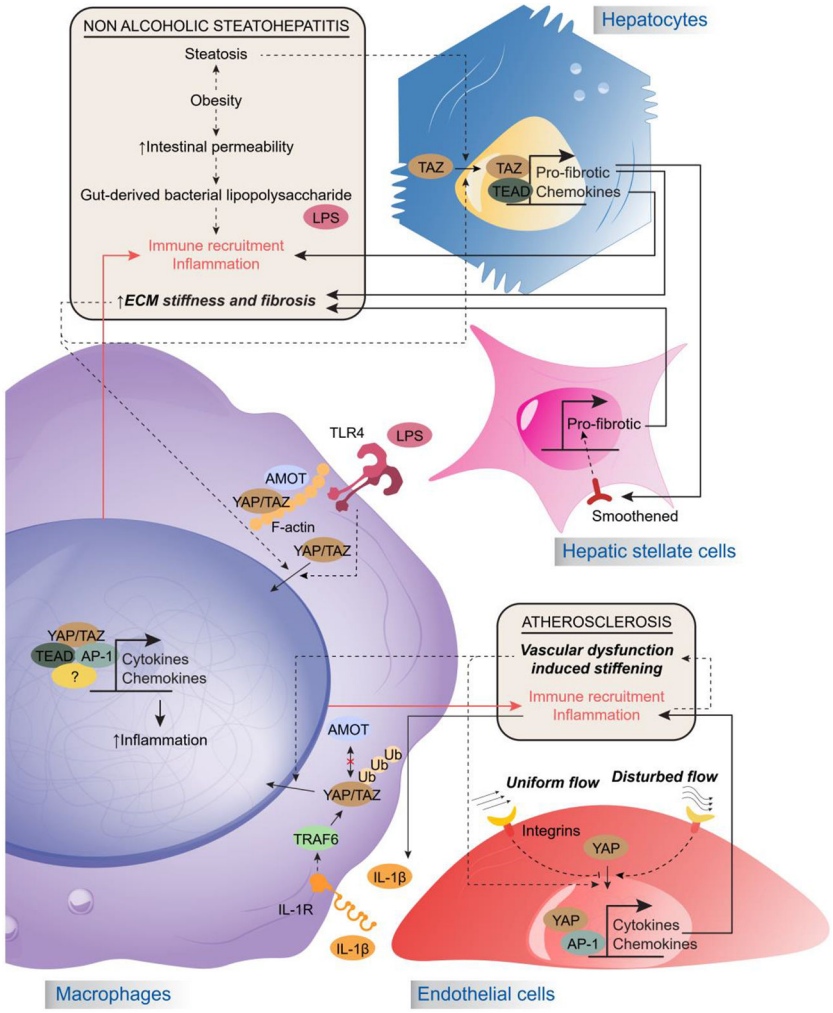

Fig 3. Macrophage YAP/TAZ contribute to diseases by promoting chronic inflammation.

YAP/TAZ activation in macrophages and other inflammation-capable cells such as endothelial cells and hepatocytes promote inflammation in diseases including atherosclerosis and NASH. Local tissue stiffening and increased immune recruitment leads to a positive feedback loop that activates YAP/TAZ, which is in turn responsible for the production of proinflammatory cytokines, chemokines, chemoattractants, and pro-fibrotic genes.

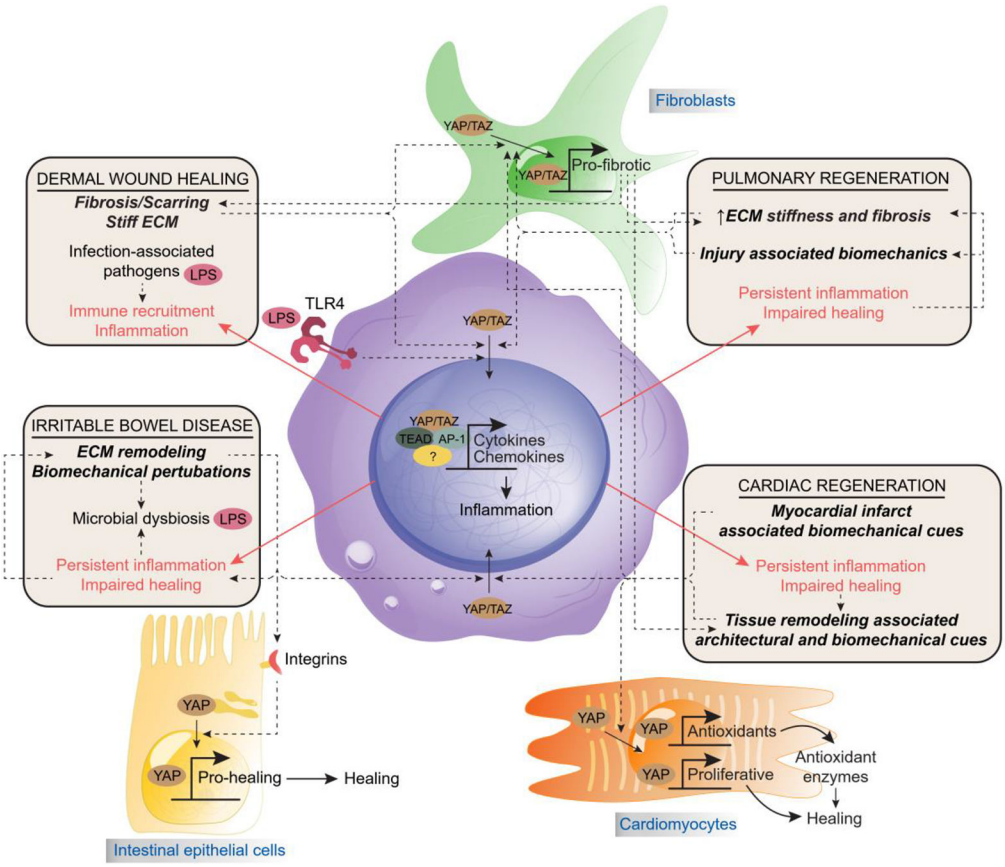

Fig 4. Macrophage YAP/TAZ contribute to diseases through inflammation associated impairment of regeneration.

In conditions such as IBD, dermal, pulmonary, and cardiac regeneration, YAP/TAZ activation in tissue resident non-immune cells can help resolve the disease by promoting cell proliferation. However, YAP/TAZ activation in fibroblasts and macrophages may have undesirable outcomes by promoting fibrosis and inflammation respectively.

Table 1.

Effects of inflammatory biochemical stimuli on YAP/TAZ expression

	Biochemical stimulus	Findings	Ref.
Cells			
Human umbilical vein endothelial cells (HUVECs)	20 ng/ml TNF-α	Higher YAP nuclear localization (Western blots and immunofluorescence)	[128]
Human umbilical vein endothelial cells (HUVECs) and human lung microvascular endothelial cells (HLMVECs)	1 μg/ml LPS, 10 ng/ml TNF-α, 500 500 μM H_2O_2	Higher YAP expression (Western blots)	[129]
Human embryonic kidney 293 cells (HEK293)	10 ng/ml TNF-α	Higher YAP and TAZ expression and nuclear localization in high cell density cultures (Western blots and immunofluorescence)	[130]
Human peripheral blood mononuclear cells (PBMCs) derived macrophages	10 ng/ml LPS	Higher YAP nuclear translocation	[11]
Murine peritoneal and bone marrow derived macrophages (BMDMs)	10 ng/ml IL-1β	Higher YAP expression and nuclear translocation (Western blots)	[9]
Murine Kupffer cells, Raw264.7 cells	1 μg/ml LPS	Higher YAP expression (immunofluorescence and qRT-PCR)	[14]
Murine peritoneal macrophages	LPS and IFN-γ	Higher YAP expression and nuclear translocation (Western blots and immunofluorescence)	[13]
Murine peritoneal macrophages and BMDMs	100 ng/ml LPS and 10 ng/ml IFN-γ (co-stimulation)	Higher YAP and TAZ expression (Western blots)	[12]
Murine peritoneal macrophages and THP-1 cells	10 ng/ml IL-4 and IL-13 (co-stimulation)	Lower YAP expression (Western blots)	[13]
Tissues and/or animal or human models			
Murine lung tissue	LPS challenge	Higher YAP expression in both the isolated lung endothelial cells and nonendothelial cells (Western blots)	[129]
Murine liver tissue	LPS challenge	Higher YAP expression in the isolated Kupffer cells (Flow cytometry and qRT-PCR)	[14]
Murine lung tissue	Mechanical ventilation associated injury and inflammation	Higher YAP expression (Western blots and qRT-PCR)	[10]
Murine atherosclerotic tissue	Hypercholesteremia induced atherosclerosis	Higher YAP and TAZ expression in atherosclerotic carotid artery and aortic arch (immunofluorescence)	[76]
Murine and human atherosclerotic tissue	Hypercholesteremia induced atherosclerosis	Higher YAP in $CD68^+$ cells with disease progression (immunofluorescence and Western blots)	[9]
Murine foam cells	Hypercholesteremia induced atherosclerosis	Higher YAP expression in $CD45^+$ $CD11b^+$ $F4/80^+$ cells with disease progression (flow cytometry)	[9]
Human patient-derived PBMCs	ST-segment elevated myocardial infarction	Higher YAP expression correlates with higher plasma IL-1β levels	[9]
Murine nonalcoholic steatohepatitis (NASH) liver	Hypercholesteremia induced NASH	Higher YAP expression in total tissue, $F4/80^+$ cells (Western blots, flow cytometry, immunofluorescence)	[14]