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Mini-review

YAP and WWTR1: New targets for skin cancer treatment

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ABSTRACT

The core components of the Hippo signaling pathway are a cascade of kinases that govern the phosphorylation of downstream transcriptional co-activators, namely, YES-associated protein (YAP) and WW domain-containing transcription regulator protein 1 (WWTR1, also known as TAZ). The Hippo signaling pathway is considered an important tumor-suppressor pathway, and its dysregulation has been noted in a variety of human cancers, in which YAP/WWTR1 enable cancerous cells to overcome contact inhibition, and to grow and spread uncontrollably. Interestingly, however, recent studies have told a somewhat different but perhaps more intriguing YAP/WWTR1 story, as these studies found that YAP/WWTR1 function as a central hub that integrates signals from multiple upstream signaling pathways, cell–cell interactions and mechanical forces and then bind to and activate different downstream transcriptional factors to direct cell social behavior and cell–cell interactions. In this review, we present the latest findings on the role of YAP/WWTR1 in skin physiology, pathology and tumorigenesis and discuss the statuses of newly developed therapeutic interventions that target YAP/WWTR1 in human cancers, as well as their prospects for use as skin cancer treatments.

Introduction

The Hippo signaling pathway and its fundamental roles in regulating cell proliferation and organ size were initially discovered in Drosophila. The pathway involves a series of kinases that eventually control the activity of Yorkie, the *Drosophila* YES-associated protein (YAP) [1,2]. Within the last decade, a large number of studies have revealed that Hippo signaling not only plays a role in developmental biology but also participates in a wide range of biological processes, including stem cell self-renewal, epithelial–mesenchymal transition (EMT), tissue regeneration and tumorigenesis [3–7]. As two major downstream effectors of the Hippo pathway, YAP and WW domain-containing transcription regulator protein 1 (WWTR1) function as signaling switches by shuttling between the nucleus and the cytoplasm to activate or deactivate specific transcriptional activities. However, nuclear YAP/WWTR1 localization (activation) or cytoplasmic retention (inactivation) can also be regulated in a Hippo-independent manner [8]. In this review, we discuss the biological activities of YAP and WWTR1 in mammals, focusing specifically on their roles and functions in skin and skin cancers.

Abbreviations: 14-3-3, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein; ABL1, ABL proto-oncogene 1; AKT, protein kinase B; AMOT, angiomotin; BCC, basal cell carcinoma; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CAF, cancer-associated fibroblast; CK1, caseine kinase-1; CXCL5, C-X-C motif chemokine ligand 5; CXCR2, C-X-C motif chemokine receptor 2; DDX17, DEAD-box helicase 17; ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; FAK, focal adhesion kinase; FZD, frizzled; GPCR, G-protein-coupled receptor; LATS1/2, large tumor suppressor kinases 1/2; LPA, lysophosphatidic acid; MDSC, myeloid-derived suppressor cell; MITF, microphthalmia-associated transcription factor; MOB1, MOB kinase activator 1; MRTF, myocardin-related transcription factor; MST1/2, mammalian sterile twenty-like kinases 1/2; NMSC, non-melanoma skin cancer; PATJ, crumbs cell polarity complex component; PI3K, phosphoinositide 3-kinase; PTPN14, tyrosine-protein phosphatase non-receptor type 14; RTK, receptor tyrosine kinase; S1P, sphingosine 1-phosphophate; SCC, squamous cell carcinoma; SCF(beta-TRCP), Skp1-Cul1-F-box-protein; SRC, proto-oncogene tyrosine-protein kinase SRC; TDU, Tondu; TEAD, TEA-domain family transcription factor; TGF-β, transforming growth factor-β; TGFR, transforming growth factor receptor; TJP2 (ZO-2), tight junction protein 2 (zona occludens 2); UV, ultraviolet; VGLL4, vestigial-like 4; WW45, salvador homolog 1; WWTR1, WW domain-containing transcription regulator protein 1; YAP, YES-associated protein.

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The core signaling cascade of the Hippo pathway

As shown in Fig. 1, YAP/WWTR1 regulation by the highly conserved Hippo signaling pathway involves a cascade of protein serine kinases, including mammalian sterile twenty-like kinases 1/2 (MST1/2, Hippo homologs; also known as STK3/4) and large tumor suppressor kinases 1/2 (LATS1/2, Warts homologs) [1]. When Hippo signaling is active, this kinase cascade is initiated by upstream signals to stimulate MST1/2 to directly phosphorylate a C-terminal hydrophobic motif of LATS1/2 [9,10]. The scaffolding protein WW45 (Salvador homolog 1, also known as SAV1) contains two WW domains and a coiled-coil region, which facilitates the binding of WW45 to MST1/2 at the coiled-coil motif and the binding of WW45 to LATS1/2 at the WW domains and effectively recruits LATS1/2 to MST1/2 [11,12]. Mps one binder (MOB) kinase activator 1 (MOB1), a LATS1/2 co-activator, binds to the auto-inhibitory motif of LATS1/2 after being activated by MST1/2, effectively completing the activation of LATS1/2 through dynamic scaffolding and allosteric mechanisms [13]. Once LATS1/2 are activated, these proteins directly bind to and phosphorylate the key downstream co-activators YAP and WWTR1 [14]. Previous studies have shown that YAP is primarily phosphorylated by LATS1/2 at serine residues Ser-127 and Ser-381 [3,15]. Phosphorylation at Ser-127 promotes the cytoplasmic retention of YAP as a result of tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (14-3-3) binding [16]. Phosphorylation of YAP at Ser-381 promotes further phosphorylation of the protein by CK1 kinases, as well as the subsequent recruitment of SCF(β-TRCP) E3 ubiquitin ligase, resulting in YAP ubiquitination and degradation [17]. Nuclear exclusion or induced degradation of YAP/WWTR1 leads to inactivation of these proteins and, consequently, repression of their biological activities.

When Hippo signaling is inactive, YAP/WWTR1 remain unphosphorylated. Thus, these proteins translocate to the nucleus, where they drive transcription of target genes. Because YAP/WWTR1 lack DNA-binding domains, the formation of complexes involving these proteins and transcription factors is required to regulate gene expression. In mammals, TEA-domain (TEAD) transcription factors (TEAD1 to TEAD4) are major transcription factors that bind to YAP and WWTR1 [18,19]. However, other transcription factors, such as DeltaNp63 [20], p73 [21,22], T-box transcription factor 5 (TBX5) [23], SMADs [24], and Pax3 [25], also interact with YAP/WWTR1, and can lead to the production of different transcriptional profiles.

Upstream signals

Although the core signaling cascade from MST1/2 to YAP/WWTR1 is well understood, recent studies have revealed the existence of a complex network of molecules and pathways that either act upstream of the core kinases or directly activate or inhibit YAP and WWTR1 activity. This network includes a variety of

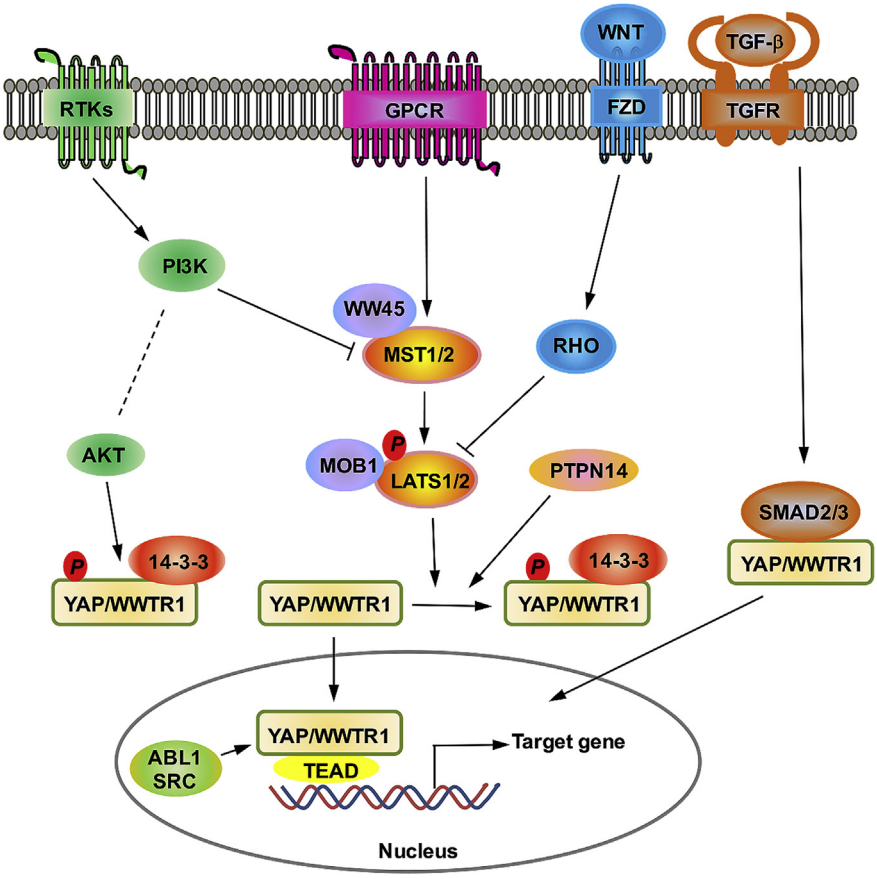

Fig. 1. Control of the core Hippo signaling cascade through upstream signals in mammals and the mode of action of the cascade. The localization and activity of the transcriptional co-activators YAP/WWTR1 are regulated by a wide range of upstream signals, including growth factors, GPCR signaling, Wnt signaling, and TGF-β signaling. These upstream signals function through a core kinase cascade including MST1/2 and LATS1/2 to regulate YAP/WWTR1 phosphorylation, nuclear translocation and cytoplasmic degradation. When YAP and WWTR1 remain unphosphorylated, they enter the nucleus and form transcriptional complexes with different transcriptional factors, such as TEADs, to initiate transcription of the target genes required for cell proliferation, differentiation and apoptosis.