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Review

The transcriptional co-activator YAP: A new player in head and neck cancer

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ABSTRACT

The Hippo-YAP (Yes-associated protein) pathway is a key regulator of tissue growth, organ size and stem cell function. More recently, a fundamental role for this pathway has emerged in stem cell function and tumorigenesis. Activation of the transcriptional co-activator YAP promotes cell-contact independent proliferation, epithelial to mesenchymal transition (EMT), cancer stem cell features and drug resistance. In this review, we describe the main components of the pathway, the microenvironment and the cell-intrinsic cues governing its activation, the downstream players of the pathway and the biological implications of their activation in the context of cancer. We will focus on the existing knowledge of this pathway in head and neck squamous carcinoma (HNSCC), its clinical value in this type of cancer as a marker of poor prognosis and resistance to therapy, as well as the most encouraging therapeutic strategies targeting the pathway.

Introduction

In different adult organs and tissues, including epithelia, cell-cell contact inhibits cell growth. Contact inhibition of cell proliferation is important for maintaining tissue homeostasis and it could be assumed that variations in the degree of contact inhibition among the cell types within the tissue in response to external stimuli or in different developmental stages are needed in order to achieve this. For example, we would expect contact inhibition to be more active in fully differentiated tissues, somehow lowered in the context of tissue regeneration (i.e. wound healing) and to be virtually switched off in scenarios such as embryo development. Thus several control mechanisms exist in cells to regulate cell proliferation in response to physical contact and accessibility to growth factors. Dysregulation in one or more of these control mechanisms occurs in cancer, allowing the cells to proliferate and disregard the inhibitory signals coming from their surrounding environment. Several pathways have been implicated in contact inhibition and the so-called Hippo pathway has been shown to be particularly relevant due to its critical role in organ size control, cell proliferation and tumour development. In this review, we will describe the core components of the Hippo-YAP (Yes-associated protein) pathway as well as the upstream mechanisms regulating its activity and the downstream consequences. Finally we will go over the current findings that reveal an important role for this pathway in the control of cell growth in head and neck cancer, as well as therapeutic opportunities aimed at the inhibition of this pathway for the treatment of cancer (see Fig. 1).

Discussion

The core complex of the Hippo-YAP pathway

The first components of the Hippo pathway were described in *Drosophila melanoganster* as proteins involved in the regulation of cell growth, proliferation and death [1–4]. However, the importance of the Hippo pathway in the control of cell growth was uncovered 15 years ago with the phenotypic and molecular characterisation of the *Drosophila* Hippo gene [5–9]. This signalling pathway is evolutionarily conserved from flies to mammals, thus highlighting its biological relevance [10].

The core complex of the Hippo pathway comprises a serine/threonine kinase cascade cytoplasmic component that integrates signalling from different upstream cues, and an effector nuclear transcriptional element responsible for the downstream activity of the pathway (Fig. 2). In mammals, when the Hippo pathway is active (Hippo ON), the serine and threonine kinases MST1 and MST2 (mammalian STE20-like protein kinase 1 and 2, respectively; also STK4 and 3) together with the adaptor protein SAV1 (salvador family WW domain containing protein 1) phosphorylate and activate the LATS1/2 kinases (large tumour suppressor kinase 1 and 2) [11–13]. LATS1/2 kinases in combination with another adaptor protein, MOB1 (MOB kinase activator 1),

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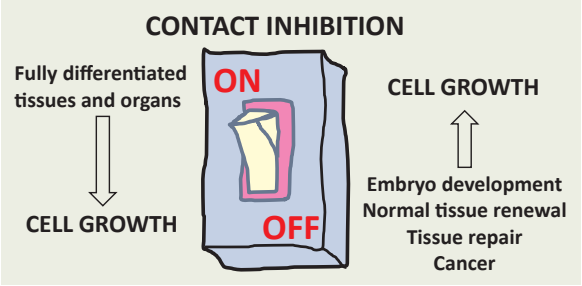

Fig. 1. Contact inhibition works to inhibit cell growth in fully differentiated tissues and organs. This mechanism can be switched off to allow embryo development, normal organ and tissue renewal, as well as tissue repair. However, cancer cells often show the capacity to switch off contact inhibition and proliferate even in conditions where cells are completely surrounded by neighbours.

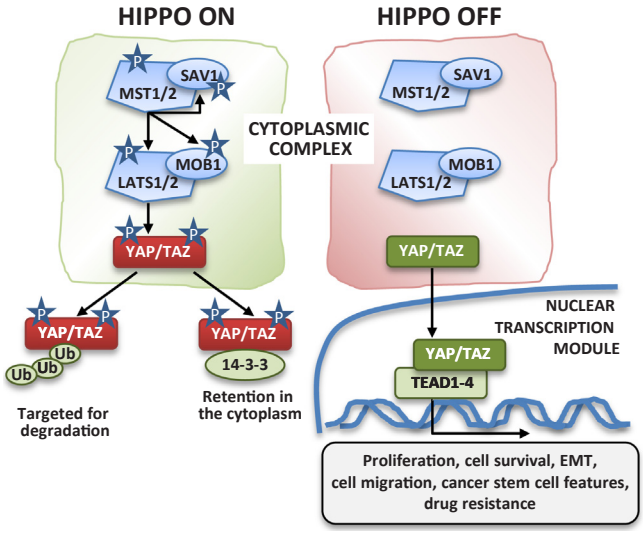

Fig. 2. The Hippo-YAP pathway core complex comprises the Ser/Thr kinases MST1/2 and LATS1/2, their dimerising partners SAV1 and MOB1, and the transcriptional regulators YAP and TAZ. Upstream stimuli phosphorylate and activate MST1/2 kinases turning the pathway to its ON state. Subsequent events culminate in the phosphorylation at conserved serine residues of YAP and TAZ by activated LATS1/2 kinases. This primes for further phosphorylation by other kinases which facilitate YAP/TAZ ubiquitination and ensuing degradation, or its binding to 14-3-3 and retention in the cytosol. In the absence of MST1/2-LATS1/2 activation (OFF state), YAP and TAZ translocate to the nucleus where they bind to the TEAD family of transcription factors promoting the transcription of genes involved in cell proliferation and survival, and conferring cell drug resistance features and cancer stem cell traits. EMT: epithelial to mesenchymal transition.

phosphorylate YAP and its paralog TAZ (transcriptional co-activator with a PDZ-binding domain) [14–16]. YAP and TAZ are the effector components of the pathway and they function in the nucleus to promote gene transcription. Their phosphorylation by LATS kinases causes YAP/TAZ nuclear exclusion, cytoplasm retention mediated by the interaction with 14-3-3 protein and ubiquitination-mediated proteosomal and lysosomal degradation [17,18]. This impedes YAP/TAZ target gene expression.

Loss of contact inhibition or growth factor signalling can inactivate the Hippo-YAP pathway (Hippo OFF) (Fig. 2). In this context, the cytoplasmic component of the pathway is not activated, and cannot phosphorylate YAP and TAZ that translocate to the nucleus. In the nucleus, these factors do not bind directly to DNA; instead they interact with DNA-binding transcription factors to regulate target gene expression (reviewed in [19]). The major transcriptional YAP/TAZ binding partner is the TEAD family of transcription factors (TEA domain transcription factors 1–4), which is considered to be responsible for the majority of the proliferative, anti-apoptotic and oncogenic activities of YAP and TAZ [20].

The Hippo-YAP pathway has been identified as one of the main oncogenic signalling pathways in a recent study comprising > 9000 tumours from 33 cancer types including head and neck squamous cell carcinoma (HNSCC) [21]. The kinases that make up the cytoplasmic complex of the Hippo-YAP pathway are considered tumour suppressors while the components of the nuclear effector transcription module act as oncogenes [21].

Upstream control of the Hippo-YAP pathway

The Hippo-YAP pathway receives inputs from the cell microenvironment as well as from cell intrinsic signals. The main microenvironment-mediated cues influencing the pathway come from cellular mechanisms involved in contact with neighbouring cells, in establishing cell orientation, or sensing the characteristics of the extracellular matrix (tight and adherens junctions proteins, cell polarity complexes, and mechanical inputs); as well as the presence of extracellular soluble growth factors. Cell autonomous signals (intrinsic) affecting the Hippo-YAP pathway include cytoskeleton organisation and metabolism (Fig. 3).

In epithelial cells apical-basolateral polarity is strictly specified. In fact loss of cell polarity leads to dysplasia. It constitutes an initial step in the process of epithelial to mesenchymal transition (EMT), a genetically activated transdifferentiation programme that induces epithelial cell change, acquiring a fibroblast-like morphology and migratory properties, which is a hallmark of cancer [22]. There are three modules localised in different positions throughout the apical-basal axis of the epithelial cells that can regulate the Hippo-YAP pathway: (i) the apical Crumbs; (ii) the basolateral Scribble polarity complexes; and (iii) the cadherin-catenin complex at the adherens junctions that separates the apical and basolateral membranes. In a polarised epithelial cell the Crumbs complex (CRB3, PALS1, PATJ and AMOT) localises at the apical membrane. AMOT acts as a scaffolding protein that recruits the Hippo core kinases and YAP to the plasma membrane promoting its phosphorylation by LATS1/2 [23–25], thus hindering YAP translocation to the nucleus. Scribble complex (SCRIB, LGL and DLG) defines the basolateral domain of the cell membrane [26] and forms a membrane-localised protein complex with Hippo core components (MST1/2, LATS1/2 and TAZ) promoting TAZ phosphorylation and its degradation [27]. In human epithelial cancers Scribble is frequently disabled [28], and its delocalisation or loss leads to the activation of YAP/TAZ and increased TEAD transcriptional activity [27,29,30]. At the adherens junctions, a cadherin-catenin complex (E-cadherin, α/β-catenin, NF2/Merlin, WWC1/Kibra) activates the Hippo-YAP signalling pathway possibly through two mechanisms: direct interaction and cytoplasmic sequestration of the YAP inhibitory complex 14-3-3/YAP by α-catenin [31,32], and NF2/Merlin mediated activation of LATS1/2 leading to concomitant phosphorylation and inactivation of YAP [33]. Importantly, cadherin-mediated activation of the Hippo-YAP pathway relies on homophilic binding of E-cadherin [34] (binding of the E-cadherin extracellular domain of one cell to another on the surface of a neighbouring cell), thus linking cell-cell contact to inhibition of cell growth. In addition to adherens junctions, tight junctions form part of the apical junctional complex and contribute to the formation and maintenance of apical-basolateral cell polarity. In the context of epithelial integrity, PAR3/6 and aPKC (atypical protein kinase C) associate with the MST1/2-SAV1 complex, regulating its apical localisation, which brings it close to LATS1/2. This, in turn, triggers the inhibition of YAP/TAZ. Interestingly, membrane delocalisation of aPKC has the opposite effect, promoting YAP activation, possibly by uncoupling MST1/2 from LATS1/2 [35]. Interaction of ZO-2, another component of tight junctions, and YAP has been reported [36].