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Review

The roles of the Hippo pathway in cancer metastasis

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ABSTRACT

Cancer metastasis refers to the sequence of events whereby tumour cells detach from their primary tissue, invade and migrate to nearby vasculature, intravasate into circulation, survive in circulation and extravasate at a distant site to establish a secondary tumour. Each step in this "metastatic cascade" is coordinated by complex molecular events that remain only incompletely understood. Given that the vast majority of cancer fatalities occur due to metastasis, there is an urgent need for an improved understanding of the specific mechanisms underlying cancer metastasis and for the development of therapeutics targeting this lethal process.

The Hippo pathway is an emerging signaling pathway that plays important roles in development and disease. In cancer cells, dysregulation of the Hippo pathway drives multiple aspects of tumour initiation and progression. Recent studies have uncovered a role for the Hippo pathway core components in promoting cancer metastasis. In this review, we summarize the clinical and biochemical evidence implicating the Hippo pathway in metastasis. Additionally, we describe the molecular mechanisms by which aberrant Hippo signaling promotes metastasis. Finally, we highlight areas for future research.

Contents

Abbreviations: ABL, Abelson tyrosine protein kinases; AMOT, angiomotin; AMOTL1, angiomotin-like protein 1; aPKC, atypical protein kinase C; AREG, amphiregulin; Baz, bazooka; BIM, BCL2-Like 11; BMP4, bone morphogenic protein 4; BC, breast cancer; CD31/44, cluster of differentiation 31/44; CDC42, cell division cycle 42; CIZ1, CDKN1A-interacting zinc finger protein 1; CK1, casein kinase 1; CSC, cancer stem cell; CTGF, connective tissue growth factor; CUL4A, Cullin 4A; CXCR2, chemokine (C-X-C motif) receptor 2; CYR61, cysteine-rich angiogenic inducer 61; Diap1, *Drosophila* inhibitor of apoptosis protein 1; DVL, dishevelled; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; Ena, enabled; ERK, extracellular signal-related kinase; Ex, expanded; FAT4, FAT atypical cadherin 4; FOS, FBJ murine osteosarcoma viral oncogene homolog; FOXC2/M1, forkhead box C2/M1; GNAQ, guanine nucleotide binding protein (G protein) Q polypeptide; GPCR, G-protein-coupled receptor; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor-1α; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HNSCC, head and neck squamous cell carcinoma; Hpo, Hippo; IAP, inhibitor of apoptosis protein; IL-6, interleukin-6; IL13Rα2, IL-13 receptor subunit α-2; ITCH, itchy E3 ubiquitin protein ligase; KIBRA, kidney and brain expressed protein; LATS1/2, large tumour suppressor kinase 1/2; LIFR, leukemia inhibitory factor receptor; LN, lymph node; LPA, lysophosphatidic acid; LPAR3, LPA receptor 3; Mats, mob as a tumour suppressor; MMP-2/9, matrix metalloproteinase-2/9; MST1/2, mammalian sterile 20-like kinase 1/2; MOB1, Mps one binder kinase activator-like 1A and 1B; NANOG, Nanog homeobox; NEGR1, neuronal growth regulator 1; NSCLC, non-small cell lung cancer; OCT4, octamer binding transcription factor 4; OSCC, oral squamous cell carcinoma; PAR1, protease-activated receptor 1; PDE5, phosphodiesterase 5; PKG, protein kinase G; PTPN14, protein tyrosine phosphatase non-receptor type 14; PyMT, polyoma middle T antigen; RARγ, retinoic acid receptor γ; RASSF1A/5, Ras association domain family 1 isoform A or 5; RHAMM, hyaluronan-mediated motility receptor; RHOA, Ras homolog family member A; Sav, Salvador; Sav1, Salvador family WW domain containing protein 1; SNAIL, SLUG, snail family zinc finger 1/2; SOX2/9, sex-determining region Y (SRY)-box 2/9; STAT5, signal transducer and activator of transcription 5; TAZ, transcriptional co-activator with PDZ-binding motif; TEAD, TEA-domain family; TGF-β, transforming growth factor-β; TWIST, twist-related protein 1; UCA1, urothelial cancer associated 1 non-coding RNA; Wts, warts; YAP, Yes-associated protein; Yki, Yorkie; ZEB1, zinc finger E-box binding homeobox 1.

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1. Introduction

1.1. Cancer metastasis

Cancer metastasis—the spread of tumour cells from a primary tissue into distant secondary sites—represents a critical point in cancer treatment and prognosis. For many patients, a diagnosis of metastatic cancer renders conventional treatment modalities ineffective and changes treatment goals from curative to non-curative (palliative). Indeed, the majority of cancer fatalities happen as a consequence of metastasis [1,2]. The poor prognosis associated with metastatic cancer is, in some ways, a product of our incomplete understanding of the mechanisms underlying metastasis such that no curative treatments exist for many patients.

Metastasis is often conceptualized as a multi-step progression of tumour cells detaching from their surrounding tissue, invading through the local extracellular matrix (ECM), migrating to lymph or blood vasculature, intravasating into circulation, surviving in circulation and then extravasating at a distant tissue to establish a secondary tumour. With recent technological advances, this simplified metastatic cascade has evolved into a more complete and sophisticated model of tumour cell dissemination and colonization. For example, it is now widely recognized that the tumour microenvironment and intratumoural heterogeneity contribute to the metastatic sequence [3,4].

There have been extensive efforts to understand metastasis at the molecular level and to develop therapeutics specifically targeting key regulators of metastasis. Numerous cellular pathways have been implicated in cancer metastasis including Notch, Wnt and transforming growth factor-β (TGF-β) signaling among others (reviewed in [5–7]). Recently, the Hippo signaling pathway has been characterized as a cell network mediating cancer metastasis. In this review, we summarize the roles of Hippo signaling in promoting cancer metastasis. We describe the clinical evidence and studies of *in vivo* mouse models that demonstrate how dysregulation of Hippo pathway core components influences metastasis. We then consider the precise mechanisms by which Hippo signaling may promote metastasis. Specifically, we highlight the Hippo pathway's involvement in epithelial-mesenchymal transition (EMT), cell migration/invasion, vascular invasion, resistance to anoikis and cancer stem cell (CSC) phenotypes. Finally, we describe potential areas for future research.

1.2. The core Hippo pathway in Drosophila melanogaster and mammals

The founding member of the Hippo signaling pathway, large tumour suppressor (*lats*) or *warts* (*wts*), was originally identified in *Drosophila.* In a genetic screen for genes involved in cell proliferation, loss of *wts* led to increased proliferation and organ size [8,9]. Subsequent loss-of-function genetic screens produced similar phenotypes, leading to the

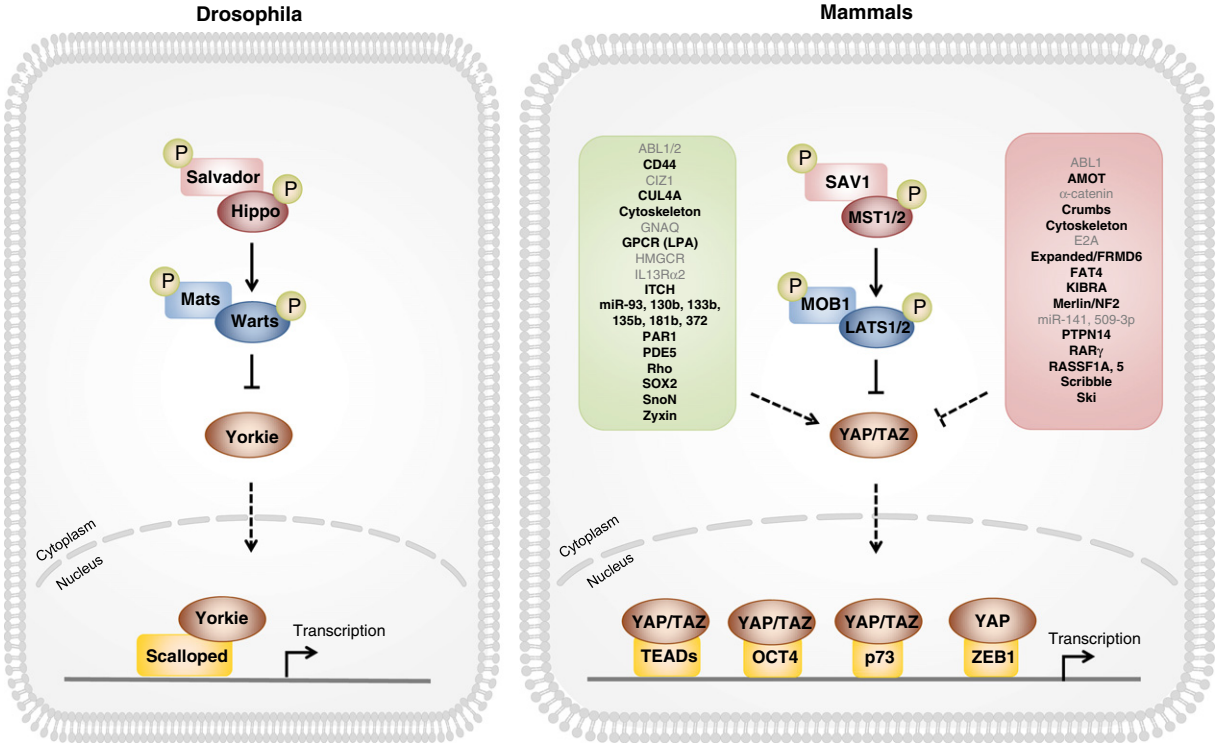

Fig. 1. Core Hippo pathway components in *Drosophila melanogaster* and mammals as summarized in Section 1.2. Arrows denote activation whereas blunted lines indicate inhibition. Proteins that directly or indirectly regulate YAP/TAZ are included in the green (activators) and red (inhibitors) boxes. Regulators which affect YAP/TAZ activity through MST1/2 or LATS1/2 are emphasized in bold font.