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Evolution of mechanotransduction via YAP/TAZ in animal epithelia

Ahmed Elbediwy and Barry J Thompson

Mechanical stretch forces can control the growth of epithelial tissues such as mammalian skin, whose surface area is precisely coordinated with body size. In skin keratinocytes cultured *in vitro*, mechanical forces acting via Integrin adhesions and the actin cytoskeleton have been shown to induce nuclear translocation of YAP/TAZ co-activators to induce cell proliferation. Furthermore, conditional knockouts of both YAP (also called YAP1) and TAZ (also called WWTR1) in mouse skin resemble the phenotype of skin-specific loss of Integrin beta1 (ITGB1), indicating that this signalling mechanism is important *in vivo*. Curiously, Integrins are dispensable in *Drosophila* to activate the sole YAP/TAZ homolog Yorkie (Yki), which has lost the C-terminal PDZ-binding motif needed to promote nuclear localization of YAP/TAZ in mammalian cells. Differences in the structure of the epidermis between deuterostomes (e.g.: stratified squamous skin of mammals) and protostomes (e.g.: monolayered columnar epidermis of *Drosophila*) may explain this evolutionary divergence. Monolayered columnar epithelia feature a well-differentiated apical membrane domain, where proteins such as Crumbs, Expanded, Merlin and Kibra activate the Hippo pathway to repress *Drosophila* Yki. Stratified squamous epithelia lack an apical domain and thus depend primarily on basal Integrin adhesions to activate YAP/TAZ in basal layer stem cells via multiple postulated signalling mechanisms. Finally, YAP and TAZ retain the ability to sense the apical domain in the columnar epithelial cells lining internal organs such as the lung bronchus, where YAP/TAZ localize to the nucleus in proliferating basal layer stem cells but translocate to the cytoplasm in differentiated columnar cells.

Address
Epithelial Biology Laboratory, The Francis Crick Institute, 1 Midland Rd, London NW1 1AT, United Kingdom

Corresponding author: Thompson, Barry J (barry.thompson@crick.ac.uk)

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Introduction

The YAP/TAZ family of transcriptional co-activators has emerged as a fundamentally important regulator of stem cell proliferation, tissue regeneration, and tumour formation in mammalian skin and other epithelia [1,2]. Recent reviews have focused either on the role of YAP/TAZ as mechanotransducers in mammals [3] or as effectors of the Hippo signalling pathway in both *Drosophila* and mammals [4,5]. Whether these two roles of YAP/TAZ are in fact distinct or overlapping remains a point of contention due to conflicting results from *Drosophila* and mammals. Here we expand on recent efforts [6] to take an evolutionary perspective on mammalian YAP/TAZ and their sole *Drosophila* homolog, Yorkie (Yki), comparing their mechanisms of regulation in different epithelial tissues from different animal species. We begin with a historical overview of the discovery of these co-activators, with the aim of illustrating how conflicting models of their role and regulation have emerged over time. We then suggest that these conflicts can be resolved by considering how evolutionary differences in protein sequence between Yki and YAP/TAZ have arisen alongside fundamental changes in the structure of epithelial tissues during animal evolution.

The early discovery of YAP/TAZ as co-activators of TEAD transcription factors

The Yes-associated protein (YAP or YAP1) was initially discovered via its ability to associate with the Src family kinase member Yes [7,8]. The first molecular function of the YAP protein was a biochemical one, with the WW domain of YAP shown to bind directly to proline-rich PPXY motifs in proteins named WBP-1 and WBP-2 [9]. YAP and a highly similar protein named TAZ (also named WWTR1) were subsequently shown to have transcriptional co-activator activity as well as to be regulated by interaction with 14-3-3 proteins (after serine phosphorylation) and by interaction with PDZ domain-containing proteins (via a C-terminal PDZ binding motif or PBM) [10,11]. YAP was then shown to co-activate transcription via the nuclear TEAD family of DNA binding transcription factors, even though the majority of the YAP protein was localized to the cytoplasm in complex with 14-3-3 proteins [12]. These early biochemical discoveries were severely hampered by the lack of any detailed genetic analysis of the function of these proteins *in vivo*, and the subsequent discovery of a *Drosophila* homolog of YAP and TAZ, named Yorkie (Yki), consequently had a great impact on the field.

Hippo (MST-LATS) signalling inhibits both Yki and YAP/TAZ

The discovery of Drosophila Yki revealed it to be the nuclear effector of the previously identified Hippo tumour suppressor pathway [13]. The Hippo pathway consists of the upstream kinase Hippo (Hpo in *Drosophila*; MST1/2 in mammals; Cdc15 in *S. cerevisiae*; Sid1/Cdc7 in *S. pombe*) and the downstream kinase Warts/LATS (Wts in Drosophila; LATS1/2 in mammals; Dbf2 in *S. cerevisiae*; Sid2 in *S. pombe*) [1,2]. Notably, the identification of MST-LATS kinases and their molecular relationship was first revealed in yeast, where they function to regulate mitotic exit and cytokinesis (reviewed in [14,15]). In *Drosophila*, loss of Wts/LATS was discovered to generate tumour formation in proliferating epithelia such as developing fly wings or eyes, indicating a novel role for these kinases in restricting the overall rate of cell proliferation in multicellular tissues [16,17]. The discovery of *Drosophila* Yki — a protein not found in yeast — as a direct target of Wts/LATS kinases and the nuclear effector responsible for driving cell proliferation downstream of the Hippo pathway was thus an important breakthrough [13] that was rapidly confirmed in both *Drosophila* [18,19] and mammalian cells [20].

As might have been predicted from the early results in mammalian cells, *Drosophila* Yki acts via a TEAD transcription factor (Scalloped or Sd in *Drosophila*) and recruits WBP-2 as a co-activator [21–24]. In contrast, unbiased forward-genetic screens in *Drosophila* soon revealed a variety of novel upstream regulators of the Hippo pathway that provided the first hints as to the possible physiological function of this pathway.

Apical proteins activate Hippo (MST-LATS) signalling

The first apical proteins identified upstream of *Drosophila* Hippo were Merlin (Mer) and Expanded (Ex), two FERM-domain containing proteins that localize to the apical cortex of epithelial cells and act in a parallel or semi-redundant manner to induce Hippo signalling [25]. Subsequently, the apical transmembrane protein Crumbs (Crb) was shown to bind to Ex [26–28] and the novel WW-containing apical protein Kibra was shown to bind to Mer to promote Hippo signalling and inhibit Yki in *Drosophila* [29–31]. Recent findings revealed that while Crb-Ex complexes are primarily localized to apical cell-cell junctions, Kib-Mer complexes are primarily localized to the medial region of the apical domain, suggesting a possible explanation for their genetic semi-redundancy [32]. The apical spectrin cytoskeleton links these FERM-domain containing complexes into a mechanically responsive cortical network, suggesting a possible role of the apical domain in sensing mechanical stretching (mechanical strain) in epithelial cells [33,34,72].

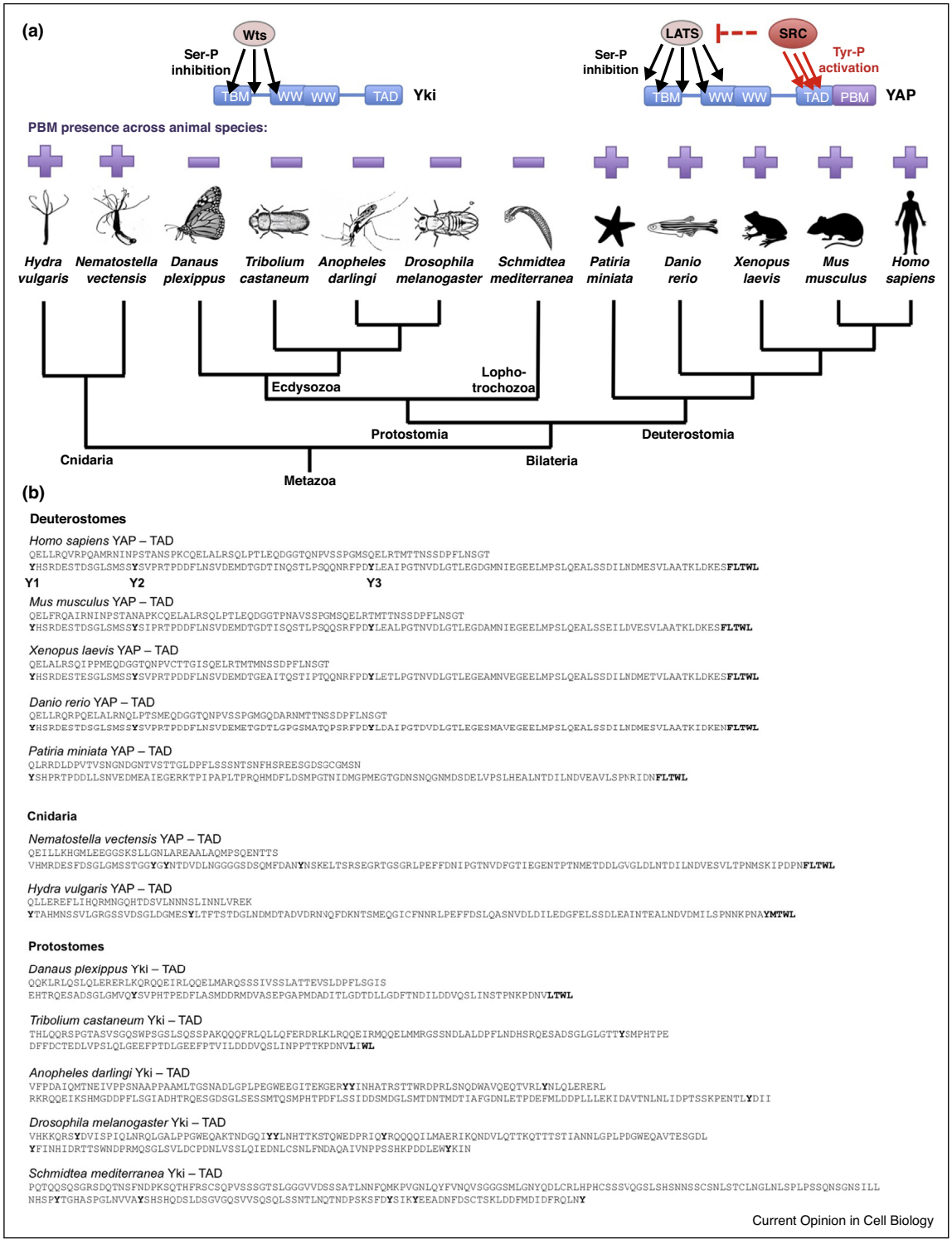
Importantly, results from mouse genetics have demonstrated a conserved role for mammalian homologs of Crb (CRB3) and Mer (NF2) in repressing YAP/TAZ activity *in vivo*. In the case of CRB3, a conserved role in activating the Hippo pathway at apical cell-cell junctions and thereby inhibiting YAP by cytoplasmic retention was shown in the bronchial airway epithelium of the lung [35]. Loss of CRB3 during bronchus development led to nuclear translocation of YAP and defective cell differentiation [35]. In the case of Mer/NF2, a conserved role in activating the Hippo pathway was demonstrated in liver development, where inactivation of Mer/NF2 generated hepatocellular carcinoma and bile duct expansion that were suppressed by deletion of YAP [36,37].

In contrast, other regulators of Hippo signalling identified in *Drosophila* do not appear to have a conserved role in mammals. For example, the Dachsous-Fat cadherin signalling pathway acts via FbxL7 and Dlish to control the Dachs myosin and thereby influences Yki activity in *Drosophila* [38–40]. However, mammalian FAT1-4 do not appear to activate a Dachs-like molecule and instead more closely resemble *Drosophila* Fat2 in their intracellular domain, which binds to the F-actin regulator Wasp and regulates the phosphatase Lar to control planar cell polarity [41–44]. Similarly, adherens junctions have been proposed to recruit the Ajuba protein to inhibit the Wts/LATS kinase and thus activate Yki in a potential mechanism of mechanotransduction in *Drosophila* [45,46]. Recent evidence from cell culture suggests that a similar direct signalling mechanism may be conserved in mammals [47], yet mouse knockouts for the crucial adherens junction component alpha-catenin do not cause loss of YAP/TAZ activity and instead lead to skin tumours due to YAP/TAZ hyperactivity [48]. Furthermore, important work indicates that adherens junction do not have a direct signalling role but rather provide cell-cell adhesion, which then allows mechanical strain (cell shape change) to be sensed by YAP/TAZ [49]. Other groups suggest that regulation of YAP/TAZ by forces acting on adherens junctions requires Merlin, a canonical Hippo pathway component that associates with tight junctions and can surprisingly also shuttle to the nucleus in mammalian cell culture [50,51].

Basal Integrin adhesions activate YAP/TAZ but not *Drosophila* Yki

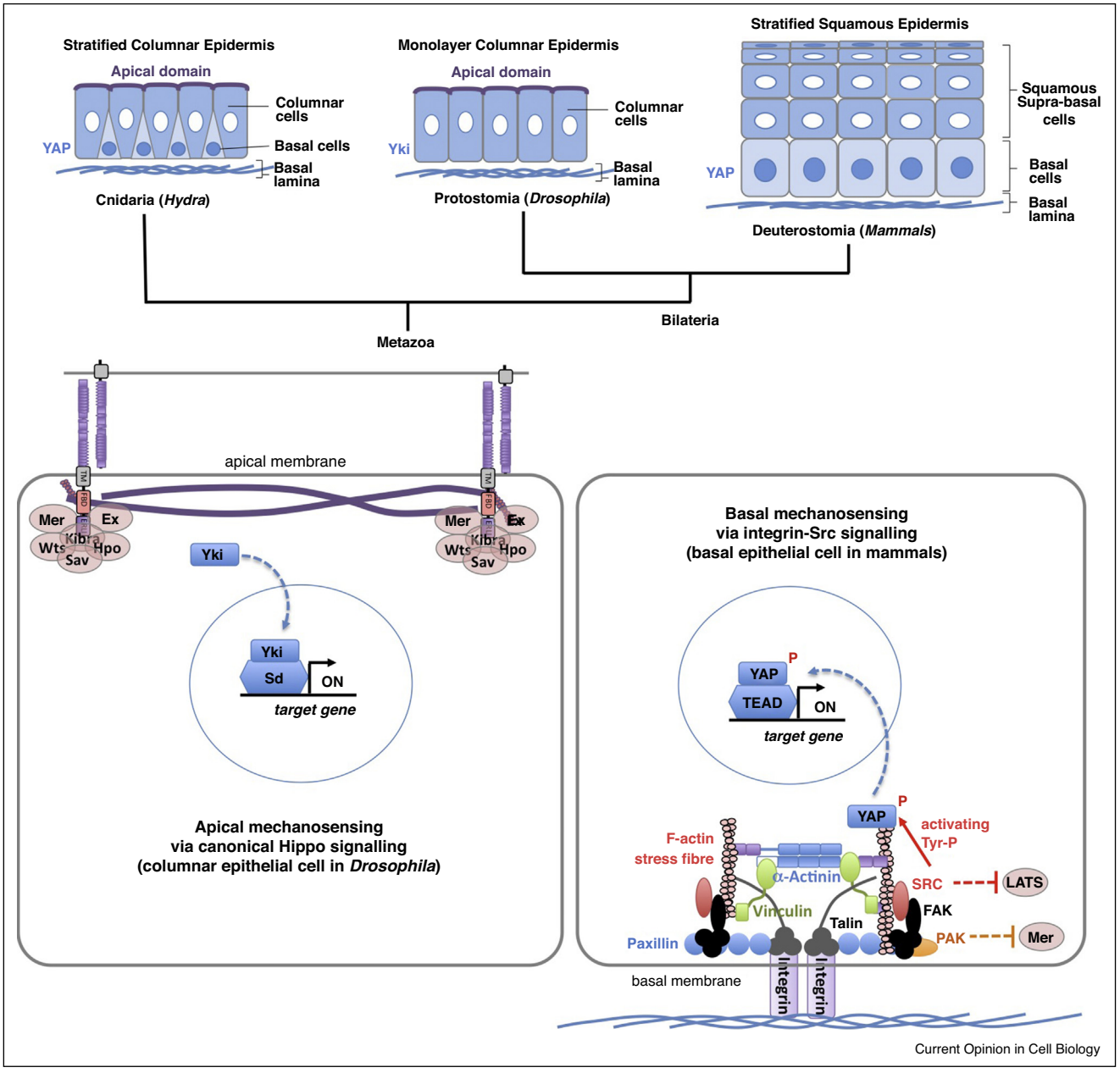
The mechanism by which YAP subcellular localization is regulated in response to cell density has been a problem of intense research interest since its initial observation [20]. Culture of cells on micropatterns and different matrix types suggested that the size of the contact cells make upon spreading over their basal substrate, substrate stiffness, and the resulting mechanical tension on F-actin stress fibres are key determinants of YAP subcellular localization in response to cell density [52,53]. However, two groups drew opposite conclusions as to whether

Figure 1



Animals with stratified epithelia (deuterostomes and cnidaria) have the YAP C-terminal PDZ-binding motif (PBM) and conserved tyrosines (Y) in the YAP transcriptional activation domain (TAD).

Figure 2



Apical versus basal mechanotransduction via Yki or YAP in different animals.

mechanical tension on stress fibres signals primarily via the Hippo pathway kinase LATS1/2 to control YAP localization [53], or via an unknown pathway [52].

Recent work has confirmed a key role for Integrin adhesion to the extracellular matrix and Integrin signalling via RhoGTPase activation and Src family kinases as important mechanosensory mechanisms that regulate YAP [54–58]. Integrin-Src signalling can affect LATS1/2 phosphorylation of YAP [55,56] possibly via direct tyrosine phosphorylation of LATS1 [59], or via Src activation of FAK [60]. Alternatively, Integrin-Src signalling can also activate YAP via direct tyrosine phosphorylation of YAP in its transcriptional activation domain [48,61]. Whether and how YAP might be recruited to Integrin adhesions in order to be directly phosphorylated by Src family kinases in response to mechanical force is an important unsolved problem. Interestingly, although Integrin and Src homologs exist in *Drosophila*, there is no evidence that they are required for Yki activity, and Yki lacks the three conserved tyrosine residues and C-terminal PDZ binding motif found in YAP due

to divergence in the sequence of the Yki and YAP transcriptional activation domains (Figure 1). Ectopic activation of Src has been proposed to activate Yki [62], although this may be an indirect effect of over-expressed Src disrupting the apical membrane domain.

An alternative mechanosensory pathway acting downstream of Integrin adhesions is the activation of the Pak-family kinases via recruitment of the small GTPases Cdc42 or Rac, which bind to Pak kinases to induce their activation [63–67]. Pak1 has been shown to directly phosphorylate Merlin/NF2 to induce its dissociation from the plasma membrane and thus inactivate its activity [68–70]. In cell culture, Pak activity may thus contribute to YAP activation via inhibiting Merlin/NF2 dependent Hippo signalling [71]. Whether this signalling pathway functions in other cell types or *in vivo* remains unclear. Notably, the mammalian Merlin phosphorylation site is not conserved in *Drosophila* Merlin, indicating that this pathway cannot exist in *Drosophila*. Thus, Integrin signalling appears to promote YAP activity by a variety of signalling pathways in mammals, yet there is no known mechanism by which it can activate Yki activity in *Drosophila*.

Evolution of epithelia after the protostome-deuterostome split

Is there an evolutionary explanation for the differences in protein sequence and regulation between mammalian YAP and insect Yki? Sequence comparisons across metazoans reveals that YAP is highly conserved among most deuterostomes, while Yki-like genes that lack the YAP-specific C-terminal PBM are found throughout protostomes (Figure 1). Interestingly, the last common ancestor of protostomal Yki and deuterostomal YAP is likely to have resembled YAP, because Cnidarians (an outgroup) also have YAP-like homologs featuring a PBM rather than Yki-like versions. This suggests that the YAP PBM was lost at the protostome-deuterostome split, giving rise to Yki-like homologs across protostomes.

Why might protostomes have lost the YAP PBM, and thus the potential for YAP to sense basal Integrin signals? One possible explanation lies in differences in the structure of the epidermis between protostomes (monolayer columnar epithelia) and deuterostomes (usually stratified squamous epithelia). The basal layer stem cells of deuterstome epidermis (e.g.: mammalian skin) lack an apical domain so must sense basal Integrins to regulate stem cell behaviour (Figure 2). In contrast, the columnar epithelial cells of protostome epidermis (e.g.: *Drosophila* epithelia) can sense apical signals, including the possible stretching of the apical domain, and thus do not necessarily require input from Integrins or a PBM (Figure 2). The Cnidarians are composed of stratified columnar epithelial tissue, with both basal layer cells (interstitial cells) and columnar cells, which may reflect the ancestral state of the epidermis before its divergence (Figure 2).

In summary, an evolutionary split appears to have occurred in the regulation of Yki and YAP in animals. This split involves divergence in the mechanosensing mechanisms, which may explain why genetic experiments have identified apically localized molecules as being central to Yki regulation while basal Integrin signals are at least as important in regulating YAP/TAZ.

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