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Review

Disclosing JAK/STAT links to cell adhesion and cell polarity

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ABSTRACT

The components of many signalling pathways are localised in specific cellular compartments in polarised cells. This is particularly clear in the case of the receptors that localise to the apical or basal membrane in the epithelial cells. In many cases this subcellular localisation is important for the activation of the signalling pathways. In this review we analyse recent developments uncovering an interesting interplay between JAK/STAT signalling and components regulating cell polarity and adhesion during development. Not only the JAK/STAT signalling components are polarised in epithelial cells but many genes controlling cell polarity and adhesion are targets of STAT and in some cases these components act as pathway activators. The fact that in most morphogenetic processes cell adhesion and polarity proteins are regulated downstream of the pathway, hints at a possible unifying mechanistic explanation for the diverse morphogenetic processes controlled by JAK/STAT during development.

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The morphogenetic movements of development subject the cells to major reorganisations of their polarity. One of the best-studied is the epithelial to mesenchymal transitions occurring when polarised epithelial cells loose their attachment to neighbouring cells and become motile. The opposite transition also occurs when motile migratory cells reach their destination and form an epithelium or integrate into a pre-existing one. Examples of such transitions exist in all organisms and are exemplified in vertebrates by the migration of the neural crest cells. Increasing our knowledge of the mechanisms controlling such major polarity reorganisations is fundamental to prevent similar processes occurring in pathological situations such as the metastatic migration of cancer cells.

Signalling pathways are among the most important developmental regulators inducing morphogenetic movements and must therefore be ultimately responsible for the cell polarity changes they control. Interestingly, the localisation of the signal transduction elements themselves is in many cases polarised in the cell, creating a potential crosstalk between polarity and signal transduction pathways. Many major signalling pathways have been shown to be partially polarised. For example, the Notch receptor localises to the apical membrane [1], and the EGFR [2–4], Patch [5] and Frizzled [6] receptors localise to the basolateral membrane. Recent results have added the JAK/STAT pathway to this list [7].

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JAK/STAT signalling has been analysed extensively in vertebrates in the development of the blood system. The generally accepted view is that in inactive cells, unphosphorylated STAT resides mainly in the cytoplasm due to its continual export from the nucleus [8] although in many instances, unphosphorylated STAT can be detected in the nucleus and STAT has also been described to be bound to the plasma membrane (see below). Cytokine activation of the transmembrane homo- or heterodimeric receptor induces a conformational change whereby the JAK kinases, which are constitutively bound to the intracellular part of the receptors, activate each other and the receptor by tyrosine phosphorylation. Cytoplasmic STAT now binds the active receptor and becomes also tyrosine phosphorylated, dimerising and translocating to the nucleus where it activates the transcription of targets genes (reviewed in [9,10]). Besides STAT nuclear translocation, and the known JAK association to the plasma membrane mediated by its binding to the receptor complex [11,12], there has not been much work done on the fine subcellular localisation of the signalling components. Analysis of the subcellular localisation of all the elements of the complete signalling pathway in all tissues is difficulted in vertebrates by the existence of a highly redundant pathway composed of 7 STAT proteins, 4 JAK kinases and a multitude of receptors and ligands [9]. In contrast, this analysis is now possible in the model organism *Drosophila melanogaster* where a streamlined JAK/STAT signalling pathway has been conserved with only one STAT, one JAK (encoded by *hopscotch*, *hop*), one homo-dimeric receptor (*domeless*, *dome*) and only three clustered ligands (*unpaired* (*upd*), *upd2* and *upd3*) [13,27]. Analysis of this system has uncovered an interesting interplay between cell polarity and JAK/STAT signalling. This involves, on the one hand, the control of several polarised and cell adhesion molecules by the pathway and, on the other, the modulation of JAK/STAT signalling by molecules involved in cell polarity. Although many of these observations come from the *Drosophila* field, we will review abundant evidence indicating there is a similar interplay in vertebrates.

1. The polarised epithelial cell

Most cells are polarised and this affects the way they interact with their environment. This is clearly established for the epithelia where the apical surface has to become specialised for secretion or absorption or to produce structures that will protect the organism from external damage or desiccation. It is thus not surprising, that the localisation of many proteins in the cell membrane is polarised. An important group of polarised proteins are those transducing signals during cell–cell communication. In this section we will briefly summarise how polarity is established and maintained.

Neighbouring epithelial cells are attached through the adherens junctions. These are constituted, among other proteins, by belts of cadherins that bind homophyllically to the cadherins of the neighbouring cell. The cadherin belt subdivides the plasma membrane in domains that differ in their composition of lipids and proteins and perform different functions. There is an apical domain facing the exterior or luminal side, a lateral domain contacting neighbouring epithelial cells, and a basal domain in contact with the basement membrane and interstitial space. These domains exist in vertebrates and invertebrates although the lateral domains differ structurally. For instance, to prevent leakage between the interstitial space and the lumen, vertebrates posses tight junctions apical to the adherens junctions while invertebrates have septate junctions basal to the adherens junctions. Besides promoting cell adhesion, adherens junctions constitute a physical barrier between the apical and basal membrane domains preventing protein diffusion between them. Several conserved proteins control the formation and maintenance of the membrane's polarity (Fig. 1). The Par-3/Par-6/aPKC complex and the Crumbs/PATJ/Pals1 complex localise apical to the cadherins while the Lgl/Dlg/Scribble complex is basal to the cadherins (reviewed in [14,15]).

The establishment of epithelial polarity has been well studied. In *Drosophila*, the first sign of epithelial polarity is the formation of the adherens junctions by accumulation of E-cadherin into apical spot junctions (Fig. 1A), a process that requires Par-3 [16]. Soon after Par-3, Crb and Dlg complexes act sequentially to direct the maturation of epithelial cell polarity. The Par-3 complex is the first and most critical apical regulator in polarity establishment (Fig. 1A). Par-3 is followed by the appearance of the transmembrane protein Crb that is stabilised in the apical membrane through phosphorylation by aPKC [17]. Crb in turn helps to stabilise the Par-3 complex, with both complexes segregating to closely apposed areas in the subapical region [18] (Fig. 1B). Finally, the basolateral Dlg complex is established with a mutual inhibition between the apical and the basolateral complexes keeping the proteins segregated to different membrane compartments (Fig. 1C) [19,20]. Despite the structural differences in the lateral membrane between vertebrates and invertebrates, these complexes and the interactions between them are highly conserved. In vertebrates, the formation of spot adherens junctions also marks the beginning of epithelial polarity establishment. In this case nectins, which do not have a clear invertebrate homolog, trigger cell–cell adhesion recruiting E-cadherin to the adherens junctions. Nectins also recruit other proteins to the apical side of the adherens junctions, among them Par-3. Par-3 is involved in the formation of the adherens junction [21], and the Par-3/Par-6/aPKC complex is also required for the formation and maintenance of the tight junctions in vertebrates (reviewed in [14,22]).

Besides setting up the epithelial polarity, apico-basal complexes also modulate the subcellular compartmentalisation or localised activation of various signalling molecules. The basolateral localisation of the EGF receptor Let-23 in the vulva of *C. elegans* depends on LIN-2, a Dlg related protein [3]. Another case is the polarised activation of the Notch pathway in the pI cell of the adult peripheral nervous system of *Drosophila* controlled by aPKC and Lgl [23–25]. A third example is the control of Notch by Crb in the imaginal wing disc epithelium. Crb regulates the γ-secretase complex, which processes the intracellular part of Notch, restricting its activity to the wing margin where there are higher levels of Crb [26].

Mesodermal tissues can also present a high level of polarisation, but the key molecules controlling it are different as neither Crb nor Par-3 are expressed in the mesoderm. This is reflected in the subcellular localisation of aPKC that in the ectoderm epithelia is apically associated while in the mesoderm it localises to the cytoplasm. An exception to this is the highly specialised follicular epithelium of the *Drosophila* gonad that despite of its mesodermal origin expresses Crb and Par-3.

2. JAK/STAT is required for the morphogenesis of several polarised epithelia

There are several cases where JAK/STAT activation results in epithelial remodelling during *Drosophila* development (reviewed in [13,27,28]). Here we will concentrate on the embryonic stages and in the female gonad development. Due to the absence of redundant signalling elements our knowledge is more advanced in *Drosophila* but many examples also exist in vertebrates (Table 1).

The use of general pathway activation reporters shows that, by and large, expression of the Upd ligands is a good indication of pathway activation [29,30]. There is only one reported case where JAK/STAT activation is Upd independent [31]. All other elements of the pathway – the receptor, JAK kinase and STAT – are ubiquitously expressed, with secondary feed back loops modulating their expression in certain regions. Of the three ligands, *upd* and *upd2*