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Unphosphorylated STATs go nuclear

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The JAK/STAT signal transduction pathway has traditionally been viewed as a cytokine-stimulated activator of gene expression consisting of a straightforward receptor/JAK kinase/STAT transcription factor cascade. Recent studies in *Drosophila*, have, however consistently identified a range of chromatin-remodelling factors as regulators of *in vivo* JAK/STAT signalling. Now, the detailed analysis of one of these, *heterochromatin protein 1* (*HP1*), has provided an insight into an unexpected non-canonical *in vivo* role for STAT. In this model, unphosphorylated STATs associate with and maintain the stability of transcriptionally repressed heterochromatin — an effect countered by the recruitment of STAT to the canonical pathway. We examine the background of this new model and its implications for JAK/STAT pathway requirements in stem cell maintenance and cancer.

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Introduction

The JAK/STAT pathway mediates gene expression in a wide range of cellular contexts and its proper regulation is critical for immunology, development, the maintenance of stem cells and multiple cancers [1–3]. A significant body of research has identified the primary pathway components and has characterised their roles in canonical pathway signalling (Figure 1a). This canonical pathway is composed of multiple cytokines and growth factors that bind to a range of type I and type II cytokine receptors [4] to induce conformational changes that activate the receptor-associated Janus kinases (JAKs). The tyrosine phosphorylation and other post-translational modifications that follow this activation [5–7] create docking sites for the signal transducers and activators of transcription (STATs). These transcription factors are themselves activated by tyrosine phosphorylation, dimerise, translocate to the nucleus and stimulate the transcription of down-stream target genes. The wave of gene expression that follows pathway stimulation has fostered the hypothesis that this canonical signal transduction cascade represents the major mechanism by which the pathway regulates gene transcription. More recently an increasingly compelling body of evidence has challenged this paradigm, calling for a fundamental re-examination of this model. Here we present the case for an epigenetic mode of STAT action as being an additional vital characteristic of the physiological and developmental roles played by this pathway. We suggest that the fundamental requirement for JAK/STAT signalling in the maintenance of both vertebrate and *in vivo Drosophila* stem cell niches indicates a potential link between STAT activity and the open chromatin configuration required for the future differentiation of a pluripotent stem cell and possibly even the widely proposed concept of cancer stem cells. Recent developments, perspectives and future directions will be discussed.

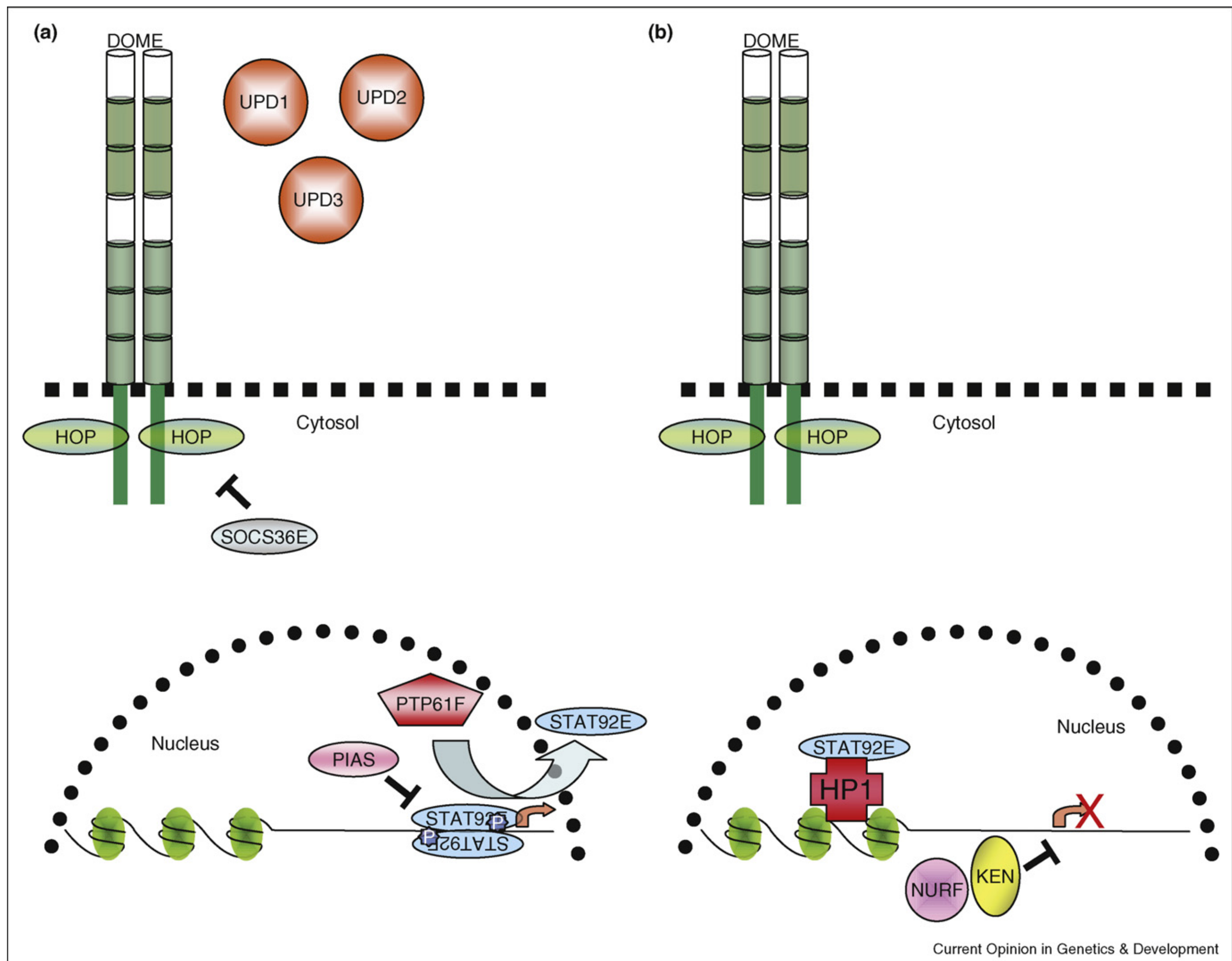
Mining for new JAK/STAT regulators

To date, two reverse genetic whole genome RNAi screens have been undertaken in cultured *Drosophila* cells to identify novel regulators of JAK/STAT pathway signalling [8•,9•]. These two screens utilised relatively different experimental designs with one employing high-level pathway stimulation via the co-transfection of an Upd-expressing plasmid [8•], whilst the other used low levels of basal signalling inherent in the cell line used [9•]. Intriguingly, both screens identified multiple chromatin regulators including the Bromo-domain containing and chromosome-associated *BRWD3* [10], the histone acetyltransferase *Enok* and *dre4*, a component of the *Drosophila* FACT complex, required for transcription elongation by disrupting H2A/H2B dimers [11]. Putative chromatin-modifying factors including *Lolal*, a BTB/POZ domain protein that interacts with Trithorx-like (GAGA factor); *moira*, a homologue of the Swi3 component of the Brahma complex; *trx*, a cysteine-rich zinc finger-like domain protein; *ash1*, which possesses SET, PHD finger and BAH (Bromo adjacent homology) domains; *Bap60* with a SWIB domain; *brm*, containing bromo and DNA-dependent ATPase/helicase domains and *jumu*, the *winged-helix nude mouse* homologue have also been identified [8•,9•] (see Table 1).

From Ken to chromatin?

In addition to cell-based RNAi-based screens, *in vivo* forward genetic screens have also been undertaken to identify mutations that modulate the phenotypes caused

Figure 1



Canonical **(a)** and non-canonical **(b)** models of JAK/STAT signalling in *Drosophila*. The cytokines of the Unpaired family (UPD) show no sequence similarity to vertebrate ligands, but all other proteins have sequence and/or domain conservation with their human orthologues. Both the canonical tyrosine phosphorylated JAK/STAT pathway composed of Dome (receptor), Hop (JAK) and STAT92E (STAT) as well as the unphosphorylated chromatin-binding function of STAT92E are shown.

by inappropriate JAK/STAT pathway activation. The first of these, using ectopic Upd expression in the eye as its assay identified a number of genes, including the histone variant, His2A.V and the *ken and barbie* (*ken*) locus [12,13] (Table 1). *ken* encodes a site-specific transcriptional repressor that binds to a DNA site made up of an essential core sequence present within the palindromic nTTCnnnGAAn sites recognised by STAT92E. Specifically, those STAT92E-binding sites containing a GAAA (i.e. an additional A in their final position) are recognised and repressed by Ken, so down-regulating a specific subset of pathway target genes at multiple stages of development [13]. More recently, Kwon *et al.* have revealed a potential mechanism for Ken-mediated transcriptional repression [14•]. Using transcript profiling approaches, sets of target genes misregulated in both *nucleosome remodelling factor* (*NURF*) mutants and gain-of-function JAK alleles were identified and shown to share a common regulator element consisting of a Ken-sensitive STAT92E-binding site. NURF is a component of an ISWI-containing chromatin-remodelling complex that catalyses nucleosome sliding and thereby alters chromatin structure and regulates transcription [15]. Further *in vitro* experiments showed NURF binding to Ken, whilst chromatin immuno-precipitation (ChIP) assays localised NURF to Ken-binding sites, suggesting that Ken recruits NURF to STAT92E/Ken mutual-binding sites (Figure 1b). The precise dynamics of transcriptional regulation mediated by Ken/NURF interactions remain to be determined, however.

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