Minireview

Of JAKs, STATs, blind watchmakers, jeeps and trains

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Abstract Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling is essential but not sufficient for full responses to the interferons (IFNs), most cytokines and some growth factors. The IFN-γ and interleukin-6 (IL-6) response pathways have been used as model systems to investigate both the signals involved and their organisation. Activated STAT1 diffuses freely in the cytoplasmic and nuclear compartments of the cell providing a 'random walk' element in the IFN-γ response. Completely foreign chimeric receptors and, remarkably, in the absence of STAT3, the endogenous IL-6 receptor can efficiently mediate an IFN-γ-like response. Accordingly all of the signals required for an IFN-γ response can be generated through physiological levels of a foreign ligand. JAK/STAT signalling, therefore, appears 'soft-wired', modular and highly flexible with substantial overlap between different response pathways. The data are consistent with a generic or 'core' set of signals from JAK/receptor complexes with 'add-on' modulation through specific receptor motifs. The cellular background likely profoundly affects the nature of the response.

Key words: Interferon-γ; Interleukin-6; Receptor chimeras; Janus kinase/signal transducer and activator of transcription signalling; Signal transducer and activator of transcription-1–green fluorescent protein

1. Introduction

The interferons (IFNs) and the interleukin-6 (IL-6) family of cytokines (including IL-6 and oncostatin M (OSM) used here) activate Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling through distinct type II and I cytokine receptors (reviewed [1,2]). For IFN-γ signalling occurs through IFN-γ receptor subunits 1 and 2 (IFNGR1 and 2) and characteristically triggers prolonged STAT1 activation. The internal membrane-proximal JAK1 and JAK2 binding domains of IFNGR1 and 2 and the distal Y440 STAT1 recruitment motif of IFNGR1 are generally accepted to be essential for activity (Fig. 1 and reviewed [3]). For IL-6, signalling occurs through dimerisation of the common gp130 signal transduction subunit of the IL-6 family of cytokine receptors (Fig. 1 and reviewed [4,5]). OSM can induce signalling through gp130 heterodimerisation with the closely gp130-related OSM or leukaemia inhibitory factor receptor subunits. In response to IL-6 and OSM, JAK1, JAK2, Tyk2, STAT1 and STAT3 are all activated, the JAKs through a conserved membrane-proximal binding domain and the STATs through four more distal tyrosine motifs [6,7]. JAK1 and STAT3 play major roles in IL-6/OSM response(s) [8]. On ligand binding in both the IFN-γ and the IL-6/OSM systems there is receptor rearrangement/dimerisation/oligomerisation with auto- and trans-phosphorylation/activation of the pre-associated JAKs, phosphorylation of tyrosine motifs in the receptor subunits, recruitment or reassortment of associated STATs which, on tyrosine phosphorylation by the JAKs, are released, dimerise, migrate to the nucleus and, with or without additional factors, activate transcription (Fig. 1). At some point in the activation cascade the ability of the STATs to induce transcription is enhanced by serine phosphorylation through mitogen-activated protein (MAP) kinase (STAT3) or yet to be identified (STAT1) kinase(s) (e.g. [9,10]).

The essential nature of JAK/STAT signalling for the IFNs, most cytokines and some growth factors has been unequivocally established by work on mutant cell lines and knock-out mice. The different ligands activate JAK/STAT and additional signalling pathways in a modular fashion through different JAK/receptor domains. There also appear to be alternative activators of the STATs, additional JAK-mediated pathways and cross-talk between the different pathways. The JAKs have a number of conserved protein domains that likely mediate the protein–protein interactions governing their response to different ligands, cross-talk and cell type specificity (reviewed [11]). JAK specificity appears to be determined mainly by protein–protein interaction rather than by any exquisite substrate specificity of the kinase domains (e.g. [12]). For different cytokines the JAKs can also signal through insulin receptor substrate 1, phosphatidylinositol 3-kinase (PI3-kinase) and the

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Abbreviations: JAK, Janus kinase; STAT, signal transducer and activator of transcription; IFN, interferon; IL-6, interleukin-6; OSM, oncostatin M; IFNGR, interferon-γ receptor; PI3-kinase, phosphatidylinositol 3-kinase; ERK, extracellular signal-regulated kinase; GFP, green fluorescent protein; MEFs, mouse embryonic fibroblasts; ISGs, interferon-stimulated genes; MHC, major histocompatibility complex

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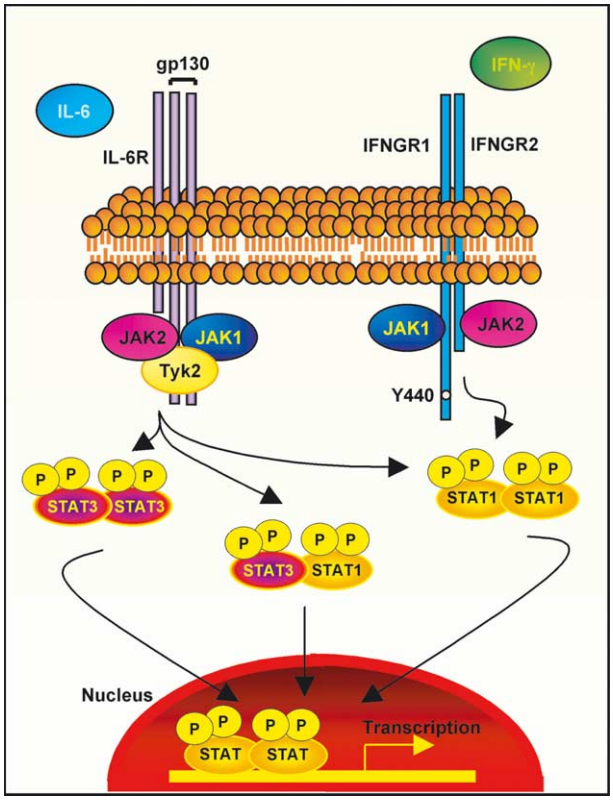

Fig. 1. Schematic representation of JAK/STAT signalling through the IL-6 and IFN-γ receptors.

extracellular signal-regulated kinase (ERK)1/2 and p38 MAP kinase pathways (e.g. [13–16], reviewed [17]) and additional JAK functions are required for the class II human leukocyte antigen and antiviral responses to IFN-γ [18,19]. Accordingly, for most cytokines and some growth factors JAK/STAT signalling is essential but not sufficient. Additional signalling pathways are required, for example, for a full IFN-γ response.

Our recent concern has been to define the minimum signalling requirements for an IFN-γ response and to determine how these are organised within the cell. One approach has been through the use of chimeric receptors. Work with these has led to the observation that a minimal completely foreign chimeric receptor can mediate an IFN-γ-like response. This prompted the observation that, in the absence of STAT3, IL-6 also mediates an IFN-γ-like response. These data together with those demonstrating the free diffusion of activated STAT1–green fluorescent protein (GFP) will be briefly reviewed together with their implications for the nature of the signalling pathways involved.

2. STAT1 from the membrane to the DNA

2.1. IFN signalling is not dependent on an intact cytoskeleton

For IFN-α/β and IFN-γ signalling, STAT1 activation and translocation to the nucleus and the induction of a representative set of IFN-inducible genes (ISGs) are independent of the actin cytoskeleton or microtubules [20].

2.2. Free diffusion of activated STAT1

The construction and characterisation of a functional STAT1–GFP, the behaviour of which is indistinguishable from native STAT1, was first described by Köster and Hauser [21]. The STAT1–GFP efficiently complements STAT1-negative U3A cells. When stably expressed at comparable levels to endogenous STAT1, the STAT1–GFP is comparably tyrosine-phosphorylated/activated, shows comparable DNA-binding activity and is efficiently translocated to the nucleus in response to IFN-γ stimulation [20]. In IFN-γ-treated and control cells both activated (tyrosine-phosphorylated) and non-activated cytoplasmic STAT1–GFP show high energy-independent mobility comparable to that of freely diffusible GFP. All activated STAT1 molecules pass through a given laser-defined 'cross-section' of the cytoplasm every few minutes. Indeed, the results of an extensive fluorescence inactivation on photobleaching and fluorescence recovery after photobleaching analysis of the behaviour of STAT1–GFP are entirely consistent with a random walk model for movement of activated STAT1 from the plasma membrane to the nuclear pore complex [20]. An immobile (non-diffusible) fraction of STAT1–GFP was not detected and can be excluded down to a level of approximately 1% of the total STAT1–GFP. Nevertheless it remains possible that at any given instant in time a very small percentage ($<1\%$) of the STAT1–GFP could be transported directionally to the nuclear pore. Access to any such putative transport system would, however, have to be available to freely diffusing, randomly distributed, activated STAT1–GFP [20]. In this model the putative translocation system would conceptually be an extension of the nuclear pore–importin complex, with random access of STAT1–GFP through free diffusion after release from the receptor. Highly dynamic interactions of the activated STAT1 with cytoplasmic protein complexes remain perfectly possible [22,23]. Such interactions would not, however, necessarily confer directionality upon the movement of STAT1. Nuclear STAT1–GFP showed similar high mobility, with exclusion from nucleoli, consistent with high rates of association/dissociation of STAT1–DNA and/or STAT1–protein complexes in the nucleoplasm of the cell [20]. The dynamic nature of transcription complexes is discussed more extensively below. Meanwhile work designed to (i) define the minimum signalling requirements for an IFN-γ response and (ii) test the interchangeabil-

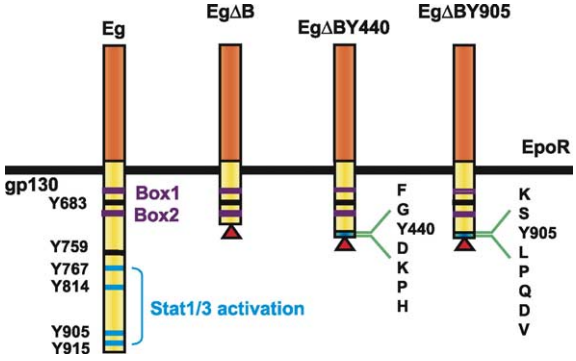

Fig. 2. Schematic representation of the Epo/gp130-based chimeric receptors. All chimeras have the extracellular region of the Epo receptor (orange) and the transmembrane and full-length or truncated internal domains of the gp130 subunit of the IL-6 receptor (yellow). Tyrosine residues in the intracellular region of gp130 are depicted as black or blue lines, box 1/2 motifs as purple boxes and Flag tags as red triangles. Chimeras with the full-length intracellular gp130 (Eg), a truncated gp130 (EgΔB) and a truncated gp130 with added tyrosine motifs from the human IFNGR1 (Y440) or gp130 (Y905), respectively, are shown.

ity of the components in different response pathways led to the conclusion that a completely foreign receptor can mediate an IFN-γ response.

3. A completely foreign chimeric receptor can mediate an IFN-γ-like response

A tripartite receptor comprising the external region of the erythropoietin (Epo) receptor, the transmembrane and JAK-binding domain of the gp130 subunit of the IL-6 receptor and a seven amino acid STAT1 recruitment 'Y440' motif from the IFNGR (Fig. 2) can efficiently mediate an IFN-γ-like response. An analogous completely foreign receptor in which the Y440 motif is replaced by the Y905 motif (Fig. 2) from gp130 also mediates an IFN-γ-like response, although slightly less efficiently [24]. Accordingly it would appear that there is nothing uniquely required that is specific to the Y440 motif.

Interestingly, these systems also provide us with a rather dramatic, if somewhat frustrating, example of cross-talk in the form of receptor cross-phosphorylation. The IFNGR is rapidly cross-phosphorylated through the endogenous OSM, IL-6 and IFN-α/β receptors and the Epo/gp130 receptor chimeras utilised here. As yet we have completely failed to establish any substantial physiological significance for this really rather striking phenomenon. Reciprocal phosphorylation of, for example, gp130 and the chimeric receptors in response to IFN-γ was not, incidentally, observed. It remains possible that in a dynamic receptor complex an appropriate conformation for the activation of JAKs and receptor phosphorylation may not, in the absence of appropriate ligand, sequentially assume the conformation required for effective signalling. In short, cross-recruitment/phosphorylation of the IFNGR through the chimeric receptors is observed in these systems. Very importantly, however, it is not required for the IFN-γ-like response. Crucially, an IFN-γ-like response through the chimeric receptors is also seen in cells completely lacking an IFNGR (figs. 7 and 8 in [24]). This last result, together with further controls, additionally rules out any possibility that the IFN-γ-like response through the chimeric receptors is secondary to the production of endogenous IFNs.

Taking this one stage further it was obvious from a comparison of the activation of STATs 1 and 3 by IL-6 versus that of STAT1 by IFN-γ (Fig. 1) to ask if, in the absence of STAT3, IL-6 can mediate an IFN-γ-like response.

4. In the absence of STAT3 IL-6 mediates an IFN-γ-like response

The biological responses to stimulation through the IL-6 and IFN-γ receptors are completely different. Remarkably, in mouse embryo fibroblasts (MEFs) lacking STAT3, IL-6 efficiently mediates an IFN-γ-like response, including prolonged STAT1 activation, the induction of an extensive set of ISGs, the expression of class II major histocompatibility complex (MHC) antigens and an antiviral state [25]. Similar results were obtained in more than one clone of STAT3-negative cells. On reintroduction of STAT3, IL-6 no longer mediated an IFN-γ-type response. Multiple controls established that the IFN-γ-like response was not through the induction of endogenous IFNs [25]. The results with the chimeric receptors just discussed make it unlikely that the γ-like response reflects a requirement for receptor cross-phosphorylation. It is more likely that it reflects a high degree of overlap in the signals generated through the IFN-γ and IL-6 receptors per se. IL-6 and IFN-γ are known to activate multiple common pathways in addition to the STATs, including those for STAT1 Ser727 phosphorylation and the PI3-kinase/Akt, and MKK1/ERK1 and 2 and p38 MAP kinase pathways (reviewed [17]), all of which are in fact activated by both ligands in both the wild-type and STAT3-negative MEFs. Consistent with this, the activation of STAT1 is essential but not sufficient, for example, for a full IFN-γ response [19]. All of the pathways necessary for a full response must, however, be activated through the highly disparate IFN-γ and IL-6 receptors in the STAT3-negative cells. This, in turn, is in accord with the concept of a generic or 'core' set of signals from JAK/receptor complexes with 'add-on' modulation through additional receptor motifs and cellular background.

These data together with those for the chimeric receptors argue strongly for modular JAK/STAT signalling and against any permanent rigid structural organisation for the 'pathways' involved. They emphasise the likely high degree of overlap between the signals generated from disparate JAK–receptor complexes and show that relatively subtle changes in such complexes and the cellular background can profoundly affect the response.

5. The nature of the signalling pathways

The major conclusions one can reach from the above work concerning the nature/organisation of the IFN-γ response pathways are summarised in Table 1. IFN-γ signalling is independent of the cytoskeleton. We know from the work with the STAT1–GFP that, first, activated STAT1 diffuses freely in the cytoplasmic and nuclear compartments of the cell and, second, the movement of STAT1 is extremely rapid in relation to the size of the cell. It is generally accepted that the activation of STAT1 is essential but not sufficient, additional signals are required for a full IFN-γ response. From the chimera work we can conclude that a minimal completely foreign receptor lacking the receptor internalisation/endocytosis motif [26] can efficiently mediate an IFN-γ-type response. Accordingly despite intriguing reports of translocation of IFN-γ [27] and IFNGR complexes [28] to the nucleus and results implicating endosomal transport in STAT translocation [23,29] it would appear unlikely that these are essential for an IFN-γ response in the human and mouse cell systems with which we are working. Similarly despite significant levels of receptor cross-phosphorylation, the results with the minimal chimeric receptor in IFNGR-negative cells excludes any requirement for such cross-phosphorylation for the IFN-γ-like response

Table 1
Characteristics of JAK/STAT1 pathway in response to IFN-γ

1	JAK/STAT1 signalling is independent of the cytoskeleton (receptor internalisation and endocytosis)
2	Activated STAT1 diffuses freely in cytoplasmic and nuclear compartments
3	Movement of STAT1 is rapid relative to the size of the cell
4	STAT1 activation is essential but not sufficient; additional signals are required
5	In wild-type or IFNGR-negative cells a completely foreign chimeric receptor can mediate an IFN-γ-like response, as can IL-6 working through the endogenous IL-6 receptor in the absence of STAT3

through the receptor chimeras. Finally, in the absence of STAT3 IL-6 mediates an IFN-γ-like response. *Accordingly, not just STAT1 but all of the signals required for an IFN-γ-like response (including the induction of class II MHC antigens and an antiviral state) can be generated through physiological levels of a completely foreign ligand working through normal endogenous levels of a completely foreign receptor.* This is an interesting and unexpected result.

We can, therefore, reach a number of conclusions with respect to the nature of JAK/STAT signalling in the IFN-γ response. Modular signalling through cytokine and growth factor receptor complexes is generally accepted, as indeed is the likelihood of substantial overlap in the signals generated. Results from microarray analyses have emphasised such overlap in the expression profiles observed in response to different growth factors (e.g. [30]). It is the degree of overlap, possibly total, for the IL-6, IFN-γ and chimeric receptors which is surprising. Accepting modularity and overlap the data are at least consistent with a 'core' set of 'generic' JAK/receptor signals with 'add-on' modulation through additional receptor motifs to give receptor type specificity and cellular background to give cell type specificity. It is particularly intriguing that analogous 'core' signalling has been proposed by Ihle and co-workers from an analysis of the responses observed through modified Epo receptors in transgenic mice [31]. The cellular background likely plays a major role. The switch from an IL-6 to an IFN-γ response in the absence of STAT3 may be an extreme example, but so profound a change in response to the presence or absence of a single transcription factor emphasises the potential for different cell types to play different tunes in response to a given signal. Given that potential it would be amazing if Mother Nature does not make substantial use of it. Indeed recent custom macroarray analysis of samples from primary peripheral blood mononuclear cells, T cells and dendritic cells and a number of cell lines established substantial cell type and donor specificity in the expression profiles obtained [32].

In addition, although the pathways have apparently 'hard-wired' components – the nuclear pore, for example, for STAT1 – the free diffusion component and, importantly, the chimera and IL-6 results suggest that STAT1 signalling is 'soft' rather than 'hard '-wired. The terms soft- and hard-wired appear intuitively understandable and singularly appropriate and are offered for the benefit of those who find them so. For those to whom these terms are an unintelligible anathema, one can only reiterate that these pathways require no fixed or 'permanently' organised three-dimensional structure to deliver a particular set of signals from a particular receptor to a particular set of genes. Provided the correct set of signals are activated it does not seem to matter, within reason, where or how this occurs – the signals will get there anyway. On this soft-wired model specificity would be provided by highly dynamic protein–protein (or protein–DNA) interactions which effectively target (although trap might be a more appropriate word conceptually), the signal to an appropriate site – the nuclear pore, governing transfer to the nucleus, or appropriate higher transcription complexes within the nucleus.

In the above the nuclear pore has been presented as an example of 'hard' wiring, but this too may be envisaged to involve multiple weak interactions between transport receptors and nuclear core components which concentrate the receptor–cargo complexes in the vicinity of the pore and facilitate diffusion through it (reviewed [33]). There is no doubt, however, that the nuclear membrane provides an effective barrier to the free diffusion of STAT1 [20] and although transport through the pore may ultimately be by diffusion, the pore itself is likely stable and confers directionality. The highly dynamic state of higher transcription complexes has been emphasised by the very elegant work from the groups of Hager and Misteli in particular, who have used very different approaches to reach a similar conclusion: the formation of such complexes is surprisingly dynamic and inefficient ([34–37], reviewed [38]). Indeed it has been likened to the work of a blind watchmaker [39]. In the nucleus the nucleolus is surprisingly dynamic. There is no nucleolar membrane and its existence requires ongoing transcription of rDNA. In more general terms, there is no active transport system known in the nucleus. RNA and RNA processing enzymes move by diffusion. "Structures visible by microscopy are the products of function rather than a pre-requisite for it" [33]. It is intriguing to speculate how general this maxim will prove to be.

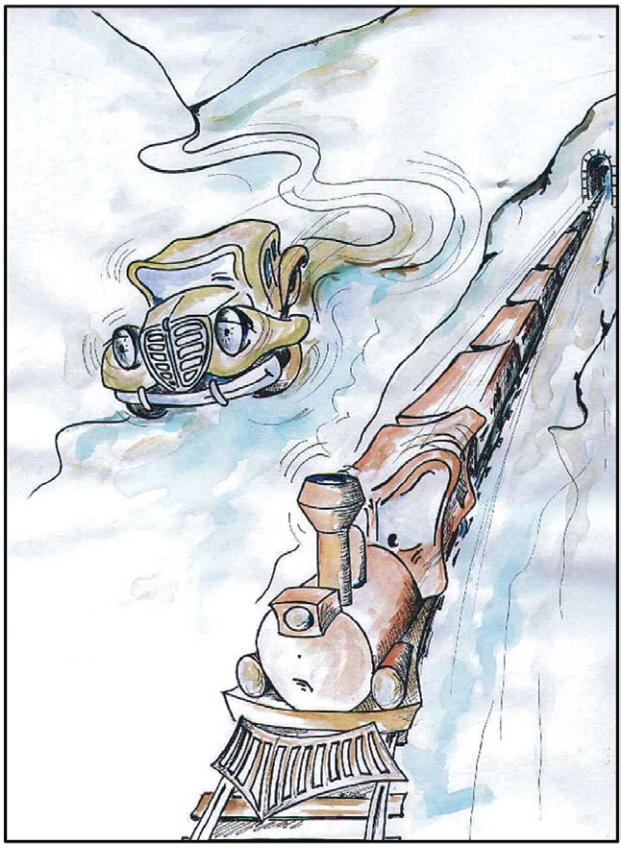

Fig. 3. The cartoon depicts the two types of 'pathway' contributing to JAK/STAT signalling. The jeep represents the freely diffusing STATs in the cytoplasm and nucleus; the train, transport through the structured nuclear pore which joins these cellular compartments. Together they yield a highly flexible, easily modulated, rapid response pathway.

To end on a lighter note, the cartoon (Fig. 3) represents the lab's current favourite view of JAK/STAT1 signalling in response to IFN-γ. Jeeps and trains represent two major means of transport, the first versatile and flexible, the second directional and tied to the rails. Thus the jeep represents the freely diffusing STAT1 in the cytoplasm and nucleus, the train the directional transport of STAT1 through the highly structured

nuclear pore joining these two compartments. Together they yield a highly flexible, easily modulated, rapid response system.

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