Pharmacological Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited Review

Linking energy sensing to suppression of JAK-STAT signalling: A potential route for repurposing AMPK activators?

Claire Speirs[a], Jamie J.L. Williams[b], Kirsten Riches[c], Ian P. Salt[a], Timothy M. Palmer[b,*]

[a] Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK
[b] School of Pharmacy and Medical Sciences, University of Bradford, Bradford BD7 1DP, UK
[c] School of Chemistry and Biosciences, University of Bradford, Bradford BD7 1DP, UK

ARTICLE INFO

Article history:
Received 11 July 2017
Received in revised form
12 September 2017
Accepted 12 October 2017
Available online xxx

Chemical compounds studied in this article:
Metformin (PubChem CID: 4091)
Tofacitinib (PubChem CID: 9926791)
AICAR (PubChem CID: 17513)
Salicylate (PubChem CID:338)
A769662 (PubChem CID: 54708532)
Aspirin (PubChem CID: 2244)
Fludarabine (PubChem CID: 3367)
Hydroxyurea (PubChem CID: 3657)
Anagrelide (PubChem CID: 2182)
Busulfan (PubChem CID: 2478)
Ruxolitinib (PubChem CID: 25126798)
Ciclosporin (PubChem CID: 5284373)
Sulfasalazine (PubChem CID: 5359476)
Methotrexate (PubChem CID: 126941)

Keywords:
AMP-activated protein kinase
Janus kinase
Rheumatoid arthritis
Myeloproliferative neoplasms
Lymphoma

ABSTRACT

Exaggerated Janus kinase-signal transducer and activator of transcription (JAK-STAT) signalling is key to the pathogenesis of pro-inflammatory disorders, such as rheumatoid arthritis and cardiovascular diseases. Mutational activation of JAKs is also responsible for several haematological malignancies, including myeloproliferative neoplasms and acute lymphoblastic leukaemia. Accumulating evidence links adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK), an energy sensor and regulator of organismal and cellular metabolism, with the suppression of immune and inflammatory processes. Recent studies have shown that activation of AMPK can limit JAK-STAT-dependent signalling pathways via several mechanisms. These novel findings support AMPK activation as a strategy for management of an array of disorders characterised by hyper-activation of the JAK-STAT pathway. This review discusses the pivotal role of JAK-STAT signalling in a range of disorders and how both established clinically used and novel AMPK activators might be used to treat these conditions.

Contents

* Corresponding author.
E-mail address: T.Palmer1@bradford.ac.uk (T.M. Palmer).

https://doi.org/10.1016/j.phrs.2017.10.001
1043-6618/

1. Introduction

The JAK[1]-STAT pathway is activated by a range of cytokines, such as interferons, IL-2, and IL-6, which control survival, proliferation and differentiation in a range of diverse cell types. Uncontrolled JAK-STAT signalling is not only a crucial driver of chronic inflammatory diseases such as rheumatoid arthritis (RA) and cardiovascular diseases (CVDs) but also several haematological disorders [1–3].

AMP-activated protein kinase (AMPK) is a Ser/Thr kinase that regulates cellular and organismal metabolism by sensing increases in the intracellular ratio of AMP to ATP following nutrient deficiency or hypoxia [4]. An increasing body of evidence has linked AMPK activation with the control of inflammation and immunity via a variety of mechanisms [4–6]. This novel finding provides a foundation for the evaluation and repurposing of well-tolerated, clinically available drugs, such as the anti-hyperglycaemic drug and AMPK activator metformin, for the treatment of a range of JAK-dependent disorders. Further insights into the novel inhibitory mechanism of AMPK might also provide a basis for the development of a new generation of selective JAK inhibitors.

Clinically available drugs can have positive effects beyond their intended targets e.g. statins, inhibitors of cholesterol production, also show anti-inflammatory effects which are beneficial for the treatment of CVDs [7]. The discovery of novel regulatory mechanisms important in disease and the positive secondary effects of existing drugs enables drug repurposing and thus expansion of available therapeutic options. Given the cost and time required to develop new drugs and test the efficacy and safety in clinical trials, re-purposing is advantageous as it increases the speed to clinic and availability of drugs while eliminating unknown variables in dosing and adverse drug reactions [8,9].

This review discusses the pivotal role of JAK-STAT signalling in inflammatory and myeloproliferative disorders and provides a molecular rationale for an additional way to manage such conditions via repurposing of clinically available AMPK activators.

2. IL-6-dependent JAK-STAT signalling

IL-6 does not signal directly but first forms a dimer with IL-6Rα (CD126) prior to binding its cognate receptor gp130. While gp130 is ubiquitously and constitutively expressed, membrane bound IL-6Rα is restricted to hepatocytes, leukocytes, and lymphocytes. However, soluble IL-6Rα (sIL-6Rα) is produced during inflammation thus increasing the repertoire of IL-6-responsive cells [10,11]. Signalling via membrane bound IL-6Rα is called 'classical signalling' while that via sIL-6Rα is referred to as 'trans-signalling' with the latter being predominant in disease-related pro-inflammatory responses. Gp130 has no intrinsic kinase activity but is constitutively associated with JAK family tyrosine (Tyr) kinases. JAKs comprise a family of four cytoplasmic tyrosine kinases (JAK1-3, and Tyk2). However gp130 only associates with JAK1-2 and Tyk2, while type I cytokine receptors for IL-2 and related cytokines use the common gamma chain (γc) to associate with JAK3 and signal downstream [12]. Cytokine-receptor ligation precedes *trans*-phosphorylation and activation of JAKs, which Tyr phosphorylate gp130 on specific Tyr residues to generate docking sites for SH2-domain-containing STAT proteins. Receptor-bound STATs are then Tyr-phosphorylated by JAKs within their SH2 domains (Tyr^{701} on STAT1, Tyr^{705} on STAT3) prior to dissociation from the receptor and formation of homo- or heterodimers, or tetramers. Following nuclear translocation and binding to target gene promoters, STATs drive transcription of target genes, which include pro-angiogenic vascular endothelial growth factor, intracellular adhesion molecule 1, monocyte chemoattractant protein 1 (MCP-1), and matrix metalloproteases 2 and 9 [12]. IL-6 also activates extracellular signal–regulated kinase (ERK)1/2 and phosphatidylinositol 3-kinase (PI3K) pathways following recruitment of SH2-containing protein Tyr phosphatase 2 to JAK-phosphorylated gp130 and ERK1/2-mediated phosphorylation and activation of Gab1. Finally, gp130 has also been shown to couple directly with Src family Tyr kinases to trigger activation of transcriptional co-activator YAP (YES- associated protein) (reviewed in [12]).

3. JAK structure and activation

JAKs share a common domain structure (Fig. 1) consisting of seven JAK-homology (JH) domains (JH1, kinase domain; JH2, pseudokinase domain, JH3-5, Src homology 2 (SH2) domain, and JH5-7, N-terminal 4.1, ezrin, radixin, moesin (FERM) domain). While FERM and SH2 domains regulate binding to the box1/2 region of cytokine receptors, the so-called "pseudokinase" (PK) domain regulates kinase activity by binding the JH1 kinase domain. Specific events of JAK activation remain unclear, however, cytokine-receptor ligation is thought to cause repositioning or reorientation of the JAK-receptor complexes, bringing JAKs into close proximity, leading to *trans*-phosphorylation of the activation loop within the JH1 kinase domain. Several distinct mechanisms have been proposed for JAK activation but in addition, unique receptor structures are also thought to enforce specific JAK orientations that might drive different modes of regulation [13]. This could be one mechanism that leads to preferential assembly of specific receptor-JAK com-

[1] JAK, Janus kinase. STAT, signal transducer and activator of transcription. IL, interleukin. RA, rheumatoid arthritis. CVD, cardiovascular disease. AMPK, AMP-activated protein kinase. IL-6R, IL-6 receptor. sIL-6Rα, soluble IL-6Rα. Tyk2, Tyr kinase 2. MCP-1, monocyte chemoattractant protein 1. ERK1/2, extracellular signal-regulated kinase 1/2. PI3K, phosphatidylinositol 3-kinase. YAP, YES-associated protein. JH, JAK-homology. SH2, Src homology 2. FERM, N-terminal 4.1, ezrin, radixin, moesin. PK, pseudokinase. ALL, acute lymphoblastic leukaemia. MPN, myeloproliferative neoplasm. WT, wild type. LKB1, liver kinase B1. AICAR, 5-aminoimidazole-4-carboxamide riboside. MKP-1, mitogen-activated protein kinase phosphatase-1. SMCs, smooth muscle cells. mTOR, mammalian target of rapamycin. TSC2, tuberous sclerosis complex 2. NOTCH1, notch homolog protein 1. CDKN2A/B, cyclin-dependent kinase Inhibitor 2A/B. FBXW7, F-box and WD repeat domain containing 7. PHF6, PHD finger protein 6. ECs, endothelial cells. HUVECs, human umbilical vein ECs. IFN, interferon. IFNAR, IFNα/β receptor. ULK1, Unc-51-like autophagy-activating kinase. HSCT, haematopoietic stem cell transplant. mAbs, monoclonal antibodies. FLT3, FMS-like tyrosine kinase 3. PV, polycythaemia vera. ET, essential thrombocythemia. PMF, primary myelofibrosis. ACPA, anti-citrullinated protein antibodies. Th, T helper. Treg, regulatory T cell. DMARDS, disease modifying anti-rheumatic drugs. TNF, tumour necrosis factor. GLINT, glucose lowering in non-diabetic hyperglycaemia trial. CRLF, cytokine-receptor like factor 2.

Please cite this article in press as: C. Speirs, et al., Linking energy sensing to suppression of JAK-STAT signalling: A potential route for repurposing AMPK activators? Pharmacol Res (2017), https://doi.org/10.1016/j.phrs.2017.10.001