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JANUS under stress—Role of JAK/STAT signaling pathway in vascular diseases

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Abstract

They were more than just another kinases (JAK), when they were first described in the late 80s and named JAK kinases. The mandatory role of this novel family of dual active janus kinases (JAK) and their substrates the signal transducers and activators of transcription (STAT) was demonstrated in mice who died during embryogenesis when lacking a functional allele, e.g. that of JAK2. Initially, the JAK/STAT signaling pathway was discovered as the primary mediator of intracellular signaling induced by interferon in hematopoietic and immune cells. Nowadays, it is well accepted that JAK kinases and STAT proteins are constitutively expressed in the vessel wall in a cell type specific manner and transfer intracellular signaling events of various receptor families, e.g. that of cytokines, growth factors and vasoactive peptides such as angiotensin II (Ang II) or endothelin. The potential impact of the JAK/STAT signaling pathway on cardiovascular pathophysiology and disease development arise from reports describing that JAKs may bind directly to the angiotensin II type I (AT_1) receptor, thereby enhancing their phosphorylation in various cell types of the vessel wall. More interestingly, these signaling events are modulated by NAD(P)H oxidase-derived superoxide anions which directly phosphorylate JAK2 and thereby control JAK2 activity. A potential impact was also described for atherosclerotic plaque development in which the activation of JAKs and STATs seems to be critical. Based on these observations, we here review the role of the JAK/STAT signaling pathways as critical regulator for cardiovascular disease development, i.e. atherosclerotic plaque progression or the manifestation of arterial hypertension.

Keywords: Vascular disease; JAK/STAT signaling pathway; Angiotensin II; Mechanical stress; Oxidative stress; IL-6/gp130 activation

1. Introduction

Why are we talking about janus effects when we are thinking of vascular alterations in response to any kind of vascular stress? Janus is the roman god of the gates; in the figurative sense the god of all beginning. He has two faces; one looking forward and the other looking back. The Janus effect is a fundamental characteristic of an entity that possesses the ability to interact with others in both authoritative and dependence roles, a fact which was discovered for the JAK/STAT signaling cascade in multiple diseases in the past. But what is the specificity of this pathway?

Sophisticated analysis of the JAK/STAT signaling pathway describes its function as modulating detrimental but also compensatory effects preventing a system breakdown thereby initiating a chain of small and extended events that nursed those disasters. In this review, we will envision new and unprecedented states in which vascular vulnerabilities and failures originating in separate, isolated areas become woven together in a spiraling crisis i.e. the importance of the JAK/STAT cascade for the development of atherosclerosis or the manifestation of arterial hypertension.

2. JAK/STAT signaling pathway — the mechanistic background

2.1. Activation

A variety of cytokines, lymphokines and growth factors use the JAK/STAT signaling pathway to transmit extracellular signals to the nucleus. JAK/STAT activation stimulates cell proliferation, differentiation, migration and apoptosis critically involved e.g. in growth control. Mechanistically, the JAK/STAT signaling pathway is relatively simple, implying a manageable

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number of signaling molecules (Kisseleva et al., 1993; O'Shea et al., 2002; Rawlings et al., 2004). As mentioned above, a variety of ligands and their receptors stimulate the JAK/STAT pathway. Intracellular activation occurs when ligand binding induces receptor subunit multi-merization, and for a complete signal transmission through either homodimers or heterodimers, the cytoplasmic domains of two receptor subunits must be associated with JAK tyrosine kinases (i.e. that of the interleukin-6 family members). The mammalian JAK family consists of four members: JAK1, JAK2, JAK3 and TYK2. Activation of JAK occurs upon ligand-mediated receptor multimerization because two JAKs are brought into close proximity, allowing *trans*-phosphorylation. Subsequently, the activated JAK phosphorylate additional targets, including the receptors and their major substrates the STATs. STAT protein act as latent transcription factors that linger in the cytoplasm until activated. The seven mammalian STATs possess a conserved tyrosine residue near to the C-terminus which is phosphorylated by JAKs, permitting dimerization of STATs through interaction with a conserved SH2 domain. After phosphorylation STATs enter the nucleus and bind in its dimerized form to specific regulatory promoter sequences inducing or inhibiting transcription of the target genes.

2.2. Inhibition

Besides a variety of activators, there are three major classes of negative regulators of the JAK/STAT signaling pathway known: (1) suppressors of cytokine signaling (SOCS), (2) protein inhibitors of activated STATs (PIAS) and (3) protein tyrosine phosphatases (PTPs) (Kile et al., 2001; Starr and Hilton, 1999; Wormald and Hilton, 2004).

The mammalian SOCS protein family contains at least eight members (SOCS1–7 and cytokine-inducible SH2 domain-containing protein (CIS)) exhibiting an SH2 domain and a SOCS box at their C-terminal end. Additionally, a small kinase inhibitory region located N-terminal to the SH2 domain so far identified in SOCS1 and SOCS3. The SOCS proteins act as a negative feedback loop in the JAK/STAT signaling pathway. Following activation, STATs stimulate SOCS gene transcription leading to SOCS protein expression which bind to phosphorylated JAKs and their receptors to switch off the entire pathway. SOCS proteins can mediate their negative regulation by three means. First, by binding to phosphotyrosines on the receptors, SOCS proteins sterically block the recruitment of STAT factors. Second, SOCS proteins can bind directly to JAKs or to the receptor inhibiting JAK kinase activity. Third, SOCS protein could interact with the elongin BC complex and cullin 2, initiating JAK ubiquitination, decreasing their protein stability and leading them to the proteasomal pathway of protein degradation.

The second class of negative JAK/STAT pathway regulators are the PIAS proteins (PIAS1, PIAS3, PIASx and PIASy). These proteins share a Zn-binding RING-finger domain in a central region, a conserved so called SAP domain at the N-terminus, and a minor conserved C-terminal domain responsible for the binding of target proteins. The PIAS proteins bind to activated STAT dimers and inhibit their binding to their binding sites on the promoter region of target genes.

Probably the simplest negative regulators of the JAK/STAT signaling pathway are the tyrosine phosphatases, which simply reverse the activity of the JAKs by dephosphorylation. The best characterized of these phosphatases is SHP-1. This enzyme contains two SH2 domains and can bind either to phosphorylated JAKs or to phosphorylated receptors to facilitate dephosphorylation of these activated signaling components.

3. JAK/STAT pathway in vascular pathophysiology

The JAK/STAT signaling pathway is considered a stress-responsive signaling cascade that transduces signals from cell surface receptors to the nucleus, thereby modulating gene expression and compensatory mechanisms. So far, various vascular stress factors are described linking activation of the JAK/STAT signaling pathway to vascular diseases, such as (1) angiotensin II effects, (2) mechanical stress, (3) oxidative stress, and (4) IL-6/gp130 activation.

3.1. Angiotensin II effects

Ang II – the effector peptide of the activated RAS – is one of the most powerful vasoconstrictors in mammalian physiology and controls the systemic blood pressure. Almost all vascular effects of Ang II are mediated via its seven transmembrane G-protein-coupled angiotensin II type I (AT_1) and type II (AT_2) receptor. AT_1 receptor activation leads to cell growth, vascular contraction, inflammatory responses and salt and water retention, whereas AT_2 receptor activation induces apoptosis, vasodilation and natriuresis. Traditionally, Ang II induces several intracellular transduction pathways, such as the phospholipase *C*-diacylglycerol-inositol trisphosphate and the mitogen-activated protein (MAP) kinase signaling pathways.

More recently, the JAK/STAT signaling pathway was shown to be activated by Ang II via stimulation of the AT_1 receptor. Similar to classical cytokine receptors, we and others demonstrated in vascular smooth muscle cells (VSMC) that Ang II stimulation of its AT_1 receptor leads to the activation of the JAK family members JAK2 and TYK2 (Ihle, 1995; Marrero et al., 1995) and subsequently enhanced the phosphorylation of STAT proteins (STAT1α/β, STAT2 and STAT3). Mechanistically, we were able show that the G beta-subunit of the heterotrimeric G-protein interacts with JAK2 thereby increasing JAK2 activity (Luchtefeld et al., 2001). JAK-phosphorylated STAT proteins translocate to the nucleus, where they activate gene transcription. In addition, it has also being reported that JAK-binding to the AT_1 receptor requires a specific binding site (Ali et al., 1997; Sayeski et al., 1999).

In order to elucidate a potential role for vascular pathophysiology, we investigated the role of the JAK/STAT signaling pathway in Ang II-induced smooth muscle cell proliferation (Marrero et al., 1997). We observed that electroporation of antibodies against STAT1 and STAT3 abolished VSMC proliferation in response to both Ang II and growth factors. This observation is conceives a critical role for the