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Integrating Interleukin-6 into depression diagnosis and treatment

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ABSTRACT

There is growing evidence of a relationship between inflammation and psychiatric illness. In particular, the cytokine Interleukin-6 (IL-6) has been linked to stress-related disorders such as depression and anxiety. Here we discuss evidence from preclinical and clinical studies examining the role of IL-6 in mood disorders. We focus on the functional role of peripheral and central release of IL-6 on the development of stress susceptibility and depression-associated behavior. By examining the contribution of both peripheral and central IL-6 to manifestations of stress-related symptomatology, we hope to broaden the way the field thinks about diagnosing and treating mood disorders.

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It is estimated that approximately 30–60% of patients with depression are not responsive to available antidepressant treatments (Krishnan and Nestler, 2008). High rates of treatment resistance may be due to heterogeneity in biological mechanisms of depression, such as increased inflammation, that are unaltered by standard antidepressants. Despite numerous correlative studies showing increased inflammation in depression, we still know little about the mechanisms through which inflammation may trigger depression or whether inflammation is simply a consequence of the experience of depression. There is growing evidence that depression alters both the brain and the body of the individual. Many patients with Major Depressive Disorder (MDD) have higher levels of multiple inflammatory markers, including the cytokine Interleukin 6 (IL-6) (Maes et al., 1995 Bob et al., 2010; Dowlati et al., 2010; Hodes et al., 2014). This cytokine is a small multifunctional protein (Tanaka and Kishimoto, 2014), that can be released from a myriad of tissues including white blood cells, endothelial cells, epithelial cells, adipose tissue, astrocytes, microglia and neurons (Coppack, 2001 Spooren et al., 2011; Rossi et al., 2015). IL-6 is primarily categorized as a pro-inflammatory cytokine, but it also has anti-inflammatory properties (Wolf et al., 2014). Recent research in both preclinical (Hodes et al., 2014) and clinical models (Khandaker et al., 2014; Hsu et al., 2015) has suggested a functional role for IL-6 in the development of depression and a potential for targeting it to treat depression in humans. Here we discuss current research examining the contribution of IL-6 to depression and stress-related behavior.

1. IL-6 signaling and its role in inflammation

IL-6 belongs to a family of proteins that use GP130 as a signal

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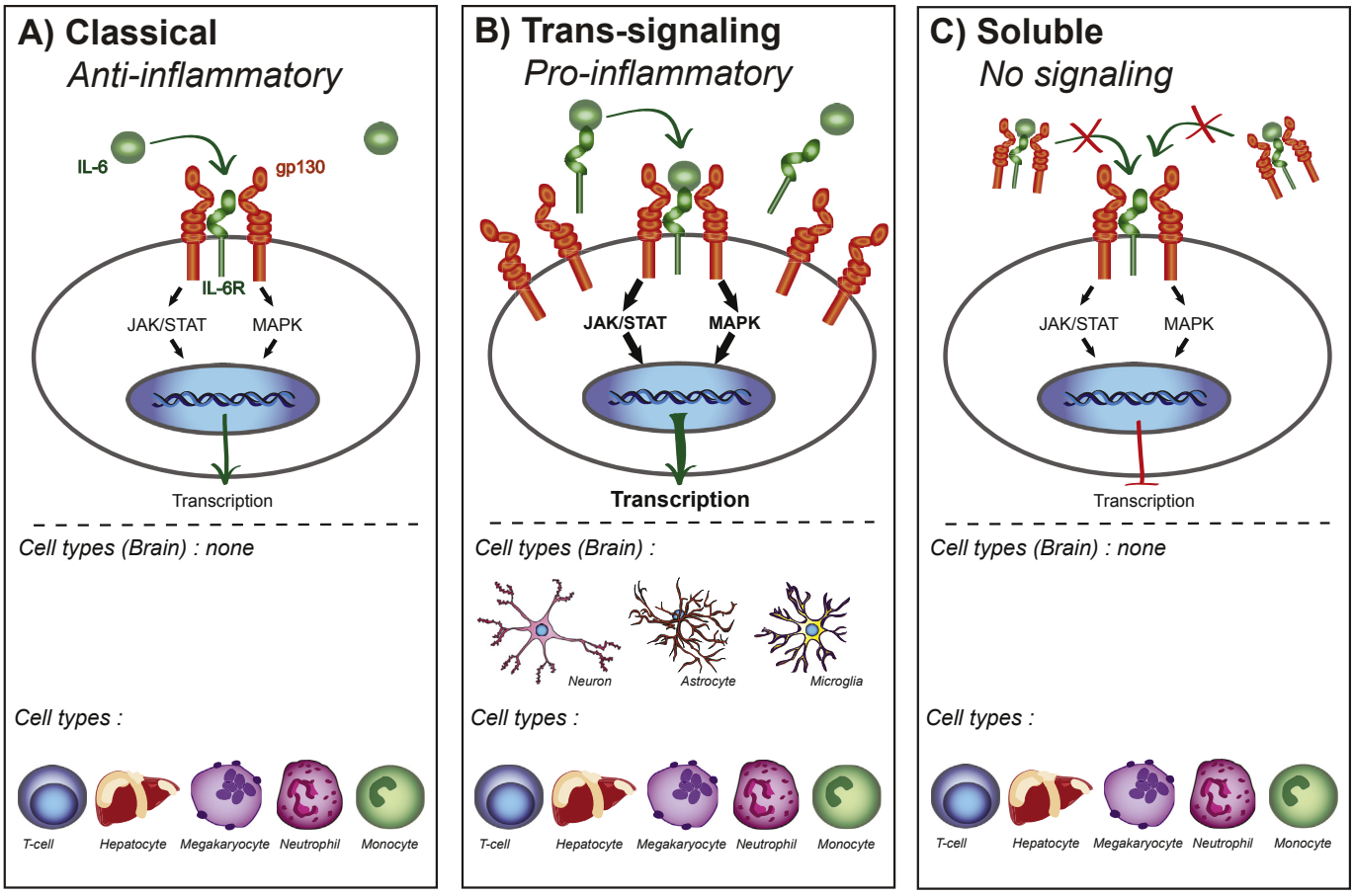

Fig. 1. Types of IL-6 signaling. A. Classical signaling only occurs in a few cells types found in the periphery. In classical signaling both the IL-6 receptor and gp130 signal transducer are membrane bound. IL-6 binds to the receptor leading transcription that is thought to be anti-inflammatory. B. IL-6 trans-signaling can occur in any cell type that has membrane bound gp130, all brain IL-6 signaling is thought to be trans-signaling. IL-6 bound to sIL-6R activates signaling through membrane bound gp130. Trans-signaling is thought to be pro-inflammatory in part though its ability to activate more gp130 signal transducers compared to classical IL-6 signaling. C. Blockade of IL-6 signaling through soluble gp130. A soluble form of gp130 can bind sIL-6R/IL-6 complexes and block trans-signaling. Soluble gp130 does not block classical IL-6 signaling.

transducer. These include Interleukins 11, 27, and 31, ciliary inhibitory factor, leukemia inhibitory factors, cardiotrophin-1, neuropoietin, neurotrophin-1/B-cell stimulating factor 3 and oncostatin M (Scheller et al., 2011; Murakami and Hirano, 2012). IL-6 signaling is complex and can result in both inflammatory and anti-inflammatory cascades depending upon the presence of either IL-6 receptor (IL-6R) or the membrane bound gp130 signal transducer, which are expressed at very different frequencies within specific cell types throughout the body.

Classical IL-6 signaling (Fig. 1a) is thought to be anti-inflammatory (Wolf et al., 2014) and occurs through binding of IL-6 to the membrane bound cell surface receptor. Classical IL-6 signaling only occurs on some subsets of T cells, hepatocytes, megakaryocytes, neutrophils and monocytes (Scheller et al., 2011). Additionally, IL-6 engages pro-inflammatory trans-signaling (Fig. 1b) in which the soluble form of the IL-6 receptor (sIL-6R) is shed from the membrane bound receptors (Lust et al., 1992; Mullberg et al., 1993). The sIL-6R binds to IL-6 and is transported to any cell type that expresses gp130 on its surface (Wolf et al., 2014). While most soluble receptors, such as the soluble receptor for tumor necrosis factor alpha (TNFα) result in antagonistic action by competing for the ligand, the sIL-6R is agonistic and increases the types of cells through which IL-6 can signal. In both classical and trans-signaling, the IL-6/IL-6R/gp130 complex activates intracellular signaling through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and the mitogen-activated protein kinase (MAPK) pathway. There is evidence that an imbalance away from the MAPK pathway via removal of regulation by suppressor of cytokine signaling 3 (SOCS3) towards the pro-inflammatory STAT3 signaling pathway contributes to autoimmune disease (Tanaka and Kishimoto, 2014) and therefore may also be a target for stress susceptibility (Fig. 2). Another method through which circulating levels of IL-6 and its downstream mechanisms are altered is via the soluble form of gp130. While sIL-6R acts as an agonist, the soluble form of gp130 acts as an antagonist sequestering IL-6 and sIL-6R in blood (Wolf et al., 2014; Garcia-Oscos et al., 2015), thereby stopping IL-6 from activating trans-signaling but not classical signaling (Fig. 1c). Further research is needed to determine whether stress alters soluble gp130 and its potential use as an antidepressant.

A number of transcription factors directly regulate the IL-6 gene including nuclear factor kappa B (NFκB), cAMP response element binding protein (CREB), activator protein 1 (AP-1) and nuclear factor for interleukin 6 (NF-IL6) (Dendorfer et al., 1994; Spooren et al., 2011). The binding of NFκB to the wild type IL-6 promoter in a variety of human cell types is necessary and sufficient to regulate IL-6 (Libermann and Baltimore, 1990 Zhang et al., 1990; Ray and Prefontaine, 1994). Through trans-repression, glucocorticoid receptors (GR) can block the ability of NFκB to act as a transcription factor, potentially comprising a method through which stress modulates IL-6 levels (Ray and Prefontaine, 1994; De Bosscher et al., 2000). Therefore, disruptions in the sensitivity of