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Indolamine 2,3-dioxygenase regulation and neuropsychiatric symptoms

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Udina et al. (2013) report that functional polymorphisms in the serotonin transporter (*SERT*) and interleukin-6 (*IL-6*) genes are associated with depressive and anxiety symptoms during antiviral therapy in patients chronically infected with the hepatitis C virus (HCV). In particular, patients carrying the G allele in the promoter region of *IL-6* (a.k.a. the “the high *IL-6* synthesizing” genotype) had increased risk of developing depressive or anxious symptoms during antiviral therapy. These are important findings, as interferon (IFN)-alpha based antiviral therapies often induce neuropsychiatric symptoms that are not well understood, can be difficult to treat, and may impede the course of antiviral therapy (Loftis and Hauser, 2004). To provide a possible mechanistic explanation for their findings, Udina et al. (2013) suggest that *IL-6* activates indoleamine 2,3-dioxygenase (IDO), an enzyme in the kynurenine pathway. This enzyme plays a role in a number of physiological activities (*e.g.*, antimicrobial and antitumor defense, immunoregulation, and antioxidant reactions), in part, through its catabolization of the essential amino acid tryptophan. Accordingly, activation of IDO has been found to reduce tryptophan and increase levels of kynurenine, resulting in lower levels of serotonin in the brain—putatively contributing to depressive symptoms (Raison et al., 2010; Kiank et al., 2010; Dantzer et al., 2011).

Consistent with an IDO-activating role for *IL-6*, Kim et al. (2012) reported that *IL-6* upregulates IDO *in vitro* and *in vivo* (hippocampus) and contributes to behavioral indices of pain and depression. However, it has also been reported that *IL-6* drives IDO degradation (Grohmann et al., 2001; Fallarino et al., 2012, Fig. 1), rather than its activation. IDO contains immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that can either induce degradation or initiate signaling activity and self-maintenance of the enzyme. In the

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Conflict of interest statement

The author has declared that there are no conflicts of interest.

presence of IL-6, two ITIMs in mouse and human IDO lead to proteasomal degradation of the enzyme. IL-6 driven degradation of IDO is considered to be a key mechanism whereby this pro-inflammatory cytokine interrupts immune tolerance in response to danger signals (Grohmann et al., 2001).

While it is well-known that tryptophan catabolism by IDO alters inflammation, it is yet to be clarified which pro-inflammatory cytokines signal degradation or self-maintenance of the enzyme, especially within local tissue microenvironments and in the context of neuropsychiatric disorders (*e.g.*, depression, anxiety) or chronic infections (*e.g.*, HCV). In addition to monoamines, inflammatory pathways are increasingly implicated in the pathogenesis of mood and cognitive impairments. Thus, identifying the cellular sources and specific immune factors [*e.g.*, IFN-gamma, transforming growth factor (TGF-) beta, IL-6] that regulate IDO will be important to better understand the effects of immunosuppression and immunoactivation on neuropsychiatric function.

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