Innate Antiviral Host Defense Attenuates TGF-beta Function through IRF3-Mediated Suppression of Smad Signaling.

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Public Summary:
TGF-beta signaling is essential in many processes, including immune surveillance, and its dysregulation controls various diseases, including cancer, fibrosis, and inflammation. Studying the innate host defense, which functions in most cell types, we found that RLR signaling represses TGF-beta responses. This regulation is mediated by activated IRF3, using a dual mechanism of IRF3-directed suppression. Activated IRF3 interacts with Smad3, thus inhibiting TGF-beta-induced Smad3 activation and, in the nucleus, disrupts functional Smad3 transcription complexes by competing with coregulators. Consequently, IRF3 activation by innate antiviral signaling represses TGF-beta-induced growth inhibition, gene regulation and epithelial-mesenchymal transition, and the generation of Treg effector lymphocytes from naive CD4+ lymphocytes. Conversely, silencing IRF3 expression enhances epithelial-mesenchymal transition, TGF-beta-induced Treg cell differentiation upon virus infection, and Treg cell generation in vivo. We present a mechanism of regulation of TGF-beta signaling by the antiviral defense, with evidence for its role in immune tolerance and cancer cell behavior.

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