The Pro-inflammatory Role of TGF?1: A Paradox?

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Abstract:

TGF?1 was initially identified as a potent chemotactic cytokine to initiate inflammation, but the autoimmune phenotype seen in TGF?1 knockout mice reversed the dogma of TGF?1 being a pro-inflammatory cytokine to predominantly an immune suppressor. The discovery of the role of TGF?1 in Th17 cell activation once again revealed the pro-inflammatory effect of TGF?1. We developed K5.TGF?1 mice with latent human TGF?1 overexpression targeted to epidermal keratinocytes by keratin 5. These transgenic mice developed significant skin inflammation. Further studies revealed that inflammation severity correlated with switching TGF?1 transgene expression on and off, and genome wide expression profiling revealed striking similarities between K5.TGF?1 skin and human psoriasis, a Th1/Th17-associated inflammatory skin disease. Our recent study reveals that treatments alleviating inflammatory skin phenotypes in this mouse model reduced Th17 cells, and antibodies against IL-17 also lessen the inflammatory phenotype. Examination of inflammatory cytokines/chemokines affected by TGF?1 revealed predominantly Th1-, Th17-related cytokines in K5.TGF?1 skin. However, the finding that K5.TGF?1 mice also express Th2-associated inflammatory cytokines under certain pathological conditions raises the possibility that deregulated TGF? signaling is involved in more than one inflammatory disease. Furthermore, activation of both Th1/Th17 cells and regulatory T cells (Tregs) by TGF?1 reversely regulated by IL-6 highlights the dual role of TGF?1 in regulating inflammation, a dynamic, context and organ specific process. This review focuses on the role of TGF?1 in inflammatory skin diseases.

Key Words:

TGF?1, skin inflammation