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Degenerative joint disease following defective cytokine receptor signaling

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Keywords

Arthritis, gene targeting, signal transduction, STAT

Context

IL-6 family members signal through the common gp130 ? chain receptor, which possesses multiple signaling domains. To study cytokine signaling *in vivo* via signal transducer and activator of transcription (STAT) proteins, gp130?^{STAT} mice were generated by 'knocking in' a mutant construct lacking all four gp130 STAT binding sites; this was necessary as gp130 knockout die as embryos (see Additional information [1]).

Significant findings

The gp130?^{STAT}/?^{STAT} 'knock-in' mice were viable with shortened life spans; similar to IL-6-null mice (see Additional information [2]), these mice exhibit impaired humoral and mucosal immunity, and like leukemia inhibitory factor (LIF)-deficient females (see Additional information [3]) were infertile. Surprisingly, these mice displayed gastrointestinal tract ulcerations and severe joint patholog; 60% developed bilateral arthritis of large weight bearing joints. Histopathology revealed cartilaginous nodules, erosions, and synovial hyperplasia but few inflammatory cells. The authors surmise that joint pathology was primarily a result of synovial hyperplasia. Synovial fibroblasts from gp130?^{STAT}/?^{STAT} mice demonstrated increased proliferation in response to IL-6 or LIF, and this correlated with prolonged activity of mitogen-activated protein kinase family members, Erk-1 and Erk-2, as well as SHP-2, a phosphatase that also binds gp130. The authors hypothesized that the lack of STAT binding to gp130 results in a lack of autoinhibitory feedback on all signaling mediated by gp130, including activation of Erk via SHP-2 and ras. This is indirectly tested by analyzing suppressor of cytokine signaling (SOCS) levels in cytokine-stimulated synovial cells from gp130?^{STAT}/?^{STAT} mice. SOCS proteins are normally

increased by activated STAT proteins and inhibit gp130 activity. Interestingly, SOCS-1 was decreased in gp130?^{STAT}/?^{STAT} cells. Increased c-*fos* promoter activity, an indirect measure of Erk activity, was noted in IL-6 stimulated gp130?^{STAT}/?^{STAT} synovial cells and was inhibited by SOCS-1 overexpression. The authors concluded that decreased STAT-mediated SOCS induction, causing sustained Erk activation, leads to synovial overgrowth and degenerative joint disease.

Comments

This paper reports a degenerative arthritis model in a mouse with defective STAT signaling via gp130. Future studies of these mice have the advantage of being able to analyse a spontaneous model of arthritis in which cartilage defects, synovial cell hyperplasia, and erosive joint disease occur. The results may provide insight to synovial cell hyperplasia in a variety of chronic human arthritides. The paper also demonstrates the importance of feedback inhibition of signaling molecules and suggests that targeting SOCS proteins may work to block some cytokine-mediated arthritis.

Methods

Gene targeting/knock-in mice, histopathology, 3H-thymidine incorporation, western blot, northern blot, ELISA, transient transfection

Additional information

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