Female Hormonal Regulation of pSTAT3 Results in Reduced Mortality Due to Enhanced TGF-β1-Mediated Pulmonary Fibrosis and Less IL-17A

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Abstract: Pulmonary fibrosis is characterized by striking distinctions in mortality according to sex, demonstrating a female predominance and a longer time to death, compared to males. Independent laboratories reported the crucial role of the Programmed Death 1 (PD-1) pathway in pulmonary fibrosis. PD-1+IL-6+CD4+ T cells induce both profibrotic cytokines, IL-17A and TGF-β1, using distinct signaling pathways. Methods: In order to more clearly understand the role of PD-1+CD4+ T cells in the observed sex distinctions and mortality, we investigated IL-6 signaling in PD-1+ CD4+ T cells in humans and murine specimens. Using flow cytometry, ELISA and the Sircol assay to investigate distinctions in pulmonary fibrosis according to sex, we assessed for distinctions among humans with Idiopathic Pulmonary Fibrosis (IPF), Sarcoidosis and Scleroderma, as well as the bleomycin murine model of pulmonary fibrosis. Results: Despite the male predominance, IPF males possessed higher serum estradiol levels and PD-1+CD4+ T cells, compared to age-matched male controls. We noted significantly higher percentages of PD-1+CD4+ T cells with higher IL-6 production in female sarcoidosis subjects, compared to males. While sarcoidosis pulmonary progression was noted in both sexes, males possessed greater percentages of CD4+IL-17A cells compared to females; whereas the female CD4+ T cells expressed significantly higher free TGF-β1. Administration of intranasal bleomycin to male and female mice possessing genetic ablation of the alpha subunit of the Estrogen Receptor (ESRα KO) revealed significant declines in IL-6 but, notably, significant increases in pSTAT3 expression. Surgical removal of ovaries confirmed the observations of significant declines in IL-6 expression from CD4+ T cells and significant increased pSTAT3 and CD4+IL-17A expression. Strikingly, exogenous replacement of estradiol and progesterone in these strains resulted in increased IL-6 expression and reduction of pSTAT3, further confirming the capacity of female hormones to inhibit pSTAT3 expression. PD-1 pathway blockade resulted in reduced collagen production in females compared to males. Conclusion: This work identifies a crucial, previously unrecognized role of female hormones on pSTAT3 signaling pathways relevant to pulmonary fibrosis, supporting a personalized approach to therapeutic intervention according to sex.

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