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Resistance to Bleomycin-Induced Lung Fibrosis in MMP-8 Deficient Mice Is Mediated by Interleukin-10

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Abstract

Background: Matrix metalloproteinases (MMPs) may have pro and antifibrotic roles within the lungs, due to its ability to modulate collagen turnover and immune mediators. MMP-8 is a collagenase that also cleaves a number of cytokines and chemokines.

Methodology and Principal Findings: To evaluate its relevance in lung fibrosis, wildtype and *Mmp8*$^{-/-}$ mice were treated with either intratracheal bleomycin or saline, and lungs were harvested at different time points. Fibrosis, collagen, collagenases, gelatinases, TGFβ and IL-10 were measured in lung tissue. *Mmp8*$^{-/-}$ mice developed less fibrosis than their wildtype counterparts. This was related to an increase in lung inflammatory cells, MMP-9 and IL-10 levels in these mutant animals. *In vitro* experiments showed that MMP-8 cleaves murine and human IL-10, and tissue from knockout animals showed decreased IL-10 processing. Additionally, lung fibroblasts from these mice were cultured in the presence of bleomycin and collagen, IL-10 and STAT3 activation (downstream signal in response to IL-10) measured by western blotting. In cell cultures, bleomycin increased collagen synthesis only in wildtype mice. Fibroblasts from knockout mice did not show increased collagen synthesis, but increased levels of unprocessed IL-10 and STAT3 phosphorylation. Blockade of IL-10 reverted this phenotype, increasing collagen in cultures.