EFFECTS OF THE p23 CO-CHAPERONE PROTEIN ON THE PULMONARY IMMUNE SYSTEM

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The lung is formed by a unique set of cell types that create a balance for diverse functions such as gas exchange, air humidification, detoxification and clearance of environmental particles. However, when this balance is disturbed it can lead to pulmonary disease. Several immunosuppressive therapies, including glucocorticoids, are available to help control pulmonary disease. However, a subset of patients does not respond well or at all to therapy, leading to a poor quality of life. The underlying cause of non-responsiveness to steroids is not well understood. The Hsp90s and associated co-chaperones that include p23 are known to regulate glucocorticoid receptor through multiple mechanisms that include the ligand-binding step. We developed a p23 murine knockout line that displayed a neonatal lethal phenotype characterized by lung developmental defects. This phenotype is similar to that of mice lacking glucocorticoid receptor. Preliminary studies revealed glucocorticoid receptor is present in murine embryonic fibroblast lines (MEFs), but has decreased ligand binding ability in p23 null and heterozygous cells. Since glucocorticoid signaling is known to profoundly effect the immune system, we hypothesized that weakened glucocorticoid receptor function in p23 heterozygous mice would alter immunological parameters and function in the lung and perhaps other tissues and cells. Using several immunological markers (ex. IL-10, TGFβ1, IL-2, T-cell subsets), our current studies have revealed an effect of p23 genetic status on immune regulation. The production of several cytokines (IL-10, IL-17, IL-2) is significantly increased in the lungs of p23 heterozygous mice. In addition, p23 null MEF lines show a pronounced (12-fold) increase in TGFβ1 mRNA production. Linking of the p23 protein to immune system function in the lung represents an unexplored area of research. Defining the role of p23 in the regulation of TGFβ1 and IL-10 expression, along with other chemokines and cytokines, could have a significant impact on understanding the mechanisms of pulmonary diseases.

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