Deficiency of KLF4 compromises the lung function in an acute mouse model of allergic asthma.

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Abstract: Asthma is defined as a chronic inflammatory disease of the airways with the underlying mechanisms not fully understood. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of monocytes that possess phenotypic plasticity. They are master regulators of the airway inflammation. We recently reported that KLF4 regulates MDSC differentiation to fibrocytes, emerging effectors in chronic inflammation. However, the role of KLF4 in asthma has not been reported. Thymic stromal lymphopoietin (TSLP) is an epithelial-cell-derived cytokine and a key initiator of allergic airway inflammation. Given the fact that TSLP promotes Th2 cytokine production that increases MDSC differentiation to fibrocytes, we postulated that KLF4 regulates asthma in a TSLP-dependent manner. In this study, we utilized a model of allergic asthma with ovalbumin challenge (OVA) in KLF4 deficient mice. We found that upon OVA treatment in the wild type mice there was increased MDSC infiltration into the lung, accompanied by up-regulation of KLF4 and TSLP gene expression and levels of Th2 cytokines including IL4 and IL13. Consistently, deficiencies of KLF4 in FSP-1-Cre/ KLF4(flox) mice that lack of KLF4 expression in monocytes and lung epithelial cells resulted in decreased fibrocyte generation and levels of Th2 cytokines. KLF4 deficiencies in these mice also led to decreased airway hyperresponsiveness (AHR), a cardinal feature of asthma, as assessed by whole body plethysmography. Moreover, trichrome staining that measures lung fibrosis and the population of CD45+COL1A1+ fibrocytes were attenuated upon KLF4 deficiency. Taken together, our results suggest that KLF4 likely promotes asthma development in a TSLP and fibrocyte dependent manner.