S1P affects lung function by triggering epithelial mesenchymal transition

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Sphingosine-1-phosphate (S1P) is considered to play a key role in chronic airway diseases such as asthma. Here we demonstrate that S1P administration to mice affects lung function through activation of the epithelial-mesenchymal trophic unit (EMTU). Airway epithelial cells, harvested from S1P-treated mice, present an increased expression of the mesenchymal markers α-SMA, vimentin and CD90, coupled to a reduction of the epithelial markers cytokeratin and CD326. EMT correlates well with an increase in airway reactivity, lung metaplasia and TGF-β secretion in the lung. Pretreatment of mice with a TGF-β antagonist abrogates both S1P-induced EMT and airway hypereactivity. Airway epithelial cells, collected from ovalbumin-sensitized mice, show morphological alterations typical of EMT such as down-regulation of epithetial markers cytokeratin and CD326 and up-regulation of mesenchymal markers vimentin, CD90 and α-SMA. Treatment of ovalbumin-sensitized mice with a sphingosine kinases inhibitor reversed all these features. The lack of EMT is coupled to the loss of overexpression of TGF-β and airway hypereactivity. EMT is reproduced in vitro by incubating murine airway epithelial cells with either TGF-β or S1P. EMT was reversed in both cases when cells were pretreated with a TGF-β antagonist. In conclusion our data demonstrate that there is a direct correlation between S1Peffect on epithelial cells and lung function with an obligatory role of TGF-β.