Sphingosine-1-phosphate administration in vivo induces airway inflammation and hypereactivity in a IgE-dependent manner

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Introduction: S1P systemic administration leads to an increased airway hyper-reactivity that involves activation of S1P receptors (1). Sphingosine-1-phosphate (S1P) is emerging as an important player at many levels in asthma but the way it exerts its effects is still unclear (2).

Aim: The aim of this study was to address the mechanism(s) involved in S1P-induced airway hyper-reactivity

Methods/Results: As previously described Balb/c mice receiving s.c. injection of 0.2ml of S1P (10ng) in sterile saline on days 0 and 7, display a dose- and time-dependent increase in airway reactivity (1). Airway hyper-reactivity was coupled to an enhanced inflammatory response. In particular, lungs harvested from S1P-treated animals stained with Hematoxylin and Eosin showed an increased cell infiltration. The inflammatory profile was further confirmed by the loss of the alveolar structure and the mucous cell metaplasia, measured as Goblet cells arbitrary score following PAS staining, was doubled. We also found a significant increase in serum levels of both PGD2 following S1P exposure (391±6.5 pg/ml vs 179±3.9 pg/ml, $p<0.01$) and IgE (128±5.9 ng/ml vs 52±4.2ng/ml, $p<0.01$). FACS analysis on lung-derived cells evidenced that mast cells identified as CD11c+cKit+ double positive were prominent (increase in 30%) . Proliferation assay of peripheral lymph nodes-derived cells showed that lymphocytes obtained from S1P-sensitized mice showed a higher proliferation rate following to concanavalin. In order to address mast cells or T cells contribution in S1P effect mast cell knock-out mice (MCKO) and nude athymic mice were used. In MCKO mice S1P-induced hyper-reactivity was lost. However, lungs harvested from MCKO still displayed an ongoing inflammatory response as demonstrated by immunohistological analysis: i) an increased cell infiltrations; ii) an altered alveolar structure iii) an increased mucous metaplasia were observed when compared to S1P-treated wild type mice. Furthermore IgE serum levels were still increased in MCKO. Conversely, the absence of T cells first dampened S1P-induced hyper-responsiveness and, more interestingly, abrogated inflammatory cell influx, goblet cell hyperplasia and mucus hypersecretion too.

Conclusions. Our data demonstrate that S1P alters lung morphology leading towards an asthma-like environment in which mucus and prostaglandins together with IgE are highly produced. These data imply that following S1P challenge there is an activation of T cells, which in turn leads to mast cell activation. Mast cells are mainly responsible for the airway increased reactivity but do not play a key role in the inflammatory effect elicited by S1P and driven by T cells.

Reference

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