Pharmacological strategies to promote resolution of inflammation in a model of asthma

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**Introduction**

Asthma is a chronic inflammatory disease of lower airways, which affects over 339 million people worldwide. Allergic asthma is a disease characterized by the presence of inflammatory infiltrate in the lower airways, in which eosinophils accumulation play a pivotal role in the pathogenesis of disease. Overwhelming inflammation can lead to tissue injury, organ dysfunction, and the progression of asthma. Thus, pro-resolving strategies that modulate the accumulation and excessive responsiveness of leukocytes may be useful to control excessive inflammation, diminish symptoms and return tissue homeostasis. In the present study, we investigated the effects of two drugs: ATB-346 (a hydrogen sulfide-releasing anti-inflammatory drug) and Y-27632 (a selective ROCK inhibitor) on eosinophilic inflammatory response and its resolution in a model of asthma induced in mice.

**Methodology**

Induction of asthma: Male Balb/c mice were sensitized by two intraperitoneal injections of 100μg of ovalbumin diluted in alum at a 7-day interval. Five days after the sensitization, mice were challenged for 8 consecutive days with intranasal ovalbumin (10µg) under anesthesia. Control mice received PBS. Treatments: ATB-346 (3mg/kg) was given orally 24 and 36 hours after the final intranasal challenge. Y-27632 (10mg/kg) was given intranasally 24 hours after the final intranasal challenge. Mice were euthanized at different times to obtain tissue and cells for further assay. The study was approved by the Ethics Committee on Animal Use (CEUA) of UFMG (CEUA protocol 20 / 2020).

**Results**

Overall, ovalbumin challenge induced a time dependent accumulation of leukocyte in lung, which peaked between 24 and 72h. The number of eosinophils peaked at 24h and decreased markedly at 96h. In addition, it was detected an increase in lung eosinophilic peroxidase (EPO) between 24 and 72 hours after the challenge. The resolution of inflammation was associated with an increase in the number of apoptotic cells, as seen from 72 to 96 h, time-points that preceded complete resolution. We observed an increase in the proportion of apoptotic eosinophils and efferocytosis at 72 and 96 hours after the last challenge. Therapeutic treatment with ATB-346 decreased the number of total cells and eosinophils in the BALF, while no difference was observed in the numbers of macrophages, lymphocytes and neutrophils. The treatment with Y27632 decreased the number of total cells, eosinophils and macrophages in the BALF.

**Conclusion**

Collectively, these results show that therapeutic administration of ATB-346 and Y27632 can resolve established eosinophilic inflammation associated to asthma.

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**Key words:** asthma, resolution, inflammation, ATB-346, Y-27632