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S 100–A New Biomarker in Asthma?

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Editorial

Asthma is a chronic inflammatory disease characterized by reversible airway obstruction, airway hyperresponsiveness, and chronic inflammation [1]. The prevalence of asthma varies a lot and unfortunately, has been increasing the last 2 decades. The Global Initiative for Asthma (GINA) estimates that the prevalence of asthma in different countries varies from 1% to 18%. Factors that may trigger or worsen asthma symptomatology are infectious due to viruses, Chlamydia, Mycoplasma or bacteria, exposure to domestic or occupational allergens (e.g., house dust mite, pollens), tobacco smoke environmental factors, exercise or stress [2,3]. It is also known that some drugs can induce asthma, e.g., beta-blockers, antibiotics aspirin or other NSAIDs [4].

S100 and asthma

S100 family proteins are Ca^{2+}-binding proteins involved in the regulation of a variety of cellular activities. Patients with chronic inflammation such as rheumatoid arthritis, inflammatory bowel disease and vascular disease have elevated serum levels of S100 proteins [5]. Previous studies have shown that asthmatics had also raised S100 proteins identified in sputum and serum [6,7]. Additionally, S100 proteins are some of the most abundant proteins found in the Bronchoalveloar Lavage Fluid (BALF) of patients with asthma, Chronic Lung Disease (CLD), Chronic Obstructive Pulmonary Disease (COPD), and Acute Respiratory Distress Syndrome (ARDS). Furthermore, Lorenz E., et al found that patients with acute and CLD had significantly higher levels of S100 (S100A8/A9 and S100A12), in comparison to healthy controls [8].

In a previous study we have also shown that anti S100 antibodies were inversely associated with asthma [9]. A possible explanation is that a-Abs cannot be detected because they form complexes with antigens which are in excess in patients with asthma. The production and serum level of a-Abs is regulated by a feed-back mechanism in relation to the level of the relevant auto antigens [10].

S100-dependent mechanisms are involvement in chronic inflammation, cell activation, hyper responsiveness, and airway obstruction (Figure 1). It is well known that the ability of the smooth muscle to contract is fundamental in airway narrowing. S100 protein signaling induces bronchial obstruction by stimulation of smooth muscles [11]. S100 proteins are highly expressed endogenously in neutrophils wherein S100A8/9 composes up to 40% of the cytosolic proteins. S100 secretion by activated neutrophils provokes mast cells (MCs) activation. Arumugam, et al. reported that sodium cromolyn and its analogs block the interactions between Receptors for Advanced Glycation End-products (RAGE) and S100P [12].

Despite the growing evidence that S100 proteins are involved in the inflammation process of asthma it is still not clear which immunological pathways are followed and what are the relevant mechanisms. Although S100 proteins are considered pro-inflammatory, Hsu et al., have proven that corticosteroids (CSs) up-regulate S100 proteins in macrophages in vitro and in vivo [13]. Bozinovski S et al suggest an anti-inflammatory function of these proteins [14]. In line with this, Zhao et al. reports that murine S100A8 inhibits IgE-mediated MCs activation and the intranasal administration of S100 by reducing key cytokines affecting eosinophil migration and mucous production minimized murine's asthma symptoms [15].

S100 proteins and the RAGE signaling pathway

S 100 proteins exert their biological functions via surface RAGE and Toll-Like receptor 4 (TLR4) [16]. S100s bind to the extracellular region of RAGE and activate various signaling pathways including the downstream pathways of Mitogen-Activated Protein Kinase (MAPK), serine protein kinase (SK), extracellular signal regulated kinase (ERK) and Nuclear Factor-kappa B (NF-kB) [17] Immunohistochemical studies show that RAGE is present in bronchial and vascular smooth muscles, as well as in alveolar macrophages. It is also expressed in numerous immune cells including neutrophils, monocytes/macrophages, lymphocytes and dentritic cells [18]. As the majority of components of the innate immune system, the encoding gene for RAGE is localized within the Major Histocompatibility (MHC) class III [19]. The ligation of RAGE by S100P leads to proinflamatory cytokines secretion and cell activation and proliferation. The physiological interaction between S100P and RAGE has been demonstrated by co-immunoprecipitation in different cell types, including embryonic fibroblast and endothelial cells [20]. Suppression of RAGE by different methods, such as dominant negative mutant of RAGE (DnRAGE), anti-RAGE antibody, and RAGE antagonist peptide, effectively inhibited S100 protein induced cell proliferation, indicate that S100 signals mainly through RAGE [21].

In conclusion, S100 has various effects at many different cells of the respiratory and immune systems. Subsequently, S 100 proteins seem to have a crucial role in the pathogenesis of asthma that needs to be further investigated.

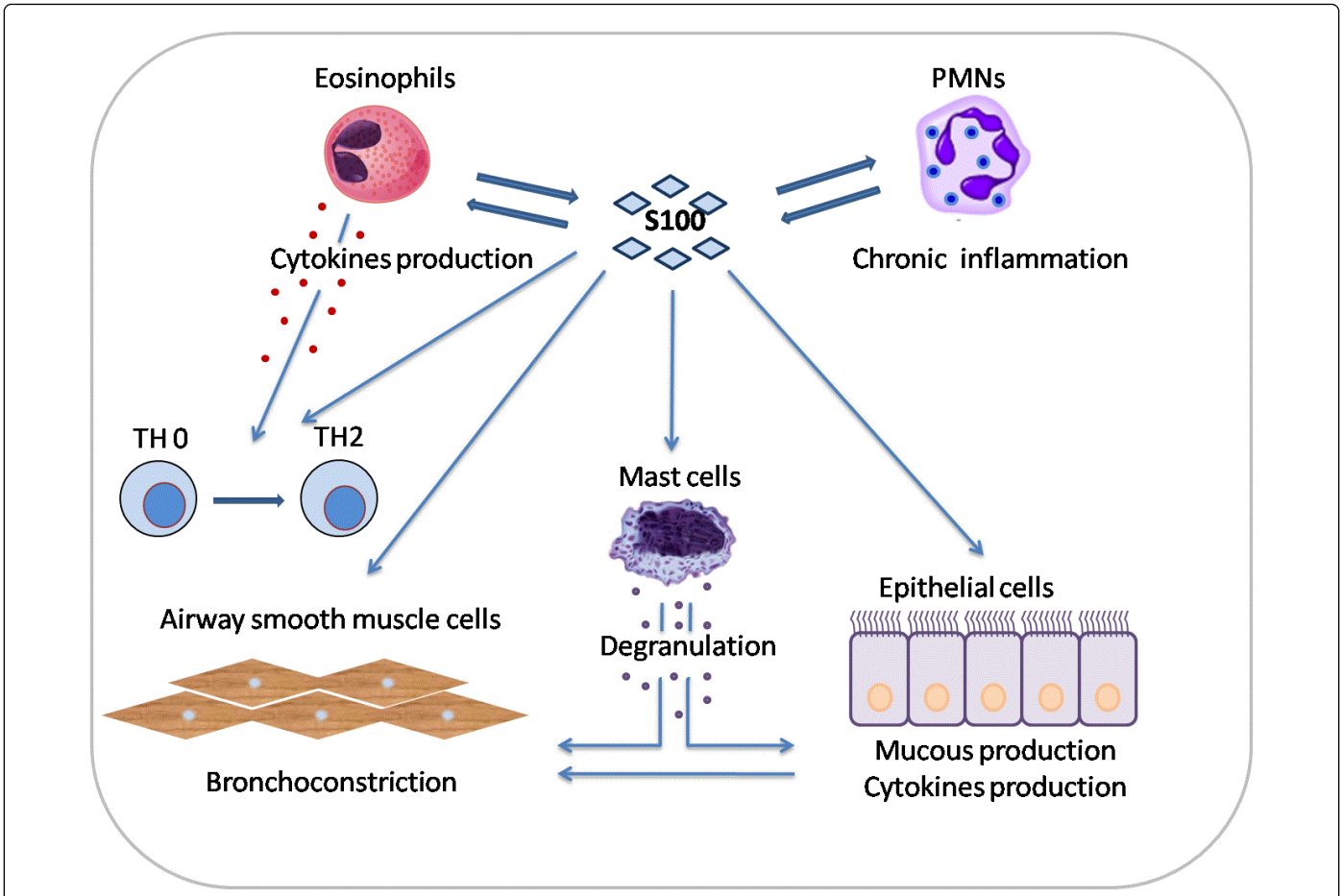

Figure 1: Role of S100 proteins in the pathogenesis of asthma. S100 proteins are expressed in neutrophils and eosinophils. Activated neutrophils and/or eosinophils stimulate the release of S100 proteins, probably by extracellular traps formation. S 100 proteins exert their biological functions via surface RAGE and Toll-Like receptor 4 (TLR4). S100 bind to the extracellular region of RAGE. Receptor-mediated uptake of S100 proteins into cells lead to the activation of many signaling cascades and cytokines production. S 100 proteins exert different effects on various cells: mast cells degranulation, activation of neutrophils, activation of eosinophils to secrete cytokines IL-5, promote Th0 cells differentiation into Th2, bronchial epithelial cells (BECs) in cytokines (IL 25, IL-33) Epithelium-derived S100 proteins and cytokines (IL-25, IL-33) provide a positive feedback to BECs and subsequently enhance production of mucous and matrix proteins. The above suggest that S100 proteins are involved in the innate defense mechanism of the bronchial epithelium.

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