Airway Obstruction and Inducible NO Synthase (iNOS)

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References


Asthma is a chronic disease characterized by airway eosinophilic inflammation and obstruction including hyperresponsiveness (AHR), airway resistance, mucus induction, and airway remodeling including per-bronchial collagen deposition [1-4]. These manifestations lead to repeat episodes of shortness of breath, and wheezing that may debilitate the individuals.

The incidence of the disease is increasing at an alarming rate affecting 1 in 10 children and 1 in 12 adults with a total of 300 million worldwide [5]. Worldwide, deaths from asthma have reached over 250,000 annually. Asthma can be controlled by a combination of an inhaled corticosteroid (anti-inflammatory) and a short or long-acting a-adrenergic agonist.

Thus, new therapies that target the symptoms of asthma are urgently needed. An increasing number of conflicting reports have demonstrated detrimental, protective, and sometimes neutral roles of inducible NO synthase (iNOS) in the pathogenesis of asthma [6]. However, it is unquestionably established that iNOS is expressed in lungs of asthmatic individuals with a subsequent production of NO and generation of the reactive metabolite ONOO [7,8].

Of note, the expression of iNOS is higher in sputum cells from asthmatics compared to those from patients with controlled disease or healthy individuals [9]. Therefore, inhibition of iNOS appears to be a very viable therapeutic target to prevent manifestation of asthma symptoms upon exposure to allergens.

This potential has been challenged by the few observation that a selective iNOS inhibitor did not affect airway inflammatory cell numbers or AHR [10]. But, it is difficult to ignore the fact that asthma protection and susceptibility are associated with polymorphisms in the iNOS gene [11]. Recently, it has been shown that iNOS gene deletion is associated with a reduction in eosinophilia, mucus hyperssecretion, and TH2 cytokine production upon an acute exposure to ovalbumin (OVA) [12,13]. Most recently, we reported that the amount of iNOS and NO are critical determinants in the modulation of AHR by selective iNOS inhibitors. Therefore, selective iNOS inhibitors in blocking AHR in human asthma should use, in particular to the humans that have uncontrolled disease.