
Pharmacological approaches targeting immune cell and oxidative biology in allergic asthma

Airway inflammation is one of the central features of asthma and chronic obstructive pulmonary disease (COPD). The mechanisms associated with the development and progression of airway inflammation have been widely studied in multiple populations and animal models. These studies have revealed involvement of various cell types and activation of intracellular signaling pathways, including Toll-like-receptors (TLRs) and transcription factors such as NF- κ B, that result in activation of inflammatory genes. These have also recently been associated with mechanisms of oxidative biology. This is of important clinical significance, as the observed inefficacy of currently available treatments for severe asthma is widely attributed to oxidative stress. In addition to the physiological stress caused by infectious diseases, the human body is also exposed to environmental hazards and therapeutic drugs, which lead to non-infectious stress. Due to the constant exposure of the respiratory system to the environment, the lung is vulnerable to infectious agents that may cause acute pulmonary diseases and noninfectious chronic lung diseases, including asthma and COPD. Our published article discusses the role of TLRs and NF- κ B in the context of asthma pathogenesis and oxidative biology, as well as the use of polyphenolic flavonoid compounds targeting oxidants and signaling pathways as potential therapeutic agents.

The severity and degree of allergic asthma exacerbations has been associated with environmental factors such as allergens, but is also dependent on the allergen type, duration and degree of exposure, and the patient's overall health and genetics. Studies have identified several genes that contribute to patient's susceptibility for allergic asthma onset, and the overall disease progression. Among these, a predominant role of TLRs, and contributions of polymorphisms in their associated genes (in particular TLR2, TLR4 and TLR7, TLR8 and TLR9) have been implicated in the physiopathology of asthma. Along with polymorphic variation in the TLR genes, genetic variation in regulatory and intracellular molecules involved in TLR signaling pathways have also been found to exhibit functions in allergic asthma onset and exacerbations.

In the past decades, multiple studies have demonstrated that NF- κ B is vigorously involved in a myriad of inflammatory mechanisms. Thus, the name "central switch" justifies its role in the regulation of expression of over 300 genes in a cell-specific and stimulus-specific manner, ranging from normal cell physiological processes, inflammation, infection, metabolism of reactive oxidative species (ROS) and DNA damage, to cancer and autoimmune diseases. As airway injury persists due to allergen exposure, smoke, or other environmental irritants such as ozone and nitric oxide, it causes not only impairment of innate immunity, but also increased susceptibility of the lower respiratory tract to pathogens.

The standard asthma treatment includes β 2-agonists and systemic corticosteroids. Although treatment with corticosteroids is considered as the gold standard, various studies have reported a significant incidence of adverse effects with high dose and long-term use. In this context, molecules known to possess antioxidant activity along with ability to regulate intracellular signaling pathways, could be used in targeted adjuvant treatment of asthma. These include: flavonoids, beta-carotenes, lycopene, omega-3 and omega-6 fatty acids, thiol antioxidants, melatonin, carotenoids, resveratrol, vitamin C and E. However, given the vast degree of naturally occurring compounds exhibiting potent antioxidant activity and signatory intercepts in intracellular pathways, our published review limits its approach to flavonoids, in particular to Kaempferol, Quercetin, and

Isorhamnetin flavonol. Overall, studies on this topic have provided evidence to show that natural molecules such as flavonoids possess strong antioxidant activity and ability to regulate intracellular signaling pathways. Therefore, these could be effectively utilized for safer and effective therapeutic approaches for asthma and other inflammatory lung diseases.

Vikas Mishra, Jaspreet Banga, Patricia Silveyra

*Departments of Pediatrics and Biochemistry and Molecular Biology, The Pennsylvania State University,
College of Medicine, Hershey, PA, USA*

Publication

[Oxidative stress and cellular pathways of asthma and inflammation: Therapeutic strategies and pharmacological targets.](#)

Mishra V, Banga J, Silveyra P
Pharmacol Ther. 2018 Jan