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TITOLO DEL PROGETTO: THE ARYL HYDROCARBON RECEPTOR AS A THERAPEUTIC TARGET IN ASTHMA: LINKING ENVIRONMENTAL EXPOSURE TO IMMUNE DYSREGULATION

The global prevalence of asthma continues to rise, particularly among populations exposed to high levels of environmental pollutants. This trend highlights the need for novel therapeutic strategies that go beyond conventional anti-inflammatory and bronchodilators treatments, especially for pollution-driven or treatment-refractory asthma. One emerging target is the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor originally recognized for its role in xenobiotic metabolism. Recent evidence suggests that AhR plays a broader role in immune regulation, epithelial barrier function, and oxidative stress responses—all central to asthma pathogenesis. Environmental pollutants, including polycyclic aromatic hydrocarbons (PAHs) and fine particulate matter ($PM_{2.5}$), act as potent AhR ligands. Once activated, AhR translocates to the nucleus and modulates gene expression involved in cytokine production (e.g., IL-17, IL-22), mucin secretion, and epithelial remodeling. Dysregulated AhR signaling has been linked to Th17-skewed immune responses, contributing to chronic inflammation and steroid-resistant asthma. Additionally, disruption of epithelial integrity through AhR activation may increase susceptibility to allergens and pathogens. Pharmacological targeting of AhR presents a promising approach. Selective AhR modulators (SAhRMs) allow for context-specific modulation of receptor activity, potentially delivering immunoregulatory benefits while limiting toxic effects. Preclinical studies demonstrate that AhR agonists can promote regulatory T cell (Treg) activity and restore pulmonary immune homeostasis, whereas antagonists may be beneficial in pollutant-induced AhR hyperactivation. The objective of this study is to evaluate the therapeutic potential of AhR modulation in asthma, with a specific focus on its role in pollution-exacerbated disease phenotypes. We aim to elucidate the molecular mechanisms through which AhR activation or inhibition influences airway inflammation, immune cell polarization, epithelial barrier integrity, and glucocorticoid responsiveness. Through a combination of in vitro cellular models and in vivo murine systems, this research will investigate the differential effects of AhR agonists and antagonists under pollutant exposure conditions. Furthermore, the study will explore the feasibility of using AhR-related biomarkers for patient stratification, ultimately laying the groundwork for the development of targeted, mechanism-based therapies for high-risk asthma subtypes.

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