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# The Role of the Non-neuronal Cholinergic System in Immune Regulation

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**ABSTRACT:**
The immune system is essential for the host's defense against potentially invasive and dangerous pathogens. Immune cells including monocytes, macrophages and dendritic cells, tightly regulate the immune response. Two decades ago, the importance of the non-neuronal cholinergic system and the nicotinic acetylcholine receptors (nAChRs) in the modulation of the immune system was raised. Since then, it has become increasingly clear that the activation of nAChRs by agonists such as acetylcholine (ACh) and nicotine can have anti-inflammatory properties via the regulation of cytokines. Additionally, recent novel class molecules termed silent agonists have been created to bind nAChRs and potentially alleviate inflammation. However, the signaling pathways regulated by the interaction between nAChR agonists and nAChRs remains unclear. The objectives of this study are to gain insights on the anti-inflammatory properties of both ACh and the nAChR silent agonists as well as to identify the signaling mechanisms modulated by the interaction between nAChR agonists and nAChRs in macrophages. For both objectives, human monocytic cell lines (THP-1 and U937) were cultured and differentiated into macrophages using PMA. Once differentiated, the cell lines were treated with separate conditions including ACh, an ACh-inhibitor, antagonists and silent agonists specific to nAChRs. Then, lipopolysaccharide (LPS), was used to induce an immune response. The presence of ACh synthesizing and degradation enzymes, choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) was analyzed via western blot. Experiments assessing cytokine expression and viability was carried out. Afterwards, multiple immune-relevant signaling cascades was assessed by quantifying total and phosphorylated protein extracted from stimulated macrophages using a Bioplex. The results suggests that Ach play important roles in immune regulation and that the nAChR silent agonists have potential for pharmacological treatments of auto-immune and inflammatory diseases.