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Cholinergic modulation of dendritic cell function ☆

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ABSTRACT

Dendritic cells (DCs) are highly specialized antigen-presenting cells with a unique ability to activate resting T lymphocytes. Acetylcholine (ACh) is the primary parasympathetic neurotransmitter and also a non-neural paracrine factor produced by different cells. Here, we analyzed the expression of the cholinergic system in DCs. We found that DCs express the muscarinic receptors M_3, M_4 and M_5, as well as the enzymes responsible for the synthesis and degradation of ACh, choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), respectively. Differentiation of DCs in the presence of the cholinergic agonist carbachol, the synthetic analog of ACh, resulted in an increased expression of HLA-DR and CD86 and the stimulation of TNF-α and IL-8 production. All these effects were prevented by atropine, a muscarinic ACh receptor (mAChR) antagonist. Carbachol, was also able to modulate the function of DCs when added after the differentiation is accomplished; it increased the expression of HLA-DR, improved the T cell priming ability of DCs, and stimulated the production of TNF-α but not IL-12 or IL-10. By contrast, carbachol significantly inhibited the stimulation of HLA-DR expression and the enhancement in the T cell priming ability of DCs triggered by LPS. Interestingly, the TNF-α antagonist etanercept completely prevented the increased expression of HLA-DR induced by carbachol, suggesting that it promotes the phenotypic maturation of DCs by stimulating the production of TNF-α. ACh induced similar effects than carbachol; it stimulated the expression of HLA-DR and the production of TNF-α, while inhibiting the stimulation of HLA-DR expression and IL-12 production triggered by LPS. Similarly, neostigmine, an inhibitor of AChE, also stimulated the expression of HLA-DR and the production of TNF-α by DCs while inhibiting the production of TNF-α and IL-12 triggered by LPS. These results support the existence of an autocrine/paracrine loop through which ACh modulates the function of DCs.

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1. Introduction

Conventional dendritic cells (DCs) are specialized antigen presenting cells with a unique ability to activate resting T cells and to direct their differentiation into different effector profiles (Guermonprez et al., 2002; Steinman, 2003; Ardavin et al., 2004; Reis e Sousa, 2006; Sabatte et al., 2007).

It is well known that the nervous system and the immune system communicate bidirectionally, and that lymphoid tissues are innervated by the autonomic nervous system (Blalock and Weigent, 1994). Moreover, increasing evidence suggests the presence of a non-neuronal cholinergic system in immunocompetent cells, which is activated during inflammation (Kurzen et al., 2007). In fact, the components of the cholinergic system; ACh, nicotinic and muscarinic receptors (n- and mAChRs), choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), were detected in mammalian non-neuronal cells, including immune cells such as B and T lymphocytes (Kawashima and Fujii, 2000). Moreover, ACh was shown to be able to modulate the function of immune cells; it stimulates the activation of T CD8+ cells (Kawashima and Fujii, 2000; Zimring et al., 2005) while inhibits the production of inflammatory cytokines by phagocytes (Borovikova et al., 2000b; Pavlov and Tracey, 2005).

There are not previous studies directed to analyze the expression of the cholinergic system in human DCs and the ability of ACh to modulate their functional profile. Here, we show that human DCs express the receptors M_3, M_4 and M_5 as well as the enzymes responsible for the synthesis and degradation of ACh. Moreover, we found that the cholinergic agonist carbachol and ACh modulate the function of DCs. Interestingly, we found that cholinergic agonists

Abbreviations: DCs, dendritic cells; ACh, acetylcholine; mAChR, muscarinic acetylcholine receptor; AChE, acetylcholinesterase; ChAT, choline acetyltransferase.

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