RESEARCH PAPER

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Thimerosal compromises human dendritic cell maturation, IL-12 production, chemokine release, and T-helper polarization

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Thimerosal is a preservative used in multidose vials of vaccine formulations to prevent bacterial and fungal contamination. We recently reported that nanomolar concentrations of thimerosal induce cell cycle arrest of human T cells activated via the TCR and inhibition of proinflammatory cytokine production, thus interfering with T-cell functions. Given the essential role of dendritic cells (DCs) in T-cell polarization and vaccine immunity, we studied the influence of non-toxic concentrations of thimerosal on DC maturation and functions. Ex-vivo exposure of human monocyte-derived DCs to nanomolar concentrations of thimerosal prevented LPS-induced DC maturation, as evidenced by the inhibition of morphological changes and a decreased expression of the maturation markers CD86 and HLA-DR. In addition thimerosal dampened their proinflammatory response, in particular the production of the Th1 polarizing cytokine IL-12, as well as TNF-α and IL-6. DC-dependent T helper polarization was altered, leading to a decreased production of IFN-γ IP10 and GM-CSF and increased levels of IL-8, IL-9, and MIP-1α. Although multi-dose vials of vaccines containing thimerosal remain important for vaccine delivery, our results alert about the ex-vivo immunomodulatory effects of thimerosal on DCs, a key player for the induction of an adaptive response

Introduction

Adaptive immunity plays a crucial role in natural host defense against pathogens and tumors, and it is central to the long-term protective effect of vaccines. The innate immune system functions to direct the adaptive immune response, both through antigen presentation by dendritic cells and by providing the key signals for the differentiation of naive $CD4^+$ T cells into functionally distinct T helper cell (Th) subtypes.[1,2] DCs act as a sentinel population that constantly samples the tissue microenvironment and takes up microbial cells through toll-like receptors (TLRs).[3] TLRs can detect multiple pathogen-associated molecular patterns (PAMPs),[4] including LPS detected by TLR4, resulting in the activation of NF-κB that drives the production of many proinflammatory cytokines, including IL-1, IL-6, TNF-α, and IL-12.[5] TLR-induced IL-12 is the key differentiation factor for Th1 cells.[6] Upon DC maturation with LPS, chemokines such as MIP1-α, MCP1, and IP-10 are rapidly upregulated for recruitment and maintenance of DCs at the inflammatory site.[7] Furthermore, a recent report highlighted the importance of DC-derived IP-10 in the development of stable DC–$CD4^+$ Th cell interactions.[8] IP-10 binds to CXCR3 on Th cells and is required for optimal Th1 cell induction in the lymph node.[8]

Thimerosal is a preservative used in multidose vials of vaccine formulations to prevent bacterial and fungal contamination.[9,10] Thimerosal is an ethylmercury-containing pharmaceutical compound that contains 49.6% mercury by weight and metabolizes into ethylmercury (etHg) and thiosalicylate.[11] Thimerosal is known as a contact allergen, and caution has been urged regarding significant side effects in therapeutic agents[12] and in vaccines[13] with specific issues related to infant-CNS.[14,15] Thimerosal has been shown to cause a number of toxic changes in vitro, including neuronal mitochondrial cell death,[16,17,18] oxidative stress and apoptosis of HeLa S epithelial cells,[19] and S phase arrest and apoptosis via inhibition of the PI3K/Akt/survivin pathway on the murine C2C12 myoblast cells.[20] Because thimerosal is one of the best-known skin sensitizers, several studies have been performed on human myeloid dendritic cells, which play an essential role in the initiation of allergic contact dermatitis. DC activation and associated immune functions are subject to regulation by their redox environment and thimerosal was reported to induce ROS production in DCs,[21] associated with their activation, as monitored by CD86 and HLA-DR overexpression,[22,23] and the secretion of TNF-α and IL-8.[24] The link between thimerosal-induced oxidative stress and DC activation was also addressed by Goth et al. who reported that thimerosal altered IL-6 synthesis elicited by exogenous ATP,

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