Oxidative modification enhances the immunostimulatory effects of extracellular mitochondrial DNA on plasmacytoid dendritic cells

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Abstract

Inflammation is associated with oxidative stress and characterized by elevated levels of damage-associated molecular pattern (DAMP) molecules released from injured or even living cells into the surrounding microenvironment. One of these endogenous danger signals is the extracellular mitochondrial DNA (mtDNA) containing evolutionary conserved unmethylated CpG repeats. Increased levels of reactive oxygen species (ROS) generated by recruited inflammatory cells modify mtDNA oxidatively resulting primarily in accumulation of 8-oxo-7,8-dihydroguanine (8-oxoG) lesions. In this study, we examined the impact of native and oxidatively modified mtDNAs on the phenotypic and functional properties of plasmacytoid dendritic cells (pDCs), which possess a fundamental role in the regulation of inflammation and T cell immunity. Treatment of human primary pDCs with native mtDNA up-regulated the expression of a co-stimulatory molecule (CD86), a specific maturation marker (CD83), and a main antigen-presenting molecule (HLA-DQ) on the cell surface, as well as increased TNF-\(\alpha\) and IL-8 production from the cells. These effects were more apparent when pDCs were exposed to oxidatively modified mtDNA. Neither native nor oxidized mtDNA molecules were able to induce interferon (IFN)-\(\alpha\) secretion from pDCs unless they formed a complex with human cathelicidin LL-37, an antimicrobial peptide. Interestingly, simultaneous administration of a Toll-like receptor (TLR)9 antagonist abrogated the effects of both native and oxidized mtDNAs on human pDCs. In a murine model, oxidized mtDNA also proved a more potent activator of pDCs compared to the native form, except for induction of IFN-\(\alpha\) production. Collectively, we demonstrate here for the first time that elevated levels of 8-oxoG bases in the extracellular mtDNA induced by oxidative stress increase the immunostimulatory capacity of mtDNA on pDCs.
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