EFFECT OF NATIVE AND OXIDATIVELY MODIFIED EXOGENOUS MITOCHONDRIAL DNA ON THE FUNCTIONS OF HUMAN PLASMACYTOID DENDRITIC CELLS

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Introduction: Plasmacytoid dendritic cells (pDCs) are a unique and rare cell population of the immune system. They are specialized for the recognition of nucleic acids of invading microbes by their selectively expressed endosomal nucleic acid-sensing Toll-like receptors (TLRs) such as TLR7 and TLR9. It has been recently demonstrated that extracellular mitochondrial DNA (mtDNA) released from injured or even living cells during inflammation can act as endogenous damage-associated molecular pattern (DAMP) molecule. Mitochondria are evolutionary endosymbionts derived from bacteria and so might carry bacterium-associated molecular motifs so we suppose that extracellular mtDNA is able to induce activation of pDCs.
Methods: mtDNA was extracted from non-treated and oxidative stress-exposed human cells. The levels of the 7,8-dihydro-8-oxoguanine (8-oxoG) in the purified mtDNA, which correlate with the oxidized state of the DNA, were measured by dot blot method. Phenotypic changes of pDCs after mtDNA treatments were monitored by flow cytometry and the cytokine and chemokine secretion of the cells was detected by ELISA.
Results: We found that treatment with mtDNA up-regulated the expression of several cell surface proteins (CD40, CD80, CD83, CD86, HLA-DQ) on pDCs and increased the type I interferon, TNF-α, and IL-8 secretion by the cells. These effects were more apparent when pDCs were treated with high 8-oxoG-containing mtDNA purified from oxidative-stress exposed cells, indicating that 8-oxoG enriched mtDNA sequences arisen under oxidative stress conditions can be more potent activators of the human pDCs than the native ones. In addition, pre-treatment of the cells with TLR9 antagonist (ODN TTAGGG sequence), strongly diminished the ability of mtDNA to induce phenotypic and functional changes in pDCs, indicating that these activation processes were manly mediated through TLR9.
Conclusions: Collectively, our data suggest that the cell-free mtDNA enriched in the extracellular matrix or circulated in the blood-stream after cell injury or inflammation is fully capable of activating human pDCs via TLR9. Furthermore, the oxidatively modified mtDNA generated during the inflammatory reactions may have a greater potencial to initiate and maintain of the immune responses.