# The role of PPARγ in clearance of apoptotic neutrophils by human macrophages and dendritic cells

Macrophages acquire their capacity for efficient phagocytosis of apoptotic cells during their differentiation from monocytes. The peroxisome proliferator activated receptor gamma (PPARγ) is highly up-regulated during this maturation program. We have shown that addition of PPARγ antagonist during differentiation of human monocytes to macrophages significantly reduces the capacity of macrophages to engulf apoptotic neutrophils, but did not influence phagocytosis of opsonized bacteria. Macrophage-specific deletion of PPARγ in mice also resulted in decreased uptake of apoptotic cells. The antagonist acted in a dose-dependent manner during the differentiation of human macrophages and could also reverse the previously observed augmentation of phagocytosis by glucocorticoids. Blocking activation of PPARγ led to down-regulation of molecular elements (CD36, AXL, TG2 and PTX3) of the engulfment process. Inhibition of PPARγ dependent gene expression did not block the anti-inflammatory effect of apoptotic neutrophils or synthetic glucocorticoid but significantly decreased production of IL-10 induced by LPS. Our results suggest that during differentiation of macrophages natural ligands of PPARγ are formed regulating the expression of genes responsible for effective clearance of apoptotic cells and macrophage-mediated inflammatory response.

Studying the effects of apoptotic neutrophil engulfment on DCs as compared to macrophages we have shown that apoptotic neutrophils are preferentially taken up by the $CD1a^-$ DC subset and similar to macrophages the activation of PPARγ regulates the capacity of DCs to engulf apoptotic neutrophils. In contrast with macrophages DCs internalizing apoptotic neutrophils get activated during the phagocytic process resulting in secretion of L-8, IL-6, TNF-α and IL-1β. In the presence of additional inflammatory stimuli such IFNγ and LPS, the uptake of apoptotic neutrophils sensitizes DCs for robust inflammatory responses. DCs engulfing apoptotic neutrophils were able to polarize autologous T cells resulting in Th1 differentiation associated with IFNγ secretion. When macrophages fed by apoptotic neutrophils were used instead of DCs no IFNγ secreting T cells were observed.

Our results suggest that the recruitment of neutrophils to inflamed tissues induces different types of responses in monocyte-derived macrophages and dendritic cells. Hence, the crosstalk of apoptotic cell-loaded macrophages and DCs through their cytokines and antigen-presenting functions may modulate the outcome of immune responses under inflammatory or other pathologic conditions.

Key words: apoptosis, cytokines, macrophages, dendritic cells, phagocytosis.