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dendritic cells (My-MoDC) unable to present lipid antigens to specific T cells. Here we show that mycobacteria inhibit CD1 expression by triggering phosphorylation of p38 mitogen-activated protein kinase (MAPK) and of the downstream activating transcription factor (ATF)-2. Moreover mycobacteria infected monocytes treated with p38 inhibitor display a reduced ATF-2 phosphorylation and finally differentiate into CD1+ve DC endowed with the capacity of presenting lipid antigens to specific CD1-restricted T cells.

We also report that a pivotal role in p38 phosphorylation during mycobacteria infection of monocytes is played by complement receptor type 3 (CR3), since CR3 blockade obtained by a specific antibody reduces p38 phosphorylation and partially abolishes the subversive effect of mycobacteria on CD1 expression.

In conclusion we propose p38/ATF-2 signalling as a novel pathway exploited by mycobacteria to affect the expression of CD1 antigen presenting family and avoid immune recognition.

Cross-presentation of caspase-cleaved apoptotic self antigens in HIV infection

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Apoptosis represents a remarkable key step in the homeostasis of the immune system, in fact it is involved in the getting rid of auto-reactive lymphocytes during central and peripheral tolerance, as well as in the termination of effector immune responses. In apoptotic cells, also the activation of caspases leads to alterations of the proteome. We found that the proteome of apoptotic T cells includes prominent fragments of cellular proteins generated by caspases and that a high proportion of distinct T cell epitopes in these fragments is recognized by CD8+ T cells during HIV infection. The frequencies of effector CD8+ T cells that are specific for apoptosis-dependent epitopes correlate with the frequency of circulating apoptotic CD4+ T cells in HIV-1–infected individuals. We propose that these self-reactive effector CD8+ T cells may contribute to the systemic immune activation during chronic HIV infection. The caspase-dependent cleavage of proteins associated with apoptotic cells has a key role in the induction of self-reactive CD8+ T cell responses, as the caspase-cleaved fragments are efficiently targeted to the processing machinery and are cross-presented by dendritic cells. These findings demonstrate a previously undescribed role for caspases in immunopathology.

Proteasome subunit composition in dendritic cells and hepatocytes of HCV-infected subjects

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Proteasome is critically involved in the production of MHC class-I restricted epitopes. It has three distinct catalytic β subunits called β1, β2, β5, which exhibit postacidic, tryptic-like, and chymotryptic-like activity, respectively. When cells are exposed to type I and II IFN, these three catalytic subunits are replaced by new components termed latent membrane protein 2 (LMP2), LMP7, and multicatalytic endopeptidase complex like-1 (MECL1), which are incorporated into a modified proteasome form known as immunoproteasome. The proteolytic activity of immunoproteasomes is characterized by a reduced cleavage after acidic amino acids and by an increased cleavage after hydrophobic and basic residues, which are the most frequent residues found at the COOH terminus of the MHC class-I binding peptides.

During the acute phase of HCV infection, both circulating dendritic cells (myeloid and plasmacytoid) and hepatocytes display a vigorous mRNA synthesis of the immunoproteasome subunits which are expressed at high levels in the cell cytoplasm. During the chronic phase of HCV infection, immunoproteasome subunits are produced and expressed at much lower levels in hepatocytes than in circulating dendritic cells, indicating a discrepancy between the repertoire of CD8+ T cells primed for antiviral responses and the viral peptides that are presented to CD8+ T cells.

Mitochondrial biogenesis during dendritic cell differentiation

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Dendritic cells (DC) are potent antigen presenting cells capable to induce T and B responses and immune tolerance. We have characterised some aspects of energy metabolism accompanying the differentiation of human monocytes into DC. DC exhibit a much higher endogenous respiratory activity compared to monocytes and a substantially higher respiratory control ratio, measured as uncoupler stimulated *vs* oligomycin inhibited respiration. This finding, together with the observation that DC respire prevalently under state 3, indicate a high capacity by these cells to synthesize ATP.

Direct analysis showed that ATP content in DC was more than six fold increased compared to their precursors. The activity of citrate synthase, a matrix marker enzyme, nearly paralleled the increase of ATP production. Moreover, TEM analysis revealed a significant increment in the number of mitochondria and, thus, an active mitochondrial biogenesis during the differentiation. The presence in the culture medium of rotenone, an inhibitor of the complex I, prevented the increase of mitochondrial number and of ATP level, without affecting cell viability. Rotenone inhibited DC differentiation, as revealed by the decreased expression of CD1a, a specific surface marker of DC differentiation, was strongly reduced.

Cell cultured in the presence of rotenone displayed a lower content of growth factors-induced, mitochondrial generated, hydrogen peroxide. A similar drop of ROS was observed upon addition to culture medium of catalase, which caused similar functional effects as those produced by rotenone.

These results suggest that the differentiation process of DC is accompanied by an active mitochondrial biogenesis and that mitochondria are an important source for ROS triggering the differentiation.