Department of Microbiology, Tumor and Cell Biology

Constrains for dendritic cell differentiation- analysis of autocrine inhibitory mechanisms with therapeutic implications

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Abstract

The discovery of dendritic cells (DCs) was followed by an intensive research period aiming at the identification of mechanisms that could induce or inhibit adaptive immune responses through the manipulation of these cells. Only in the recent years the role of metabolic pathways in DC regulation has started to become clear. Metabolic regulators might allow the generation of DCs with prominent immunogenicity or the interference with chronic immune activation accompanying autoimmune responses or HIV-1 infection. Therefore the focus of this thesis is on novel mechanisms that regulate DC function, the relevance of these in generation of DC vaccines and on the delineation of pathways that potentially contribute to the unbalanced immune responses during HIV-1 infection. In **paper I,** we show that lactate inhibits the differentiation of human inflammatory DCs in a cell culture concentration dependent manner. DCs differentiating in the presence of low lactate concentrations are immune-stimulatory as shown by the production of inflammatory cytokines, the induction of Th1 differentiation and the migration in a trans-well system. In contrast, DCs from dense cultures produce high levels of IL-10 and trans-differentiate into osteoclasts. In **paper II,** we demonstrate an efficient modulation of DC vaccine immunogenicity by modulating cell culture density during DC development. DCs from sparse cultures migrated more efficiently to draining lymph nodes and induced more robust antigen-specific T cell activation *in vivo* as compared to dense DC cultures. In addition, DCs developing in sparse cultures exhibited a transcriptional profile associated with increased cholesterol and lipid biosynthesis, suggesting a link between lipid biosynthetic pathways and DC activities. In**, paper III** we explored the role of DC plasticity in regulating DC/HIV-1 interactions. We showed that DC responses to HIV-1 were largely dependent on the functional characteristics of the cells and strain-specific features of the virus. Suppressed DCs up-regulated production of inflammatory cytokines after HIV-1 exposure, whereas the virus could block cytokine production in the more immunogenic DC types suggesting unique viral pathways induced in the different DC lineages. Finally, in **Paper IV** we provided evidence that the population of CD4+CD70+ T cells is expanded in lymphopenic HIV-1 infected individuals potentially contributing to B cell abnormalities. In conclusion, the studies presented in this thesis identified new mechanisms and metabolic components that regulate DC immunogenicity and novel immune-modulatory pathways operating during HIV-1 infection.