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Dendritic Cells and Virus Infection

With 24 Figures and 2 Tables

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Preface

In the first part of this volume the interactions between Dendritic cells (DCs) and several viruses will be presented and discussed.

DCs are the best antigen presenting cells (APCs) know to date, and since DCs are the only APCs able to induce naïve T cells they are also known as "nature's adjuvant". Thus, DC play a crucial role in the induction of anti-viral immune responses. On the other hand, many viruses are capable of developing a vast armentarium in order to interfere with DC-biology, thereby blocking anti-viral immune responses. DCs often play a dual role in viral infections, influencing both pathogenesis as well as protective mechanisms. This has been shown, for instance, in the case of HIV-1 and SIV, where HIV-1 infects selected DC-populations. In addition HIV-1 uses DCs as a vector to reach the lymphoid tissues where they infect T cells. The cell surface molecule DC-SIGN has been identified as such a DC-specific HIV-1 receptor, which plays a key-role in the dissemination of HIV-1 by DCs. On the other hand, DCs are efficient APCs for HIV-1 and SIV antigens to both $CD4^+$ and $CD8^+$ T cells. In addition DCs can cross-present non-replicating viral antigens on class I MHC molecules, thereby allowing the stimulation of $CD8^+$ T cells after the uptake of anti-body-coated HIV-1 and dying infected T cells.

DCs also play a crucial role in Epstein-Barr virus (EBV) infection. There is growing evidence that DCs, and not EBV-transformed B cells, are responsible for protective antiviral immunity and that EBV nuclear antigen 1 (EBNA1) is the crucial antigen regarding the resistance against all types of EBV-associated malignancies.

Measles virus (MV) infection is the major cause of childhood mortality in developing countries and is accompanied by a severe immunosuppression of the infected host. However, virus-specific immunity is efficiently induced, leading to viral clearance and long-term induction of protective immunity. On the one hand, DCs play a crucial role in the induction of antiviral immune responses, while on the other hand MV infects DCs, thereby interfering with DC biology. Inhibition of stimulated IL-12 production from MV-infected DCs might affect T cell responses and favour Th2 and suppressing Th1 responses. In addition, viral protein expressed on the cell surface of infected DCs most likely also inhibit T cell responses.

DCs also express the receptor (α-dystroglycan) for lymhocytic choriomeningitis virus (LCMV), Lassa fever virus (LFV) and several other arenaviruses. It has been shown that LCMV strains which bind to the receptor with high affinity replicate in the majority of DCs, causing a generalized immunosuppression, and establish a persistent infection. This immune suppression is caused by the loss of MHC class II molecules and costimulatory molecules on the cell surface of the DCs. Furthermore, the migratory capacity of DCs is hampered by LCMV infections. It is noted, however, that LCMV strains which bind with low affinity rarely replicate in DCs, and generate a potent anti-LCMV response, which is able to clear the infection.

HSV-1 is a further example of a virus which down-modulates DC functions by interfering with the expression of DC specific molecules such as CD83. In fact, CD83 is completely degraded in HSV-1 infected DCs, which coincides with a clearly reduced T cell stimulation, representing yet another new escape strategy.

The second part of this volume concentrates on DC-specific strategies in order to strengthen antiviral immune responses.
DC-based vaccination strategies represent one of the most promising approaches for the immunotherapy of cancer and infectious diseases. Several clinical trials have already been performed showing only minimal toxicity in tumor patients. Both induction of antigen specific T cells as well as some clinical responses have been reported using this strategy, even in far advanced tumor patients. Nevertheless, DC-based immunotherapy is still at an early stage and many variables have still to be addressed. However, the increasing knowledge of DC biology will help to improve and further develop this new strategy.

Data derived from animal models, regarding the induction of LCMV-specific immunity with various DC-vaccination approaches will be discussed. In addition, the interplay between human papillomaviruses (HPV) and DCs will be presented. Here, DCs (including Langerhans cells) are pivotal for the induction of T cell dependent immunity. This, however, depends exclusively on cross-presentation of viral antigens by DCs. This exogenous pathway of MHC class I-restricted antigen presentation plays an important role in the generation of antiviral immunity against several viruses. Finally, viral vectors which could be used for DC-based immunotherapy will be presented and their advantages and disadvantages will be discussed respectively.

April 2003 Alexander Steinkasserer

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(Their addresses can be found at the beginning of their respective chapters)