Centrum för Infektionsmedicin

Institutionen for Medicin, Huddinge

Regulation of Human Dendritic Cells and T Cells by Adenovirus Vectors Types 5 and 35: Implications for Vaccine Design

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i 4U Solen, Alfred Nobels Allé 8, Karolinska Universitetssjukhuset, Huddinge.

Fredagen den 10 juni, 2011, kl 10.30

av

William C. Adams

Huvudhandledare:
Docent Karin Loré
Karolinska Institutet
Institutionen för Medicin
Centrum för infektionsmedicin

Bihandledare:
Senior Investigator Richard A. Koup
US National Institutes of Health
Vaccine Research Center

Fakultetsopponent:
Senior Research Fellow Steven Patterson
Imperial College London
Department of Medicine

Betygsnämnd:
Docent Ola Winqvist
Karolinska Institutet
Institutionen för medicin, Solna

Docent Niklas Arnberg
Umeå Universitet
Institutionen för klinisk mikrobiologi - virologi

Assistant Professor Michael Uhlin
Karolinska Institutet
Institutionen för laboratoriemedicin

Stockholm 2011

ABSTRACT

Following viral infection or vaccination dendritic cells (DC) perform an intricate series of roles at the interface of innate and adaptive immunity. Peripheral DC recognition of pathogen associated molecular patterns initiates signaling cascades leading to morphological and phenotypic maturation. The differentiation to a mature phenotype licenses DCs to efficiently prime T- and B-lymphocytes. Thus, DCs shape early innate immune responses that limit viral replication and initiate the generation of protective and adaptive immunological memory.

In this thesis, we began by studying the interaction of human primary DCs with human adenovirus (AdV). While the causative agent of a variety of human diseases, AdVs are also a valuable research tool for probing virological, immunological, and cellular mechanisms of nature. Recombinant human AdVs (rAdV), rendered replication incompetent and thus unable to cause disease, have gained prominence as gene delivery vehicles in multiple vaccine trials. In light of the clinical importance of AdV vectors, we employed a reductionist approach to study mechanisms of virus-mediated regulation of human DC function. Since DCs activate adaptive immunity, we extended our investigations to the impact of rAdV on the activation of T-lymphocytes. These studies are particularly relevant since the induction of potent T-cell responses is one objective of rAdV based vaccine vectors.

In assessing the interaction of rAdV with primary human blood myeloid and plasmacytoid DC subsets, we found that activation of these cells was dependent on rAdV type. rAdV-35 more efficiently infected DCs than rAdV-5, and matured blood DCs and strongly induced interferon-α in plasmacytoid DCs. Infection by rAdV-35 was dependent on the receptor CD46, whereas the receptor for rAdV-5 was less clear. We then showed that lactoferrin facilitated rAdV-5 infection of multiple DC subsets in a similar manner to epithelial cells. rAdV-exposed DCs were able to process and present rAdV encoded transgenes and activate polyfunctional memory T cells, which indicated that rAdV infected DCs retained their antigen presentation capacity. However, it remained unclear from these studies whether rAdV affected the activation of naive T cells, which is an important step for vaccination. To this end, rAdV-35 was found to strongly inhibit activation of naive CD4+ T cells through binding of its cellular attachment receptor, CD46. Attenuated activation was characterized by lower proliferation and IL-2 production, as well as deficient NF-κB nuclear translocation. Further studies showed that cross-linking with CD46 monoclonal antibodies and recombinant trimeric rAdV-35 knob proteins was sufficient to cause similar suppression as the whole virus, substantiating the role of CD46 in regulating CD4+ T-cell function.

Our findings provide insights into the mechanisms by which host immune cells respond to rAdV and also how the virus may act to modulate host cell function. These findings may also guide the development of rAdVs as vaccine vectors.