Summary

Retroviruses are genome invaders that have shared a long history of coevolution with vertebrates and their immune system. Found endogenously in genomes as traces of past invasions, retroviruses are also considerable threats to human health when they exist as exogenous viruses such as HIV. The immune response to retroviruses is engaged by germline-encoded sensors of innate immunity that recognize viral components and damage induced by the infection. This response develops with the induction of antiviral effectors and launching of the clonal adaptive immune response, which can contribute to protective immunity. However, retroviruses efficiently evade the immune response, owing to their rapid evolution. The failure of specialized immune cells to respond, a form of neglect, may also contribute to inadequate antiretroviral immune responses. Here, we discuss the mechanisms by which immune responses to retroviruses are mounted at the molecular, cellular, and organismal levels. We also discuss how intrinsic, innate, and adaptive immunity may cooperate or conflict during the generation of immune responses.

Summary

Dendritic cells (DCs) are critical for the launching of protective T cell immunity in response to viral infection. Viruses can directly infect DCs, thereby compromising their viability and suppressing their ability to activate immune responses. How DC function is maintained in light of this paradox is not understood. By analyzing the susceptibility of primary human DC subsets to viral infections, we report that CD141+ DCs have an innate resistance to infection by a broad range of enveloped viruses, including HIV and influenza virus. In contrast, CD1c+ DCs are susceptible to infection, which enables viral antigen production but impairs their immune functions and survival. The ability of CD141+ DCs to resist infection is conferred by RAB15, a vesicle-trafficking protein constitutively expressed in this DC subset. We show that CD141+ DCs rely on viral antigens produced in bystander cells to launch cross-
presentation-driven T cell responses. By dissociating viral infection from antigen presentation, this mechanism protects the functional capacity of DCs to launch adaptive immunity against viral infection.


**Intrinsic antiproliferative activity of the innate sensor STING in T lymphocytes**

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**Summary**

Activation of the cyclic dinucleotide sensor stimulator of interferon (IFN) genes (STING) is critical for IFN and inflammatory gene expression during innate immune responses. However, the role of STING in adaptive immunity is still unknown. In this study, we show that STING activation reduces the proliferation of T lymphocytes. This activity was independent of TBK1 and IRF3 recruitment and of type I IFN but required a distinct C-terminal domain of STING that activates NF-κB. Inhibition of cell proliferation by STING required its relocalization to the Golgi apparatus and caused mitotic errors. T lymphocytes from patients carrying constitutive active mutations in _TMEM173_ encoding STING showed impaired proliferation and reduced numbers of memory cells. Endogenous STING inhibited proliferation of mouse T lymphocytes. Therefore, STING, a critical innate sensor, also functions intrinsically in cells of the adaptive immune system to inhibit proliferation.

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**Immune-Complexed Adenovirus Induce AIM2-Mediated Pyroptosis in Human Dendritic Cells.**

_PLoS pathogens_ : e1005871 : DOI : 10.1371/journal.ppat.1005871

**Summary**

Human adenoviruses (HAdVs) are nonenveloped proteinaceous particles containing a linear double-stranded DNA genome. HAdVs cause a spectrum of pathologies in all populations regardless of health standards. Following repeat exposure to multiple HAdV types, we develop robust and long-lived humoral and cellular immune responses that provide life-long protection from de novo infections and persistent HAdV. How HAdVs, anti-HAdV antibodies and antigen presenting cells (APCs) interact to influence infection is still incompletely understood. In our study, we used physical, pharmacological, biochemical, fluorescence and electron microscopy, molecular and cell biology approaches to dissect the impact of immune-complexed HAdV (IC-HAdV) on human monocyte-derived dendritic cells (MoDCs). We show that IC-HAdV generate stabilized complexes of ~200 nm that are efficiently internalized by, and aggregate in, MoDCs. By comparing IC-HAdV, IC-empty capsid, IC-Ad2ts1
(a HAdV-C2 impaired in endosomal escape due to a mutation that impacts protease encapsidation) and IC-AdL40Q (a HAdV-C5 impaired in endosomal escape due to a mutation in protein VI), we demonstrate that protein VI-dependent endosomal escape is required for the HAdV genome to engage the DNA pattern recognition receptor AIM2 (absent in melanoma 2). AIM2 engagement induces pyroptotic MoDC death via ASC (apoptosis-associated speck protein containing a caspase activation/recruitment domain) aggregation, inflammasome formation, caspase 1 activation, and IL-1β and gasdermin D (GSDMD) cleavage. Our study provides mechanistic insight into how humoral immunity initiates an innate immune response to HAdV-C5 in human professional APCs.