

Microrganismi ed evasione della risposta immunitaria aa 2024-2025

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SARS-CoV-2 accessory proteins ORF7a and ORF3a use distinct mechanisms to down-regulate MHC-I surface expression

[Najla Arshad](#)–, [Maudry Laurent-Rolle](#), [Wesam S Ahmed](#), [Jack Chun-Chieh Hsu](#), [Susan M Mitchell](#), [Joanna Pawlak](#), [Debrup Sengupta](#), [Kabir H Biswas](#), [Peter Cresswell](#)

Abstract

Major histocompatibility complex class I (MHC-I) molecules, which are dimers of a glycosylated polymorphic transmembrane heavy chain and the small-protein β_2 -microglobulin (β_2m), bind peptides in the endoplasmic reticulum that are generated by the cytosolic turnover of cellular proteins. In virus-infected cells, these peptides may

include those derived from viral proteins. Peptide-MHC-I complexes then traffic through the secretory pathway and are displayed at the cell surface where those containing viral peptides can be detected by CD8⁺ T lymphocytes that kill infected cells. Many viruses enhance their in vivo survival by encoding genes that down-regulate MHC-I expression to avoid CD8⁺ T cell recognition. Here, we report that two accessory proteins encoded by SARS-CoV-2, the causative agent of the ongoing COVID-19 pandemic, down-regulate MHC-I expression using distinct mechanisms. First, ORF3a, a viroporin, reduces the global trafficking of proteins, including MHC-I, through the secretory pathway. The second, ORF7a, interacts specifically with the MHC-I heavy chain, acting as a molecular mimic of β_2m to inhibit its association. This slows the exit of properly assembled MHC-I molecules from the endoplasmic reticulum. We demonstrate that ORF7a reduces antigen presentation by the human MHC-I allele HLA-A*02:01. Thus, both ORF3a and ORF7a act post-translationally in the secretory pathway to lower surface MHC-I expression, with ORF7a exhibiting a specific mechanism that allows immune evasion by SARS-CoV-2.

[Trends Microbiol.](#) 2017 Mar;25(3):170-172. doi: 10.1016/j.tim.2017.01.009. Epub 2017 Feb
Langerhans Cells: the 'Yin and Yang' of HIV Restriction and Transmission.

[Mayr L](#), [Su B](#), [Moog C](#)

Abstract Langerhans cells are specialized sentinels present in the epidermis expressing Langerin, a specific C-type lectin receptor involved in HIV capture and destruction. Recently, the specific mechanism leading to this HIV restriction was discovered. Nevertheless, Langerhans cells can be infected and the way HIV escapes this restriction needs to be unraveled.

Frontiers in Immunol. 10, 2485 2019 Oct 23 eCollection 2019

Dendritic Cells, the Double Agent in the War Against HIV-1

[Alba Martín-Moreno](#)^{1, 2}, [M^a Angeles Muñoz-Fernández](#)

Abstract Human Immunodeficiency Virus (HIV) infects cells from the immune system and has thus developed tools to circumvent the host immunity and use it in its advance. Dendritic cells (DCs) are the first immune cells to encounter the HIV, and being the main antigen (Ag) presenting cells, they link the innate and the adaptive immune responses. While DCs work to promote an efficient immune response and halt the infection, HIV-1 has ways to take advantage of their role and uses DCs to gain faster and more efficient access to CD4⁺ T cells. Due to their ability to activate a specific immune response, DCs are promising candidates to achieve the functional cure of HIV-1 infection, but knowing the molecular partakers that determine the relationship between virus and cell is the key for the rational and successful design of a DC-based therapy. In this review, we summarize the current state of knowledge on

how both DC subsets (myeloid and plasmacytoid DCs) act in presence of HIV-1, and focus on different pathways that the virus can take after binding to DC. First, we explore the consequences of HIV-1 recognition by each receptor on DCs, including CD4 and DC-SIGN. Second, we look at cellular mechanisms that prevent productive infection and weapons that turn cellular defense into a Trojan horse that hides the virus all the way to T cell. Finally, we discuss the possible outcomes of DC-T cell contact.

[Cell](#). 2014 Dec 18;159(7):1497-509. doi: 10.1016/j.cell.2014.11.024.

Host evasion and exploitation schemes of *Mycobacterium tuberculosis*.

[Cambier CJ](#), [Falkow S](#), [Ramakrishnan L](#).

Abstract

Tuberculosis, an ancient disease of mankind, remains one of the major infectious causes of human death. We examine newly discovered facets of tuberculosis pathogenesis and explore the evolution of its causative organism *Mycobacterium tuberculosis* from soil dweller to human pathogen. *M. tuberculosis* has coevolved with the human host to evade and exploit host macrophages and other immune cells in multiple ways. Though the host can often clear infection, the organism can cause transmissible disease in enough individuals to sustain itself. Tuberculosis is a near-perfect paradigm of a host-pathogen relationship, and that may be the challenge to the development of new therapies for its eradication.

[Immunol Rev](#). 2015 Mar;264(1):220-32. doi: 10.1111/imr.12268.

Immuno-evasion and immunosuppression of the macrophage by *Mycobacterium tuberculosis*.

[Hmama Z¹](#), [Peña-Díaz S](#), [Joseph S](#), [Av-Gay Y](#).

Abstract

By virtue of their position at the crossroads between the innate and adaptive immune response, macrophages play an essential role in the control of bacterial infections. Paradoxically, macrophages serve as the natural habitat to *Mycobacterium tuberculosis* (Mtb). Mtb subverts the macrophage's mechanisms of intracellular killing and antigen presentation, leading ultimately to the development of tuberculosis (TB) disease. Here, we describe mechanisms of Mtb uptake by the macrophage and address key macrophage functions that are targeted by Mtb-specific effector molecules enabling this pathogen to circumvent host immune response. The macrophage functions described in this review include fusion between phagosomes and lysosomes, production of reactive oxygen and nitrogen species, antigen presentation and major histocompatibility complex class II expression and trafficking, as well as autophagy and apoptosis. All these are Mtb-targeted key cellular pathways, normally working in concert in the macrophage to recognize, respond, and activate 'proper' immune responses. We further analyze and discuss major molecular interactions between Mtb

virulence factors and key macrophage proteins and provide implications for vaccine and drug development.

Review Curr Opin Microbiol . 2020 Apr;54:103-110. doi: 10.1016/j.mib.2020.01.011

Mycobacterium tuberculosis pathogenicity viewed through the lens of molecular Koch's postulates

[Lalita Ramakrishnan](#)¹

Abstract

Thirty years ago Stanley Falkow formulated molecular Koch's postulates as a framework to help dissect the contribution of microbial genes to their pathogenicity (Box 1). Three years later, his advice led me to develop *Mycobacterium marinum*, a close genetic relative of *Mycobacterium tuberculosis*, as a model for tuberculosis pathogenesis. Here, I discuss insights into *M. tuberculosis* pathogenicity from studying *M. marinum* in the zebrafish, and frame them in terms of molecular Koch's postulates. The highly orchestrated life cycle of *M. tuberculosis* is achieved in substantial measure not by "traditional" pathogen-exclusive virulence genes acquired along its evolutionary history, but rather by genes that are shared with its environmental ancestors. Together, these genes support its tactics of subterfuge and exploitation to overcome host immunity so as to produce the transmissible disease that ensures the evolutionary survival of this obligate human pathogen.

J Allergy Clin Immunol 2020 Jul;146(1):18-22. doi: 10.1016/j.jaci.2020.05.001. Epub 2020 May 8.

COVID-19: Unanswered questions on immune response and pathogenesis

[Enrico Maggi](#), [Giorgio Walter Canonica](#), [Lorenzo Moretta](#)

Abstract

The novel coronavirus disease 2019 has rapidly increased in pandemic scale since it first appeared in Wuhan, China, in December 2019. In these troubled days the scientific community is asking for rapid replies to prevent and combat the emergency. It is generally accepted that only achieving a better understanding of the interactions between the virus and the host immune response and of the pathogenesis of infection is crucial to identify valid therapeutic tools to control virus entry, replication, and spread as well as to impair its lethal effects. On the basis of recent research progress of severe acute respiratory syndrome coronavirus 2 and the results on previous coronaviruses, in this contribution we underscore some of the main unsolved problems, mostly focusing on pathogenetic aspects and host immunity to the virus. On this basis, we also touch important aspects regarding the immune response in asymptomatic subjects, the immune evasion of severe acute respiratory syndrome coronavirus 2 in severe patients, and differences in disease severity by age and sex.

The Role of Type I Interferons in the Pathogenesis and Treatment of COVID-19

[Gideon Schreiber](#)¹

Abstract

Type I interferons (IFN-I) were first discovered over 60 years ago in a classical experiment by Isaacs and Lindenman, who showed that IFN-Is possess antiviral activity. Later, it became one of the first approved protein drugs using heterologous protein expression systems, which allowed its large-scale production. It has been approved, and widely used in a pleiotropy of diseases, including multiple-sclerosis, hepatitis B and C, and some forms of cancer. Preliminary clinical data has supported its effectiveness against potential pandemic pathogens such as Ebola and SARS. Still, more efficient and specific drugs have taken its place in treating such diseases. The COVID-19 global pandemic has again lifted the status of IFN-Is to become one of the more promising drug candidates, with initial clinical trials showing promising results in reducing the severity and duration of the disease. Although SARS-CoV-2 inhibits the production of IFN β and thus obstructs the innate immune response to this virus, it is sensitive to the antiviral activity of externally administrated IFN-Is. In this review I discuss the diverse modes of biological actions of IFN-Is and how these are related to biophysical parameters of IFN-I-receptor interaction and cell-type specificity in light of the large variety of binding affinities of the different IFN-I subtypes towards the common interferon receptor. Furthermore, I discuss how these may guide the optimized use IFN-Is in combatting COVID-19.

[Nat Rev Immunol](#). 2009 Jul;9(7):503-13. doi: 10.1038/nri2575.

MHC class I antigen presentation: learning from viral evasion strategies.

Hansen TH, [Bouvier M](#).

Abstract

The cell surface display of peptides by MHC class I molecules to lymphocytes provides the host with an important surveillance mechanism to protect against invading pathogens. However, in turn, viruses have evolved elegant strategies to inhibit various stages of the MHC class I antigen presentation pathway and prevent the display of viral peptides. This Review highlights how the elucidation of mechanisms of viral immune evasion is important for advancing our understanding of virus-host interactions and can further our knowledge of the MHC class I presentation pathway as well as other cellular pathways.

[Curr Opin Immunol](#). 2008 Feb;20(1):30-8. doi: 10.1016/j.coi.2007.11.002.

Immune evasion of natural killer cells by viruses.

[Jonjić S](#), [Babić M](#), [Polić B](#), [Krmptić A](#).

Abstract

Natural killer (NK) cells are important in the host resistance to viral infections. They are among the first cells to sense the release of proinflammatory cytokines, as well as the downregulation of surface MHC class I molecules and molecules induced by viral invasion of cells. Various viral functions have evolved to counter NK cell responses illustrating the evolutionary struggles between viruses and NK cells. Ligands for NK cell receptors are primary targets for viral immunoevasion. In order to counteract NK cell activation via the 'missing self'-axis, viruses encode proteins which serve as ligands for inhibitory NK cell receptors. Viruses also downmodulate the ligands for the activating NK cell receptors and encode soluble ligands which block these receptors. In addition to viral immunoregulatory proteins, regulatory RNAs can also inhibit the expression of ligands for NK cell receptors. Improving our understanding of viral regulation of NK cell function could be essential for designing more efficient measures in the prophylaxis and treatment of virus-induced pathology.

[Nat Rev Immunol](#). 2008 Apr;8(4):259-68. doi: 10.1038/nri2276. Epub 2008 Mar 14.

Evolutionary struggles between NK cells and viruses.

[Lanier LL](#).

Abstract

Natural killer (NK) cells are well recognized for their ability to provide a first line of defence against viral pathogens and they are increasingly being implicated in immune responses against certain bacterial and parasitic infections. Reciprocally, viruses have devised numerous strategies to evade the activation of NK cells and have influenced the evolution of NK-cell receptors and their ligands. NK cells contribute to host defence by their ability to rapidly secrete cytokines and chemokines, as well as to directly kill infected host cells. In addition to their participation in the immediate innate immune response against infection, interactions between NK cells and dendritic cells shape the nature of the subsequent adaptive immune response to pathogens.