Bloom syndrome protein restrains innate immune sensing of micronuclei by cGAS.

The Journal of experimental medicine: DOI : jem.20181329

Résumé

Cellular innate immune sensors of DNA are essential for host defense against invading pathogens. However, the presence of self-DNA inside cells poses a risk of triggering unchecked immune responses. The mechanisms limiting induction of inflammation by self-DNA are poorly understood. BLM RecQ-like helicase is essential for genome integrity and is deficient in Bloom syndrome (BS), a rare genetic disease characterized by genome instability, accumulation of micronuclei, susceptibility to cancer, and immunodeficiency. Here, we show that BLM-deficient fibroblasts show constitutive up-regulation of inflammatory interferon-stimulated gene (ISG) expression, which is mediated by the cGAS-STING-IRF3 cytosolic DNA-sensing pathway. Increased DNA damage or down-regulation of the cytoplasmic exonuclease TREX1 enhances ISG expression in BLM-deficient fibroblasts. cGAS-containing cytoplasmic micronuclei are increased in BS cells. Finally, BS patients demonstrate elevated ISG expression in peripheral blood. These results reveal that BLM limits ISG induction, thus connecting DNA damage to cellular innate immune response, which may contribute to human pathogenesis.


The N-Terminal Domain of cGAS Determines Preferential Association with Centromeric DNA and Innate Immune Activation in the Nucleus.

Cell reports : DOI : S2211-1247(19)30365-1

Résumé

NONO Detects the Nuclear HIV Capsid to Promote cGAS-Mediated Innate Immune Activation.

Résumé

Detection of viruses by innate immune sensors induces protective antiviral immunity. The viral DNA sensor cyclic GMP-AMP synthase (cGAS) is necessary for detection of HIV by human dendritic cells and macrophages. However, synthesis of HIV DNA during infection is not sufficient for immune activation. The capsid protein, which associates with viral DNA, has a pivotal role in enabling cGAS-mediated immune activation. We now find that NONO is an essential sensor of the HIV capsid in the nucleus. NONO protein directly binds capsid with higher affinity for weakly pathogenic HIV-2 than highly pathogenic HIV-1. Upon infection, NONO is essential for cGAS activation by HIV and cGAS association with HIV DNA in the nucleus. NONO recognizes a conserved region in HIV capsid with limited tolerance for escape mutations. Detection of nuclear viral capsid by NONO to promote DNA sensing by cGAS reveals an innate strategy to achieve distinction of viruses from self in the nucleus.


**Hepatitis B Virus Evasion From Cyclic Guanosine Monophosphate-Adenosine Monophosphate Synthase Sensing in Human Hepatocytes.**
*Hepatology (Baltimore, Md.)* : 1695-1709 : DOI : 10.1002/hep.30054

Résumé

Chronic hepatitis B virus (HBV) infection is a major cause of chronic liver disease and cancer worldwide. The mechanisms of viral genome sensing and the evasion of innate immune responses by HBV infection are still poorly understood. Recently, the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) was identified as a DNA sensor. In this study, we investigated the functional role of cGAS in sensing HBV infection and elucidate the mechanisms of viral evasion. We performed functional studies including loss-of-function and gain-of-function experiments combined with cGAS effector gene expression profiling in an infectious cell culture model, primary human hepatocytes, and HBV-infected human liver chimeric mice. Here, we show that cGAS is expressed in the human liver, primary human hepatocytes, and human liver chimeric mice. While naked relaxed-circular HBV DNA is sensed in a cGAS-dependent manner in hepatoma cell lines and primary human hepatocytes, host cell recognition of viral nucleic acids is abolished during HBV infection, suggesting escape from sensing, likely during packaging of the genome into the viral capsid. While the hepatocyte cGAS pathway is functionally active, as shown by reduction of viral covalently closed circular DNA levels in gain-of-function studies, HBV infection suppressed cGAS expression and function in cell culture models and humanized mice. Conclusion: HBV exploits multiple strategies to evade sensing and antiviral activity of cGAS and its effector
pathways.

Anvita Bhargava, Xavier Lahaye, Nicolas Manel (2018 Mar 13)
**Let me in: Control of HIV nuclear entry at the nuclear envelope.**
*Cytokine & growth factor reviews* : 59-67 : [DOI : S1359-6101(18)30029-7]

**Résumé**

The nuclear envelope is a physical barrier that isolates the cellular DNA from the rest of the cell, thereby limiting pathogen invasion. The Human Immunodeficiency Virus (HIV) has a remarkable ability to enter the nucleus of non-dividing target cells such as lymphocytes, macrophages and dendritic cells. While this step is critical for replication of the virus, it remains one of the less understood aspects of HIV infection. Here, we review the viral and host factors that favor or inhibit HIV entry into the nucleus, including the viral capsid, integrase, the central viral DNA flap, and the host proteins CPSF6, TNPO3, Nucleoporins, SUN1, SUN2, Cyclophilin A and MX2. We review recent perspectives on the mechanism of action of these factors, and formulate fundamental questions that remain. Overall, these findings deepen our understanding of HIV nuclear import and strengthen the favorable position of nuclear HIV entry for antiviral targeting.

SAEZ-CIRION Asier, MANEL Nicolas (2018 Jan 12)
**Immune Responses to Retroviruses**
*Annual Review of Immunology* : [DOI : 10.1146/annurev-immunol-051116-052155]

**Résumé**

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.
Constitutive resistance to viral infection in human CD141+ dendritic cells

Science Immunology : DOI : 10.1126/sciimmunol.aai8071

Résumé

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

Résumé

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.

Nuclear Envelope Protein SUN2 Promotes Cyclophilin-A-Dependent Steps of HIV Replication.

Résumé

During the early phase of replication, HIV reverse transcribes its RNA and crosses the nuclear envelope while escaping host antiviral defenses. The host factor Cyclophilin A (CypA) is essential for these steps and binds the HIV capsid; however, the mechanism underlying this effect remains elusive. Here, we identify related capsid mutants in HIV-1, HIV-2, and SIVmac that are restricted by CypA. This antiviral restriction of mutated viruses is conserved across
species and prevents nuclear import of the viral cDNA. Importantly, the inner nuclear envelope protein SUN2 is required for the antiviral activity of CypA. We show that wild-type HIV exploits SUN2 in primary CD4(+) T cells as an essential host factor that is required for the positive effects of CypA on reverse transcription and infection. Altogether, these results establish essential CypA-dependent functions of SUN2 in HIV infection at the nuclear envelope.

ESCRT III repairs nuclear envelope ruptures during cell migration to limit DNA damage and cell death
Science (New York, N.Y.) : DOI : 10.1126/science.aad7611

Résumé

In eukaryotic cells, the nuclear envelope separates the genomic DNA from the cytoplasmic space and regulates protein trafficking between the two compartments. This barrier is only transiently dissolved during mitosis. Here we found that it also opened at high frequency in migrating mammalian cells during interphase, allowing nuclear proteins to leak out and cytoplasmic proteins to leak in. This transient opening was caused by nuclear deformation and was rapidly repaired in an ESCRT (endosomal sorting complexes required for transport)-dependent manner. DNA double strand breaks coincided with nuclear envelope opening events. As a consequence, survival of cells migrating through confining environments depended on efficient nuclear envelope and DNA repair machineries. Nuclear envelope opening in migrating leukocytes could potentially have important consequences for normal and pathological immune responses.

Matteo Gentili, Nicolas Manel (2016 Mar 25)
cGAS-STING do it again: pivotal role in RNase H2 genetic disease.
The EMBO journal : DOI : e201694226

Résumé

Année de publication : 2015

Transmission of innate immune signaling by packaging of cGAMP in viral particles.
Science : DOI : 10.1126/science.aab3628
Résumé

Infected cells detect viruses through a variety of receptors that initiate cell-intrinsic innate defense responses. Cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS) is a cytosolic sensor for many DNA viruses and HIV-1. In response to cytosolic viral DNA, cGAS synthesizes the second messenger 2’3’-cyclic GMP-AMP (cGAMP), which activates antiviral signaling pathways. We show that in cells producing virus, cGAS-synthesized cGAMP can be packaged in viral particles and extracellular vesicles. Viral particles efficiently delivered cGAMP to target cells. cGAMP transfer by viral particles to dendritic cells activated innate immunity and antiviral defenses. Finally, we show that cell-free murine cytomegalovirus and Modified Vaccinia Ankara virus contained cGAMP. Thus, transfer of cGAMP by viruses may represent a defense mechanism to propagate immune responses to uninfected target cells.

Yanick J Crow, Nicolas Manel (2015 Jun 9)
Aicardi-Goutières syndrome and the type I interferonopathies
Nature Reviews Immunology : 429-40 : DOI : 10.1038/nri3850

Résumé

Dissection of the genetic basis of Aicardi-Goutières syndrome has highlighted a fundamental link between nucleic acid metabolism, innate immune sensors and type I interferon induction. This had led to the concept of the human interferonopathies as a broader set of Mendelian disorders in which a constitutive upregulation of type I interferon activity directly relates to disease pathology. Here, we discuss the molecular and cellular basis of the interferonopathies, their categorization, future treatment strategies and the insights they provide into normal physiology.

Sumoylation coordinates the repression of inflammatory and anti-viral gene-expression programs during innate sensing.
Nature Immunology : 140-9 : DOI : 10.1038/ni.3342

Résumé

Innate sensing of pathogens initiates inflammatory cytokine responses that need to be tightly controlled. We found here that after engagement of Toll-like receptors (TLRs) in myeloid cells, deficient sumoylation caused increased secretion of transcription factor NF-κB-dependent inflammatory cytokines and a massive type I interferon signature. In mice, diminished sumoylation conferred susceptibility to endotoxin shock and resistance to viral infection. Overproduction of several NF-κB-dependent inflammatory cytokines required expression of the type I interferon receptor, which identified type I interferon as a central...
sumoylation-controlled hub for inflammation. Mechanistically, the small ubiquitin-like modifier SUMO operated from a distal enhancer of the gene encoding interferon-β (Ifnb1) to silence both basal and stimulus-induced activity of the Ifnb1 promoter. Therefore, sumoylation restrained inflammation by silencing Ifnb1 expression and by strictly suppressing an unanticipated priming by type I interferons of the TLR-induced production of inflammatory cytokines.