

Année de publication : 2020

Bchir Ahlem, Njima Manel, Ben Abdeljalil Nouha, Ben Hammouda Seiffeddine, Mighri Khalifa, Njim Leila, Zakhama Abdelfateh (2020 Dec 22)

High grade transformation of adenoid cystic carcinoma in the palate: Case report with review of literature.

International journal of surgery case reports : 162-166 : [DOI : S2210-2612\(20\)31203-7](https://doi.org/10.1016/j.ijscr.2020.11.037)

Résumé

Adenoid cystic carcinoma (ACC) is a rare tumor developed in minor salivary glands, the palate being the most common site.

A J Lomakin, C J Cattin, D Cuvelier, Z Alraies, M Molina, G P F Nader, N Srivastava, P J Sáez, J M Garcia-Arcos, I Y Zhitnyak, A Bhargava, M K Driscoll, E S Welf, R Fiolka, R J Petrie, N S De Silva, J M González-Granado, N Manel, A M Lennon-Duménil, D J Müller, M Piel (2020 Oct 16)

The nucleus acts as a ruler tailoring cell responses to spatial constraints.

Science (New York, N.Y.) : [DOI : eaba2894](https://doi.org/10.1126/science.aba2894)

Résumé

The microscopic environment inside a metazoan organism is highly crowded. Whether individual cells can tailor their behavior to the limited space remains unclear. In this study, we found that cells measure the degree of spatial confinement by using their largest and stiffest organelle, the nucleus. Cell confinement below a resting nucleus size deforms the nucleus, which expands and stretches its envelope. This activates signaling to the actomyosin cortex via nuclear envelope stretch-sensitive proteins, up-regulating cell contractility. We established that the tailored contractile response constitutes a nuclear ruler-based signaling pathway involved in migratory cell behaviors. Cells rely on the nuclear ruler to modulate the motive force that enables their passage through restrictive pores in complex three-dimensional environments, a process relevant to cancer cell invasion, immune responses, and embryonic development.

Laurent Zablocki-Thomas, Sam A Menzies, Paul J Lehner, Nicolas Manel, Philippe Benaroch (2020 Apr 7)

A genome-wide CRISPR screen identifies regulation factors of the TLR3 signalling pathway.

Innate immunity : 459-472 : [DOI : 10.1177/1753425920915507](https://doi.org/10.1177/1753425920915507)

Résumé

A subset of TLRs is specialised in the detection of incoming pathogens by sampling endosomes for nucleic acid contents. Among them, TLR3 senses the abnormal presence of

double-stranded RNA in the endosomes and initiates a potent innate immune response via activation of NF- κ B and IRF3. Nevertheless, mechanisms governing TLR3 regulation remain poorly defined. To identify new molecular players involved in the TLR3 pathway, we performed a genome-wide screen using CRISPR/Cas9 technology. We generated TLR3 reporter cells carrying a NF- κ B-responsive promoter that controls GFP expression. Cells were next transduced with a single-guide RNA (sgRNA) library, subjected to sequential rounds of stimulation with poly(I:C) and sorting of the GFP-negative cells. Enrichments in sgRNA estimated by deep sequencing identified genes required for TLR3-induced activation of NF- κ B. Among the hits, five genes known to be critically involved in the TLR3 pathway, including TLR3 itself and the chaperone UNC93B1, were identified by the screen, thus validating our strategy. We further studied the top 40 hits and focused on the transcription factor aryl hydrocarbon receptor (AhR). Depletion of AhR had a dual effect on the TLR3 response, abrogating IL-8 production and enhancing IP-10 release. Moreover, in primary human macrophages exposed to poly(I:C), AhR activation enhanced IL-8 and diminished IP-10 release. Overall, these results reveal AhR plays a role in the TLR3 cellular innate immune response.

Johnson JS1, De Veaux N2, Rives AW2, Lahaye X3, Lucas SY4, Perot BP5, Luka M5, Garcia-Paredes V5, Amon LM4, Watters A2, Abdesslem G5, Aderem A6, Manel N3, Littman DR7, Bonneau R8, Ménager MM9. (2020 Jan 21)

A Comprehensive Map of the Monocyte-Derived Dendritic Cell Transcriptional Network Engaged upon Innate Sensing of HIV.

Cell reports : 30 : Cell Rep. 2020 Jan 21;30(3):914-931.e9. doi: 10.1016/j.celrep.2019.12.054. : 914,931 : [DOI : 10.1016/j.celrep.2019.12.054](https://doi.org/10.1016/j.celrep.2019.12.054)

Résumé

Transcriptional programming of the innate immune response is pivotal for host protection. However, the transcriptional mechanisms that link pathogen sensing with innate activation remain poorly understood. During HIV-1 infection, human dendritic cells (DCs) can detect the virus through an innate sensing pathway, leading to antiviral interferon and DC maturation. Here, we develop an iterative experimental and computational approach to map the HIV-1 innate response circuitry in monocyte-derived DCs (MDDCs). By integrating genome-wide chromatin accessibility with expression kinetics, we infer a gene regulatory network that links 542 transcription factors with 21,862 target genes. We observe that an interferon response is required, yet insufficient, to drive MDDC maturation and identify PRDM1 and RARA as essential regulators of the interferon response and MDDC maturation, respectively. Our work provides a resource for interrogation of regulators of HIV replication and innate immunity, highlighting complexity and cooperativity in the regulatory circuit controlling the response to infection.

Année de publication : 2019

Haifa B1, Ines Z1, Manel N2, Amira D3, Sonia Z3, Laila N2, Houda M4, Anis H1, Raja F1. (2019)

Oct 14)

Clear cell gynecologic carcinomas: about 5 cases.*The Pan African Medical Journal* : 34 : 87 : [DOI : 10.11604/pamj.2019.34.87.18505](https://doi.org/10.11604/pamj.2019.34.87.18505)**Résumé**

Gratia M1,2,3, Rodero MP4,5, Conrad C1, Bou Samra E2,3, Maurin M1, Rice GI6, Duffy D7, Revy P4, Petit F8, Dale RC9, Crow YJ#10,5,11, Amor-Gueret M#12,3,13, Manel N#14. (2019 May 6)

Bloom syndrome protein restrains innate immune sensing of micronuclei by cGAS.*Journal of experimental medicine* : 216(5) : 1199-1213 : [DOI : 10.1084/jem.20181329](https://doi.org/10.1084/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.

Matthieu Gratia, Mathieu P Rodero, Cécile Conrad, Elias Bou Samra, Mathieu Maurin, Gillian I Rice, Darragh Duffy, Patrick Revy, Florence Petit, Russell C Dale, Yanick J Crow, Mounira Amor-Gueret, Nicolas Manel (2019 Apr 1)

Bloom syndrome protein restrains innate immune sensing of micronuclei by cGAS.*The Journal of experimental medicine* : [DOI : jem.20181329](https://doi.org/10.1084/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.

Matteo Gentili, Xavier Lahaye, Francesca Nadalin, Guilherme P F Nader, Emilia Puig Lombardi, Solène Herve, Nilushi S De Silva, Derek C Rookhuizen, Elina Zueva, Christel Goudot, Mathieu Maurin, Aurore Bochnakian, Sebastian Amigorena, Matthieu Piel, Daniele Fachinetti, Arturo Londoño-Vallejo, Nicolas Manel (2019 Mar 28)

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

Cell reports : 3798 : [DOI : S2211-1247\(19\)30365-1](https://doi.org/10.1016/j.celrep.2019.01.105)

Résumé

Gentili M1, Lahaye X1, Nadalin F1, Nader GPF2, Puig Lombardi E3, Herve S4, De Silva NS1, Rookhuizen DC1, Zueva E1, Goudot C1, Maurin M1, Bochnakian A1, Amigorena S1, Piel M2, Fachinetti D4, Londoño-Vallejo A3, Manel N5. (2019 Feb 26)

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

Cell reports : 26(9) : 2377-2393 : [DOI : 10.1016/j.celrep.2019.01.105](https://doi.org/10.1016/j.celrep.2019.01.105)

Résumé

Manel N1, Di Santo JP2. (2019 Feb 2)

Editorial overview: Pillars of innate immunity: constantly learning and trying to remember. Manel N1,

Current opinion in immunology : 56 : [DOI : 10.1016/j.coi.2019.03.002](https://doi.org/10.1016/j.coi.2019.03.002)

Résumé

Année de publication : 2018

Xavier Lahaye, Matteo Gentili, Aymeric Silvin, Cécile Conrad, Léa Picard, Mabel Jouve, Elina Zueva, Mathieu Maurin, Francesca Nadalin, Gavin J Knott, Baoyu Zhao, Fenglei Du, Marlène Rio,

Jeanne Amiel, Archa H Fox, Pingwei Li, Lucie Etienne, Charles S Bond, Laurence Colleaux, Nicolas Manel (2018 Oct 2)

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

Cell : 488-501.e22 : [DOI : S0092-8674\(18\)31163-2](https://doi.org/10.1016/j.cell.2018.09.022)

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.

Eloi R Verrier, Seung-Ae Yim, Laura Heydmann, Houssein El Saghire, Charlotte Bach, Vincent Turon-Lagot, Laurent Mailly, Sarah C Durand, Julie Lucifora, David Durantel, Patrick Pessaux, Nicolas Manel, Ivan Hirsch, Mirjam B Zeisel, Nathalie Pochet, Catherine Schuster, Thomas F Baumert (2018 Apr 22)

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](https://doi.org/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](https://doi.org/10.1016/j.cytogfr.2018.03.002)

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](https://doi.org/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.

Année de publication : 2017

SILVIN Aymeric, YU Chun, LAHAYE Xavier, IMPERATORE Francesco, BRAULT Jean-Baptiste, CARDINAUD Sylvain, BECKER Christian, KWAN Wing-Hong, CONRAD Cécile, MAURIN Mathieu, GOUDOT Christel, MARQUES-LADEIRA Santy, WANG Yuanyuan, PASCUAL Virginia, ANGUIANO Esperanza, ALBRECHT Randy, IANNAcone Matteo, GARCÍA-SASTRE Adolfo, GOUD Bruno, DALOD Marc, MORIS Arnaud, MERAD Miriam, PALUCKA Karolina, MANEL Nicolas (2017 Jul 7)

Constitutive resistance to viral infection in human CD141+ dendritic cells

Science Immunology : [DOI : 10.1126/sciimmunol.aai8071](https://doi.org/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.