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# Human Endogenous Retroviruses and AIDS
## Research: Confusion, Consensus, or Science?

**Etienne de Harven, M.D.**

Human Endogenous Retroviruses (HERVs) are confounding factors in HIV/AIDS research that cannot be ignored. Evidence suggests that "viral load" may actually be measuring retroviral nucleoside sequences associated with HERVs. HERVs also provide a valid explanation for the presence of retroviruses recognizable by electron microscopy (EM) in the original 1983 publication from the Institut Pasteur, and may account for claims of innumerable "mutations" of the putative HIV pathogen. The interference of HERVs in AIDS research brings into question the subject of study in so-called "AIDS Research" and the very existence of an exogenous HIV pathogen itself.

http://www.jpands.org/vol15no3/deharven.pdf

J Infect Dis. 2011 Jul 15;204(2):299-308.

# Endometrial epithelial cell responses to coinfecting viral and bacterial pathogens in the genital tract can activate the HIV-1 LTR in an NF{kappa}B-and AP-1-dependent manner.

Ferreira VH, Nazli A, Khan G, Mian MF, Ashkar AA, Gray-Owen S, Kaul R, Kaushic C.

### Source

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### Abstract

## BACKGROUND:

Sexually transmitted infections (STIs) are associated with increased human immunodeficiency virus type 1 (HIV-1) susceptibility and viral shedding in the genital tract, but the mechanisms underlying this association are poorly understood.

## METHODS:

Direct activation of HIV long terminal repeats (LTRs), a proxy measure for HIV-1 replication, was measured after treatment of 1G5 T cells with Toll-like receptor (TLR) ligands, herpes simplex virus type 1 or 2 (HSV-1/2), or Neisseria gonorrhoeae. For indirect activation, 1G5 T cells were incubated with supernatants from female primary genital epithelial cells (GECs) previously exposed to these agents. Proinflammatory cytokines and

chemokines were measured in GEC supernatants. Proinflammatory pathways were blocked to determine the mechanisms of direct and indirect HIV-LTR activation.

## RESULTS:

HSV-1/2, N. gonorrhoeae, and TLR ligands FimH (TLR-4), flagellin (TLR-5), and Poly (I:C) (TLR-3) directly induced HIV-LTR activation in 1G5 T cells. Supernatants collected from GECs incubated with these agents indirectly induced HIV-LTR activation. Production of tumor necrosis factor α, interleukin 6, interleukin 8, and monocyte chemoattractant protein-1 was elevated in GECs exposed to copathogens. Inhibition of nuclear factor κB and activator protein-1 (AP-1) signaling pathways in 1G5 T cells abrogated both direct and indirect HIV-LTR activation.

## CONCLUSIONS:

STIs may increase HIV-1 replication in the female genital tract via proinflammatory signaling pathways directly and indirectly via their effects on GECs. This increased HIV-1 replication may enhance sexual and vertical HIV transmission.

## *Supplemental Content*


AIDS. 2008 Nov 30;22(18):2429-39. doi: 10.1097/QAD.0b013e32831940bb.

# Mitochondrial DNA haplogroups influence AIDS progression.

Hendrickson SL, Hutcheson HB, Ruiz-Pesini E, Poole JC, Lautenberger J, Sezgin E, Kingsley L, Goedert JJ, Vlahov D, Donfield S, Wallace DC, O'Brien SJ.

### Source

Laboratory of Genomic Diversity, National Cancer Institute, Frederick, Maryland 21702-1201, USA. hendricksons@mail.nih.gov

### Abstract

## OBJECTIVE:

Mitochondrial function plays a role in both AIDS progression and HAART toxicity; therefore, we sought to determine whether mitochondrial DNA variation revealed novel AIDS restriction genes, particularly as mitochondrial DNA single-nucleotide polymorphisms are known to influence regulation of oxidative phosphorylation, reactive oxygen species production, and apoptosis.

## DESIGN:

This is a retrospective cohort study.

## METHODS:

We performed an association study of mitochondrial DNA haplogroups among 1833 European American HIV-1 patients from five US cohorts: the Multicenter AIDS Cohort Study, the San Francisco City Clinic Study, Hemophilia Growth and Development Study, the Multicenter Hemophilia Cohort Study, and the AIDS Linked to Intravenous Experiences cohort to determine whether the mitochondrial DNA haplogroup correlated with AIDS progression rate.

## RESULTS:

Mitochondrial DNA haplogroups J and U5a were elevated among HIV-1 infected people who display accelerated progression to AIDS and death. Haplogroups Uk, H3, and IWX appeared to be highly protective against AIDS progression.

## CONCLUSION:

The associations found in our study appear to support a functional explanation by which mitochondrial DNA variation among haplogroups, influencing ATP production, reactive oxygen species generation, and apoptosis, is correlated to AIDS disease progression; however, repeating these results in cohorts with different ethnic backgrounds would be informative. These data suggest that mitochondrial genes are important indicators of AIDS disease progression in HIV-1 infected persons.

### *Supplemental Content*



Arthritis Rheum. 2012 Sep;64(9):2927-36. doi: 10.1002/art.34508.

# Mitochondrial dysfunction increases inflammatory responsiveness to cytokines in normal human chondrocytes.

Vaamonde-García C, Riveiro-Naveira RR, Valcárcel-Ares MN, Hermida-Carballo L, Blanco FJ, López-Armada MJ.

### Source

INIBIC-Complexo Hospitalario Universitario A Coruña, A Coruña, Spain.

### Abstract

## OBJECTIVE:

Alterations in mitochondria play a key role in the pathogenesis of osteoarthritis (OA). The role of inflammation in the progression of OA has also acquired important new dimensions. This study was undertaken to evaluate the potential role of mitochondrial dysfunction in increasing the inflammatory response of normal human chondrocytes to cytokines.

## METHODS:

Mitochondrial dysfunction was induced by commonly used inhibitors. Interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) were used as inflammatory mediators. IL-8 and cyclooxygenase 2 (COX-2) protein and messenger RNA (mRNA) expression and prostaglandin E(2) (PGE(2) ) levels were assessed. The chemotactic activity of neutrophils was assayed. Additionally, inhibitors of reactive oxygen species (ROS) and NF-κB were used to identify possible inflammatory response pathways induced by mitochondrial dysfunction, and the effects of the natural antioxidant resveratrol were tested.

## RESULTS:

Pretreatment with antimycin A or oligomycin (inhibitors of mitochondrial respiratory chain complexes III and V, respectively) triggered a strong potentiation of IL-1β-induced IL-8 mRNA and protein expression (mean ± SEM at 18 hours 5,932 ± 1,995 pg/50,000 cells for IL-1β alone versus 16,241 ± 5,843 pg/50,000 cells for antimycin A plus IL-1β and 20,087 ± 5,407 pg/50,000 cells for oligomycin plus IL-1β; $P < 0.05$). Similar results were observed with TNFα or when expression of the inflammatory mediator COX-2 or PGE(2) production was assessed. Mitochondrial dysfunction increased the chemotactic activity induced by cytokines, and ROS and NF-κB inhibitors decreased the production of IL-8. Resveratrol significantly reduced the inflammatory response.

## CONCLUSION:

Our findings indicate that mitochondrial dysfunction could amplify the responsiveness to cytokine-induced chondrocyte inflammation through ROS production and NF-κB activation. This pathway might lead to the impairment of cartilage and joint function in OA.

## *Supplemental Content*



J Biomed Biotechnol. 2011;2011:473097. Epub 2011 May 3.

# Role of natural killer and dendritic cell crosstalk in immunomodulation by commensal bacteria probiotics.

Rizzello V, Bonaccorsi I, Dongarrà ML, Fink LN, Ferlazzo G.

### Source

Laboratory of Immunology and Biotherapy, Department of Human Pathology, University of Messina, 98125 Messina, Italy.

### Abstract

A cooperative dialogue between natural killer (NK) cells and dendritic cells (DCs) has been elucidated in the last years. They help each other to acquire their complete functions, both in the periphery and in the secondary lymphoid organs. Thus, NK cells' activation by dendritic cells allows the killing of transformed or infected cells in the periphery but may also be

important for the generation of adaptive immunity. Indeed, it has been shown that NK cells may play a key role in polarizing a Th1 response upon interaction with DCs exposed to microbial products. This regulatory role of DC/NK cross-talk is of particular importance at mucosal surfaces such as the intestine, where the immune system exists in intimate association with commensal bacteria such as lactic acid bacteria (LAB). We here review NK/DC interactions in the presence of gut-derived commensal bacteria and their role in bacterial strain-dependent immunomodulatory effects. We particularly aim to highlight the ability of distinct species of commensal bacterial probiotics to differently affect the outcome of DC/NK cross-talk and consequently to differently influence the polarization of the adaptive immune response.

## *Supplemental Content*


Mucosal Immunol. 2011 Nov;4(6):658-70. doi: 10.1038/mi.2011.31. Epub 2011 Jul 27.

# Synergy between intraepithelial lymphocytes and lamina propria T cells drives intestinal inflammation during infection.

Egan CE, Maurer KJ, Cohen SB, Mack M, Simpson KW, Denkers EY.

### Source

Department of Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA. cee22@cornell.edu

### Abstract

Oral infection of C57BL/6 mice with Toxoplasma gondii triggers severe necrosis in the ileum within 7-10 days of infection. Lesion development is mediated by Th-1 cytokines, CD4+ T cells, and subepithelial bacterial translocation. As such, these features share similarity to Crohn's disease. Recently, we uncovered a role for intraepithelial lymphocytes (IELs) in mediating pathology after Toxoplasma infection. We show here that αβ and not γδ T-cell IELs mediate intestinal damage. By adoptive transfer of mucosal T cells into naive Rag1□/□ mice, we demonstrate that IELs do not function alone to cause inflammatory lesions, but act with CD4+ T lymphocytes from the lamina propria (LP). Furthermore, recipient mice pretreated with broad-spectrum antibiotics to eliminate intestinal flora resisted intestinal disease after transfer of IELs and LP lymphocytes. Our data provide valuable new insights into the mechanisms of intestinal inflammation, findings that have important implications for understanding human inflammatory bowel disease.

## *Supplemental Content*


Blood. 2011 Nov 10;118(19):5152-62. Epub 2011 Sep 19.

# Overactivation of plasmacytoid dendritic cells inhibits antiviral T-cell responses: a model for HIV immunopathogenesis.

Boasso A, Royle CM, Doumazos S, Aquino VN, Biasin M, Piacentini L, Tavano B, Fuchs D, Mazzotta F, Lo Caputo S, Shearer GM, Clerici M, Graham DR.

## Source

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## Abstract

A delicate balance between immunostimulatory and immunosuppressive signals mediated by dendritic cells (DCs) and other antigen-presenting cells (APCs) regulates the strength and efficacy of antiviral T-cell responses. HIV is a potent activator of plasmacytoid DCs (pDCs), and chronic pDC activation by HIV promotes the pathogenesis of AIDS. Cholesterol is pivotal in maintaining HIV envelope integrity and allowing HIV-cell interaction. By depleting envelope-associated cholesterol to different degrees, we generated virions with reduced ability to activate pDCs. We found that APC activation was dissociated from the induction of type I IFN-α/β and indoleamine-2,3-dioxygenase (IDO)-mediated immunosuppression in vitro. Extensive cholesterol withdrawal, resulting in partial protein and RNA loss from the virions, rendered HIV a more powerful recall immunogen for stimulating memory CD8 T-cell responses in HIV-exposed, uninfected individuals. These enhanced responses were dependent on the inability of cholesterol-depleted HIV to induce IFN-α/β.

## *Supplemental Content*



Retrovirology. 2007 Oct 21;4:76.

# The contribution of peroxynitrite generation in HIV replication in human primary macrophages.

Aquaro S, Muscoli C, Ranazzi A, Pollicita M, Granato T, Masuelli L, Modesti A, Perno CF, Mollace V.

## Source

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## Abstract

## BACKGROUND:

Monocytes/Macrophages (M/M) play a pivotal role as a source of virus during the whole course of HIV-1 infection. Enhanced oxidative stress is involved in the pathogenesis of HIV-1 infection. HIV-1 regulatory proteins induce a reduction of the expression and the activity of MnSOD, the mitochondrial isoform leading to a sustained generation of superoxide anions and peroxynitrite that represent important mediators of HIV-1 replication in M/M. MnTBAP (Mn(III)tetrakis(4-benzoic acid)porphrin chloride), a synthetic peroxynitrite decomposition catalyst, reduced oxidative stress subsequent to peroxynitrite generation.

## RESULTS:

Virus production was assessed by p24 ELISA, western blot, and electron microscopy during treatment with MnTBAP. MnTBAP treatment showed a reduction of HIV-1 replication in both acutely and chronically infected M/M: 99% and 90% inhibition of p24 released in supernatants compared to controls, respectively. Maturation of p55 and p24 was strongly inhibited by MnTBAP in both acutely and chronically infected M/M. EC50 and EC90 are 3.7 (+/- 0.05) microM and 19.5 (+/- 0.5) microM, in acutely infected M/M; 6.3 (+/- 0.003) microM and 30 (+/- 0.6) microM, in chronically infected M/M. In acutely infected peripheral blood limphocytes (PBL), EC50 and EC90 are 7.4 (+/- 0.06) microM and of 21.3 (+/- 0.6) microM, respectively. Treatment of acutely-infected M/M with MnTBAP inhibited the elevated levels of malonildialdehyde (MDA) together with the nitrotyrosine staining observed during HIV-1 replication. MnTBAP strongly reduced HIV-1 particles in infected M/M, as shown by electron microscopy. Moreover, in presence of MnTBAP, HIV-1 infectivity was reduced of about 1 log compared to control.

## CONCLUSION:

Results support the role of superoxide anions in HIV-1 replication in M/M and suggest that MnTBAP may counteract HIV-1 replication in combination with other antiretroviral treatments.

## *Supplemental Content*



Nat Med. 2012 Mar 25;18(4):538-46. doi: 10.1038/nm.2657.

# Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation.

Hill DA, Siracusa MC, Abt MC, Kim BS, Kobuley D, Kubo M, Kambayashi T, Larosa DF, Renner ED, Orange JS, Bushman FD, Artis D.

### Source

Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

### Abstract

Commensal bacteria that colonize mammalian barrier surfaces are reported to influence T helper type 2 (T(H)2) cytokine-dependent inflammation and susceptibility to allergic disease, although the mechanisms that underlie these observations are poorly understood. In this report, we find that deliberate alteration of commensal bacterial populations via oral antibiotic treatment resulted in elevated serum IgE concentrations, increased steady-state circulating basophil populations and exaggerated basophil-mediated T(H)2 cell responses and allergic inflammation. Elevated serum IgE levels correlated with increased circulating basophil populations in mice and subjects with hyperimmunoglobulinemia E syndrome. Furthermore, B cell-intrinsic expression of myeloid differentiation factor 88 (MyD88) was required to limit serum IgE concentrations and circulating basophil populations in mice. Commensal-derived signals were found to influence basophil development by limiting proliferation of bone marrow-resident precursor populations. Collectively, these results identify a previously unrecognized pathway through which commensal-derived signals influence basophil hematopoiesis and susceptibility to T(H)2 cytokine-dependent inflammation and allergic disease.

### Comment in

- Breathe easy: microbes protect from allergies. [Nat Med. 2012]

### *Supplemental Content*


Science. 2011 Jan 21;331(6015):337-41. Epub 2010 Dec 23.

# Induction of colonic regulatory T cells by indigenous Clostridium species.

Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, Cheng G, Yamasaki S, Saito T, Ohba Y, Taniguchi T, Takeda K, Hori S, Ivanov II, Umesaki Y, Itoh K, Honda K.

### Source

Department of Immunology, Graduate School of Medicine, University of Tokyo, Tokyo 113-0033, Japan.

### Abstract

CD4(+) T regulatory cells (T(regs)), which express the Foxp3 transcription factor, play a critical role in the maintenance of immune homeostasis. Here, we show that in mice, T(regs) were most abundant in the colonic mucosa. The spore-forming component of indigenous intestinal microbiota, particularly clusters IV and XIVa of the genus Clostridium, promoted T(reg) cell accumulation. Colonization of mice by a defined mix of Clostridium strains provided an environment rich in transforming growth factor-β and affected Foxp3(+) T(reg) number and function in the colon. Oral inoculation of Clostridium during the early life of conventionally reared mice resulted in resistance to colitis and systemic immunoglobulin E responses in adult mice, suggesting a new therapeutic approach to autoimmunity and allergy.

## Comment in

- Bacterial modulation of Tregs/Th17 in intestinal disease: a balancing act? [Inflamm Bowel Dis. 2012]
- Indigenous clostridium species regulate systemic immune responses by induction of colonic regulatory T cells. [Gastroenterology. 2011]
- Commensal microbiota determine intestinal iTreg. [Am J Transplant. 2012]
- Peaceful mutualism in the gut: revealing key commensal bacteria for the creation and maintenance of immunological homeostasis. [Cell Host Microbe. 2011]
- Immunology. The gut's Clostridium cocktail. [Science. 2011]

PMID:
21205640
[PubMed - indexed for MEDLINE]
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## *Supplemental Content*



J Immunol. 2008 Jan 1;180(1):464-74.

# Neutrophils clear bacteria associated with parasitic nematodes augmenting the development of an effective Th2-type response.

Pesce JT, Liu Z, Hamed H, Alem F, Whitmire J, Lin H, Liu Q, Urban JF Jr, Gause WC.

### Source

Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

### Abstract

Infection with the parasitic nematode Nippostrongylus brasiliensis induces a potent Th2 response; however, little is known about early stages of the innate response that may contribute to protective immunity. To examine early events in this response, chemokine expression in the draining lymph node was examined after N. brasiliensis inoculation. Pronounced increases of several chemokines, including CCL2, were observed. Compared with wild-type mice, elevations in a Gr-1bright population in the draining lymph node was significantly decreased in CCL2-/- mice after N. brasiliensis inoculation. Further flow cytometric and immunofluorescent analysis showed that in wild-type mice, Gr-1+ cells transiently entered and exited the draining lymph node shortly after N. brasiliensis inoculation. The Gr-1bright population was comprised of neutrophils expressing TGF-beta and TNF-alpha. Following Gr-1+ cell depletion, N. brasiliensis infection resulted in transient, but significantly increased levels of IFN-gamma, increased serum IgG2a, reduced Th2 cytokines and serum IgE, greatly increased mortality, and delayed worm expulsion. Furthermore, bacteria were readily detected in vital organs. Infection of Gr-1+ cell-depleted mice with N. brasiliensis larvae that were pretreated with antibiotics prevented bacterial

dissemination, Th1 inflammatory responses, and decreases in host survival. This study indicates that parasitic nematodes can be an important vector of potentially harmful bacteria, which is typically controlled by CCL2-dependent neutrophils that ensure the optimal development of Th2 immune responses and parasite resistance.

## *Supplemental Content*


J Biol Chem. 2006 Sep 29;281(39):28699-711. Epub 2006 Aug 1.

# Inhibition of HIV-1 replication by amphotericin B methyl ester: selection for resistant variants.

Waheed AA, Ablan SD, Mankowski MK, Cummins JE, Ptak RG, Schaffner CP, Freed EO.

### Source

Virus-Cell Interaction Section, HIV Drug Resistance Program, NCI-Frederick, National Institutes of Health, Frederick, Maryland 21702-1201, USA.

### Abstract

Membrane cholesterol plays an important role in human immunodeficiency virus type 1 (HIV-1) particle production and infectivity. Here, we have investigated the target and mechanism of action of a cholesterol-binding compound, the polyene antifungal antibiotic amphotericin B methyl ester (AME). We found that AME potently inhibited the replication of a highly divergent panel of HIV-1 isolates in various T-cell lines and primary cells irrespective of clade or target cell tropism. The defects in HIV-1 replication caused by AME were due to profoundly impaired viral infectivity as well as a defect in viral particle production. To elucidate further the mechanism of action of AME, we selected for and characterized AME-resistant HIV-1 variants. Mutations responsible for AME resistance mapped to a highly conserved and functionally important endocytosis motif in the cytoplasmic tail of the transmembrane glycoprotein gp41. Interestingly, truncation of the gp41 cytoplasmic tail in the context of either HIV-1 or rhesus macaque simian immunodeficiency virus also conferred resistance to AME. The infectivity of HIV-1 virions bearing murine leukemia virus or vesicular stomatitis virus glycoproteins was unaffected by AME. Our data define the target and mechanism of action of AME and provide support for the concept that cholesterol-binding compounds should be pursued as antiretroviral drugs to disrupt HIV-1 replication.

## *Supplemental Content*


Chin Med J (Engl). 2010 Sep;123(17):2440-5.

# Intracellular CMTM2 negatively regulates human immunodeficiency virus type-1 transcription through targeting the transcription factors AP-1 and CREB.

Song HS, Shi S, Lu XZ, Gao F, Yan L, Wang Y, Zhuang H.

## Source

Department of Microbiology, Peking University Health Science Center, Beijing 100191, China.

## Abstract


### BACKGROUND:

The CKLF-like MARVEL transmembrane domain-containing family (CMTM) is a novel family of proteins linking chemokines and TM4SF. Different members exhibit diverse biological functions. In this study, the effect of intracellular CMTM2 on regulating human immunodeficiency virus type-1 (HIV-1) transcription was evaluated.

### METHODS:

The effects of CMTM2 on regulating full-length HIV-1 provirus and the HIV-1 long terminal repeat (LTR)-directed transcription were assessed by luciferase assay. Transcription factor assays, using the luciferase reporter plasmids of AP-1, CRE, and NF-κB were conducted to explore the signaling pathway(s) that may be regulated by CMTM2. The potential relationship between CMTM2 and the transcription factor AP-1 was further analyzed by Western blotting analyses to investigate the effect of CMTM2 on PMA-induced ERK1/2 phosphorylation.

### RESULTS:

The results from the current study revealed that CMTM2 acts as a negative regulator of HIV-1 transcription. CMTM2 exerted a suppressive action on both full-length HIV-1 provirus and HIV-1 LTR-directed transcription. Transcription factor assays showed that CMTM2 selectively inhibited basal AP-1 and CREB activity. Co-expression of HIV-1 Tat, a potent AP-1 and CREB activator, can not reverse CMTM2-mediated AP-1 and CREB inhibition, suggesting a potent and specific effect of CMTM2 on negatively regulating these two signaling pathways.

### CONCLUSION:

Intracellular CMTM2 can negatively regulate HIV-1 transcription, at least in part, by targeting the AP-1 and CREB pathways. Exploring the mechanisms further may lead to new ways to control HIV-1 replication.


## *Supplemental Content*

Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2011 Nov;36(11):1037-45.

# Prospect of IL-2, IL-7, IL-15 and IL-21 for HIV immune-based therapy.

Diallo M, Zheng Y, Chen X, He Y, Zhou H, Chen Z.

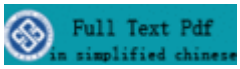
## Source

AIDS Research Laboratory, Department of Infectious Diseases, Second Xiangya Hospital, Central South University, Changsha 410011, China.

## Abstract

Although highly active antiretroviral therapy (HAART) can effectively reduce the HIV replication, complete recovery of CD4(+) T cells does not always occur, even among patients with high virological control. Current researches on γ-chain cytokines have understood the biology and their crucial roles in initiating, maintaining, and regulating the immunologic homeostasis and the inflammatory processes. Due to the multiple functions such as the regulatory and effector cellular function in healthy and disease state, these molecules, their receptors, and their signal transduction pathways are promising candidates for therapeutic interference. The common γ-chain cytokines IL-2, IL-7, IL-15, and IL-21 are primary regulators of T cell homeostasis and thus have been considered prime immunotherapeutic candidates, both for increasing T cell levels/function and augmenting vaccine-elicited viral-specific T cell responses in immunocompromised AIDS patients. The Objective of this review is to update the role of the common γ-chain cytokines IL-2, IL-7, IL-15, and IL-21 in HIV AIDS pathogenesis.

## *Supplemental Content*




# Altered phenotype of regulatory T cells associated with lack of human immunodeficiency virus (HIV)-1-specific suppressive function.

Burton CT, Westrop SJ, Eccles-James I, Boasso A, Nelson MR, Bower M, Imami N.

## Source

Department of Medicine, Imperial College London, Chelsea and Westminster Hospital, London, UK.

## Abstract

Mechanisms by which CD4+ regulatory T cells (T(regs)) mediate suppression of virus-specific responses remain poorly defined. Adenosine, mediated via CD39 and CD73, has been shown to play a role in the action of murine T(regs) . In this study we investigate the phenotype of T(regs) in the context of human immunodeficiency virus (HIV)-1 infection, and

the function of these cells in response to HIV-1-Gag and cytomegalovirus (CMV) peptides. Phenotypic data demonstrate a decrease in forkhead box transcription factor 3 (FoxP3+) T(reg) numbers in the peripheral blood of HIV-1+ individuals compared to healthy controls, which is most pronounced in those with high HIV-1 RNA plasma load. Due to aberrant expression of CD27 and CD127 during HIV-1 disease, these markers are unreliable for T(reg) identification. The CD3+ CD4+ CD25(hi) CD45RO+ phenotype correlated well with FoxP3 expression in both the HIV-1+ and seronegative control cohorts. We observed expression of CD39 but not CD73 on T(regs) from HIV-1+ and healthy control cohorts. We demonstrate, through T(reg) depletion, the suppressive potential of T(regs) over anti-CMV responses in the context of HIV-1 infection; however, no recovery of the HIV-1-specific T cell response was observed indicating a preferential loss of HIV-1-specific T(reg) function. We propose that before immunotherapeutic manipulation of T(regs) is considered, the immunoregulatory profile and distribution kinetics of this population in chronic HIV-1 infection must be elucidated fully.

## *Supplemental Content*



http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2249.2011.04451.x/pdf

PLoS Pathog. 2012;8(4):e1002620. Epub 2012 Apr 5.

# Regulation of Mycobacterium tuberculosis-dependent HIV-1 transcription reveals a new role for NFAT5 in the toll-like receptor pathway.

Ranjbar S, Jasenosky LD, Chow N, Goldfeld AE.

### Source

Immune Disease Institute and Program in Cellular and Molecular Medicine, Children's Hospital Boston, Boston, Massachusetts, United States of America.

### Abstract

Tuberculosis (TB) disease in HIV co-infected patients contributes to increased mortality by activating innate and adaptive immune signaling cascades that stimulate HIV-1 replication, leading to an increase in viral load. Here, we demonstrate that silencing of the expression of the transcription factor nuclear factor of activated T cells 5 (NFAT5) by RNA interference (RNAi) inhibits Mycobacterium tuberculosis (MTb)-stimulated HIV-1 replication in co-infected macrophages. We show that NFAT5 gene and protein expression are strongly induced by MTb, which is a Toll-like receptor (TLR) ligand, and that an intact NFAT5 binding site in the viral promoter of R5-tropic HIV-1 subtype B and subtype C molecular clones is required for efficent induction of HIV-1 replication by MTb. Furthermore, silencing by RNAi of key components of the TLR pathway in human monocytes, including the downstream signaling molecules MyD88, IRAK1, and TRAF6, significantly inhibits MTb-induced NFAT5 gene expression. Thus, the innate immune response to MTb infection induces NFAT5 gene and protein expression, and NFAT5 plays a crucial role in MTb regulation of HIV-1 replication via a direct interaction with the viral promoter. These findings also

demonstrate a general role for NFAT5 in TLR- and MTb-mediated control of gene expression.

## *Supplemental Content*


PLoS One. 2011;6(8):e23673. Epub 2011 Aug 18.

# A signature in HIV-1 envelope leader peptide associated with transition from acute to chronic infection impacts envelope processing and infectivity.

Asmal M, Hellmann I, Liu W, Keele BF, Perelson AS, Bhattacharya T, Gnanakaran S, Daniels M, Haynes BF, Korber BT, Hahn BH, Shaw GM, Letvin NL.

### Source

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### Abstract

Mucosal transmission of the human immunodeficiency virus (HIV) results in a bottleneck in viral genetic diversity. Gnanakaran and colleagues used a computational strategy to identify signature amino acids at particular positions in Envelope that were associated either with transmitted sequences sampled very early in infection, or sequences sampled during chronic infection. Among the strongest signatures observed was an enrichment for the stable presence of histidine at position 12 at transmission and in early infection, and a recurrent loss of histidine at position 12 in chronic infection. This amino acid lies within the leader peptide of Envelope, a region of the protein that has been shown to influence envelope glycoprotein expression and virion infectivity. We show a strong association between a positively charged amino acid like histidine at position 12 in transmitted/founder viruses with more efficient trafficking of the nascent envelope polypeptide to the endoplasmic reticulum and higher steady-state glycoprotein expression compared to viruses that have a non-basic position 12 residue, a substitution that was enriched among viruses sampled from chronically infected individuals. When expressed in the context of other viral proteins, transmitted envelopes with a basic amino acid position 12 were incorporated at higher density into the virus and exhibited higher infectious titers than did non-signature envelopes. These results support the potential utility of using a computational approach to examine large viral sequence data sets for functional signatures and indicate the importance of Envelope expression levels for efficient HIV transmission.

## *Supplemental Content*


Virology. 2010 Oct 10;406(1):12-20. Epub 2010 Jul 29.

# MHC class I chain-related protein A shedding in chronic HIV-1 infection is associated with profound NK cell dysfunction.

Nolting A, Dugast AS, Rihn S, Luteijn R, Carrington MF, Kane K, Jost S, Toth I, Nagami E, Faetkenheuer G, Hartmann P, Altfeld M, Alter G.

### Source

Ragon Institute of Massachusetts General Hospital, Harvard University, Boston, MA, USA.

### Abstract

Natural killer (NK) cells play a critical role in host defense against viral infections. However chronic HIV-1 infection is associated with an accumulation of dysfunctional NK cells, that poorly control viral replication. The underlying mechanisms for this NK cell mediated dysfunction are not understood. Certain tumors evade NK cell mediated detection by dampening NK cell activity through the downregulation of NKG2D, via the release of soluble NKG2D-ligands, resulting in a potent suppression of NK cell function. Here we show that chronic HIV-1 infection is associated with a specific defect in NKG2D-mediated NK cell activation, due to reduced expression and transcription of NKG2D. Reduced NKG2D expression was associated with elevated levels of the soluble form of the NKG2D-ligand, MICA, in patient sera, likely released by HIV+CD4+ T cells. Thus, like tumors, HIV-1 may indirectly suppress NK cell recognition of HIV-1-infected CD4+ T cells by enhancing NKG2D-ligand secretion into the serum resulting in a profound impairment of NK cell function.

## *Supplemental Content*



PLoS One. 2009;4(5):e5427. Epub 2009 May 1.

# CD27(-) B-cells produce class switched and somatically hyper-mutated antibodies during chronic HIV-1 infection.

Cagigi A, Du L, Dang LV, Grutzmeier S, Atlas A, Chiodi F, Pan-Hammarström Q, Nilsson A.

### Source

Department of Microbiology, Tumor and Cell biology, Karolinska Institutet, Stockholm, Sweden. Alberto.Cagigi@ki.se

### Abstract

Class switch recombination and somatic hypermutation occur in mature B-cells in response to antigen stimulation. These processes are crucial for the generation of functional antibodies. During HIV-1 infection, loss of memory B-cells, together with an altered differentiation of

naïve B-cells result in production of low quality antibodies, which may be due to impaired immunoglobulin affinity maturation. In the current study, we evaluated the effect of HIV-1 infection on class switch recombination and somatic hypermutation by studying the expression of activation-induced cytidine deaminase (AID) in peripheral B-cells from a cohort of chronically HIV-1 infected patients as compared to a group of healthy controls. In parallel, we also characterized the phenotype of B-cells and their ability to produce immunoglobulins in vitro. Cells from HIV-1 infected patients showed higher baseline levels of AID expression and increased IgA production measured ex-vivo and upon CD40 and TLR9 stimulation in vitro. Moreover, the percentage of CD27(-)IgA+ and CD27(-)IgG+ B-cells in blood was significantly increased in HIV-1 infected patients as compared to controls. Interestingly, our results showed a significantly increased number of somatic hypermutations in the VH genes in CD27(-) cells from patients. Taken together, these results show that during HIV-1 infection, CD27(-) B-cells can also produce class switched and somatically hypermutated antibodies. Our data add important information for the understanding of the mechanisms underlying the loss of specific antibody production observed during HIV-1 infection.

## *Supplemental Content*



PLoS One. 2012;7(4):e35572. Epub 2012 Apr 24.

# Inflammation-driven reprogramming of CD4+ Foxp3+ regulatory T cells into pathogenic Th1/Th17 T effectors is abrogated by mTOR inhibition in vivo.

Yurchenko E, Shio MT, Huang TC, Da Silva Martins M, Szyf M, Levings MK, Olivier M, Piccirillo CA.

### Source

Department of Microbiology and Immunology, McGill University, Montreal, Quebec, Canada.

### Abstract

While natural CD4(+)Foxp3(+) regulatory T (nT(REG)) cells have long been viewed as a stable and distinct lineage that is committed to suppressive functions in vivo, recent evidence supporting this notion remains highly controversial. We sought to determine whether Foxp3 expression and the nT(REG) cell phenotype are stable in vivo and modulated by the inflammatory microenvironment. Here, we show that Foxp3(+) nT(REG) cells from thymic or peripheral lymphoid organs reveal extensive functional plasticity in vivo. We show that nT(REG) cells readily lose Foxp3 expression, destabilizing their phenotype, in turn, enabling them to reprogram into Th1 and Th17 effector cells. nT(REG) cell reprogramming is a characteristic of the entire Foxp3(+) nT(REG) population and the stable Foxp3(NEG) T(REG) cell phenotype is associated with a methylated foxp3 promoter. The extent of nT(REG) cell reprogramming is modulated by the presence of effector T cell-mediated signals, and occurs independently of variation in IL-2 production in vivo. Moreover, the gut microenvironment or parasitic infection favours the reprogramming of Foxp3(+) T(REG) cells into effector T cells and promotes host immunity. IL-17 is predominantly produced by

reprogrammed Foxp3(+) nT(REG) cells, and precedes Foxp3 down-regulation, a process accentuated in mesenteric sites. Lastly, mTOR inhibition with the immunosuppressive drug, rapamycin, stabilizes Foxp3 expression in T(REG) cells and strongly inhibits IL-17 but not RORγt expression in reprogrammed Foxp3(-) T(REG) cells. Overall, inflammatory signals modulate mTOR signalling and influence the stability of the Foxp3(+) nT(REG) cell phenotype.

## *Supplemental Content*



J Drugs Dermatol. 2012 May;11(5):626-30.

# Lessons of leprosy: the emergence of TH17 cytokines during type II reactions (ENL) is teaching us about T-cell plasticity.

Martiniuk F, Giovinazzo J, Tan AU, Shahidullah R, Haslett P, Kaplan G, Levis WR.

### Source

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### Abstract

## BACKGROUND:

Leprosy was the first disease classified according to the thymus derived T-cell in the 1960s and the first disease classified by the cytokine profile as intact interferon-γ (IFN-γ) and interleukin-2 (IL2) or TH1 (tuberculoid) and deficient IFN-γ and IL2 or TH2 (lepromatous), in the 1980s. Objective: In the present study, we set out to explore the T helper 17 (TH17) lymphocyte subset, the hallmark of T-cell plasticity, in skin biopsies from patients with erythema nodosum leprosum (ENL) who were treated with thalidomide.

## METHOD:

RNA was extracted from paraffin embedded tissue before and after thalidomide treatment of ENL and RT-PCR was performed.

## RESULTS:

IL17A, the hallmark of TH17, was consistently seen before and after thalidomide treatment, confirming the TH17 subset to be involved in ENL and potentially up-regulated by thalidomide.

## CONCLUSION:

A reduction in CD70, GARP, IDO, IL17B (IL-20), and IL17E (IL-25), coupled with increases in RORγT, ARNT, FoxP3, and IL17C (IL-21) following thalidomide treatment, opens the door to understanding the complexity of the immunomodulatory drug thalidomide, which can operate as an anti-inflammatory while simultaneously stimulating cell-mediated immunity (CMI). We conclude that TH17 is involved in the immunopathogenesis of ENL and that thalidomide suppresses inflammatory components of TH17, while enhancing other components of TH17 that are potentially involved in CMI.

## *Supplemental Content*



Retrovirology. 2010 Dec 2;7:104.

# Hepcidin induces HIV-1 transcription inhibited by ferroportin.

Xu M, Kashanchi F, Foster A, Rotimi J, Turner W, Gordeuk VR, Nekhai S.

### Source

Center for Sickle Cell Disease, Department of Medicine, Howard University, Washington, DC 20060, USA.

### Abstract

## BACKGROUND:

Physiological regulation of cellular iron involves iron export by the membrane protein, ferroportin, the expression of which is induced by iron and negatively modulated by hepcidin. We previously showed that iron chelation is associated with decreased HIV-1 transcription. We hypothesized that increased iron export by ferroportin might be associated with decreased HIV-1 transcription, and degradation of ferroportin by hepcidin might in turn induce HIV-1 transcription and replication. Here, we analyzed the effect of ferroportin and hepcidin on HIV-1 transcription.

## RESULTS:

Expression of ferroportin was associated with reduced HIV-1 transcription in 293T cells and addition of hepcidin to ferroportin-expressing cells counteracted this effect. Furthermore, exposure of promonocytic THP-1 cells to hepcidin was associated with decreased ferroportin expression, increased intracellular iron and induction of reporter luciferase gene expression. Finally, exposure of human primary macrophages and CD4+ T cells to hepcidin and iron was also associated with induction of viral production.

## CONCLUSION:

Our results suggest that the interplay between ferroportin-mediated iron export and hepcidin-mediated degradation of ferroportin might play a role in the regulation of HIV-1 transcription and may be important for understanding of HIV-1 pathogenesis.

## *Supplemental Content*



Clin Exp Immunol. 2012 Aug;169(2):182-9. doi: 10.1111/j.1365-2249.2012.04603.x.

# Lenalidomide enhancement of human T cell functions in human immunodeficiency virus (HIV)-infected and HIV-negative CD4 T lymphocytopenic patients.

Lim H, Kane L, Schwartz JB, Hesdorffer CS, Deeks SG, Greig N, Ferrucci L, Goetzl EJ.

### Source

Department of Medicine, University of California and San Francisco General Hospital, CA, USA.

### Abstract

Suppressed T cell functions in human immunodeficiency virus (HIV) infection were identified and corrected by lenalidomide in middle-aged HIV-infected patients. Chemotaxis of T cells from HIV-infected men (n = 6, mean 43 years) to sphingosine 1-phosphate (S1P) and CCL21 was significantly lower than that of HIV-negative men (n = 6, mean 41 years), and was enhanced significantly up to control levels by 100 and 1000 nM lenalidomide. Generation of interleukin (IL)-2, but not interferon (IFN)-γ, by T cells of middle-aged HIV-infected men was significantly lower than that for controls and was increased significantly by 10-1000 nM lenalidomide up to a maximum of more than 300%. CD4 and CD8 T cells isolated from healthy middle-aged men and reconstituted in vitro at a low CD4 : CD8 ratio typical of HIV infection had depressed chemotaxis to S1P, but not CCL21, and generation of IL-2, but not IFN-γ. Significant enhancement of chemotaxis to S1P and CCL21 was induced by 100-1000 nM lenalidomide only for normal T cells at a low CD4 : CD8 ratio. T cells from HIV-negative middle-aged CD4 T lymphocytopenic patients (n = 3), with a CD4 : CD8 ratio as low as that of HIV-infected patients, had similarly diminished chemotaxis to S1P and CCL21, and depressed generation of IL-2, but not IFN-γ. Lenalidomide at 30-1000 nM significantly enhanced chemotaxis to S1P and IL-2 generation for T cells from HIV-negative CD4 T lymphocytopenic patients as from HIV-infected patients, with less effect on CCL21-elicited chemotaxis and none for IFN-γ generation. Defects in functions of T cells from middle-aged HIV-infected men are partially attributable to CD4 T lymphocytopenia and are corrected by lenalidomide.

Virology. 2010 Oct 10;406(1):12-20. Epub 2010 Jul 29.

# MHC class I chain-related protein A shedding in chronic HIV-1 infection is associated with profound NK cell dysfunction.

Nolting A, Dugast AS, Rihn S, Luteijn R, Carrington MF, Kane K, Jost S, Toth I, Nagami E, Faetkenheuer G, Hartmann P, Altfeld M, Alter G.

### Source

Ragon Institute of Massachusetts General Hospital, Harvard University, Boston, MA, USA.

### Abstract

Natural killer (NK) cells play a critical role in host defense against viral infections. However chronic HIV-1 infection is associated with an accumulation of dysfunctional NK cells, that poorly control viral replication. The underlying mechanisms for this NK cell mediated dysfunction are not understood. Certain tumors evade NK cell mediated detection by dampening NK cell activity through the downregulation of NKG2D, via the release of soluble NKG2D-ligands, resulting in a potent suppression of NK cell function. Here we show that chronic HIV-1 infection is associated with a specific defect in NKG2D-mediated NK cell activation, due to reduced expression and transcription of NKG2D. Reduced NKG2D expression was associated with elevated levels of the soluble form of the NKG2D-ligand, MICA, in patient sera, likely released by HIV+CD4+ T cells. Thus, like tumors, HIV-1 may indirectly suppress NK cell recognition of HIV-1-infected CD4+ T cells by enhancing NKG2D-ligand secretion into the serum resulting in a profound impairment of NK cell function.

## *Supplemental Content*



Afr Health Sci. 2011 Aug;11 Suppl 1:S24-7.

# Prevalence of intestinal parasitic infections among HIV/AIDS patients from two health institutions in Abuja, Nigeria.

Abaver DT, Nwobegahay JM, Goon DT, Iweriebor BC, Anye DN.

### Source

Department of Biological Sciences, University of Abuja, Abuja, Nigeria.

### Abstract

### BACKGROUND:

Intestinal parasitic infections play a vital role in the prognosis of HIV/AIDS in patients.

## OBJECTIVES:

The aim of this study was to determine the prevalence of intestinal parasitic infections (IPIs) in HIV-infected individuals in two health facilities in Abuja-Nigeria.

## METHODS:

A cross sectional study was conducted in two sites: the GEDE AIDS and Infectious Diseases Research Institute (GAIDRI), and the Human Virology Institute-General Hospital Asokoro-Abuja, Nigeria. A total of 119 subjects were recruited (85 HIV infected and 34 HIV negative). Stool specimens collected were analyzed macroscopically and microscopically for consistency and the presence of enteric parasites.

## RESULTS:

The overall prevalence rate of enteroparasites obtained in this study was 22.7% (27/119). The prevalence of intestinal parasitic infections in HIV infected patients was 24.7 %; while in HIV negative persons, it was 17.6%. However, the high rate obtained for HIV infected patients was not statistically significant (p> 0.05).

## CONCLUSION:

Although the prevalence rate of enteric parasites in HIV/AIDS patients was higher than in HIV negative individuals, this difference is not statistically significant. Even though there was no statistical difference in the two groups, parasitic infections in HIV/AIDS patients often result in debilitating illness.

## *Supplemental Content*



Proc Natl Acad Sci U S A. 2011 Jan 11;108(2):722-7. Epub 2010 Dec 27.

# Vitamin A-dependent transcriptional activation of the nuclear factor of activated T cells c1 (NFATc1) is critical for the development and survival of B1 cells.

Maruya M, Suzuki K, Fujimoto H, Miyajima M, Kanagawa O, Wakayama T, Fagarasan S.

### Source

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### Abstract

B1 cells represent a distinct subset of B cells that produce most of the natural serum IgM and much of the gut IgA and function as an important component of early immune responses to pathogens. The development of B1 cells depends on the nuclear factor of activated T cells c1

(NFATc1), a transcription factor abundantly expressed by B1 cells but not by conventional B2 cells. However, the factors that regulate the expression of NFATc1 in B1 cells remain unknown. Here we show that a vitamin A-deficient diet results in reduction of NFATc1 expression in B1 cells and almost complete loss of the B1 cell compartment. As a consequence, vitamin A-deficient mice have reduced serum IgM and are unable to mount T cell-independent antibody responses against bacterial antigens. We demonstrate that injection of all-trans retinoic acid induces the expression of NFATc1, particularly from the constitutive P2 promoter, and leads to the increase of the B1 cells. Thus, the retinoic acid-dependent pathway is critical for regulating NFATc1 expression and for maintenance of the natural memory B cell compartment.

## *Supplemental Content*



Cell Death Dis. 2012 Mar 15;3:e282. doi: 10.1038/cddis.2012.21.

# HIV-1 Tat protein directly induces mitochondrial membrane permeabilization and inactivates cytochrome c oxidase.

Lecoeur H, Borgne-Sanchez A, Chaloin O, El-Khoury R, Brabant M, Langonné A, Porceddu M, Brière JJ, Buron N, Rebouillat D, Péchoux C, Deniaud A, Brenner C, Briand JP, Muller S, Rustin P, Jacotot E.

### Source

Theraptosis SA, Pasteur BioTop Research Laboratory, Institut Pasteur, Paris, France.

### Abstract

The Trans-activator protein (Tat) of human immunodeficiency virus (HIV) is a pleiotropic protein involved in different aspects of AIDS pathogenesis. As a number of viral proteins Tat is suspected to disturb mitochondrial function. We prepared pure synthetic full-length Tat by native chemical ligation (NCL), and Tat peptides, to evaluate their direct effects on isolated mitochondria. Submicromolar doses of synthetic Tat cause a rapid dissipation of the mitochondrial transmembrane potential ($\Delta\Psi(m)$) as well as cytochrome c release in mitochondria isolated from mouse liver, heart, and brain. Accordingly, Tat decreases substrate oxidation by mitochondria isolated from these tissues, with oxygen uptake being initially restored by adding cytochrome c. The anion-channel inhibitor 4,4'-diisothiocyanostilbene-2,2'-disulfonic acid (DIDS) protects isolated mitochondria against Tat-induced mitochondrial membrane permeabilization (MMP), whereas ruthenium red, a ryanodine receptor blocker, does not. Pharmacologic inhibitors of the permeability transition pore, Bax/Bak inhibitors, and recombinant Bcl-2 and Bcl-XL proteins do not reduce Tat-induced MMP. We finally observed that Tat inhibits cytochrome c oxidase (COX) activity in disrupted mitochondria isolated from liver, heart, and brain of both mouse and human samples, making it the first described viral protein to be a potential COX inhibitor.

## *Supplemental Content*


Mol Cells. 2012 Apr;33(4):335-41. doi: 10.1007/s10059-012-2287-0. Epub 2012 Mar 23.

# Extracellular HIV-1 Tat induces human beta-defensin-2 production via NF-kappaB/AP-1 dependent pathways in human B cells.

Ju SM, Goh AR, Kwon DJ, Youn GS, Kwon HJ, Bae YS, Choi SY, Park J.

### Source

Department of Biomedical Science, Research Institute for Bioscience and Biotechnology, Hallym University, Chunchon 200-702, Korea.

### Abstract

Defensins, a family of antimicrobial peptides, are one of the first lines of host defense. Human beta-defensins (hBD) such as hBD-2 and -3 have anti-HIV activity. Previous studies have shown that HIV-1 virion can induce the expression of hBD, although the exact components of HIV-1 virion that are responsible for hBD expression have not yet been elucidated. In this study, we examined the effect of HIV-1 Tat on the expression of hBD in B cells. Stimulation of B cells with HIV-1 Tat protein significantly increased the mRNA and protein levels of hBD-2. HIV-1 Tat also induced the activation of a reporter gene for hBD-2 in a dose-dependent manner in B cells. Pretreatment of B cells with a JNK inhibitor suppressed HIV-1 Tat-induced hBD-2 expression. Pretreatment of B cells with AP-1 inhibitors or NF-κB inhibitors led to a decrease in HIV-1 Tat-induced protein and mRNA expression of hBD-2. Taken together, our results indicate that HIV-1 Tat can up-regulate the expression of hBD-2 via JNK-NF-κB/AP-1-dependent pathways in human B cells.

## *Supplemental Content*


PLoS One. 2010 Jul 22;5(7):e11733. doi: 10.1371/journal.pone.0011733.

# HIV-1 inhibits autophagy in bystander macrophage/monocytic cells through Src-Akt and STAT3.

Van Grol J, Subauste C, Andrade RM, Fujinaga K, Nelson J, Subauste CS.

### Source

Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, Ohio, United States of America.

## Abstract

Autophagy is a homeostatic mechanism of lysosomal degradation. Defective autophagy has been linked to various disorders such as impaired control of pathogens and neurodegeneration. Autophagy is regulated by a complex array of signaling pathways that act upstream of autophagy proteins. Little is known about the role of altered regulatory signaling in disorders associated with defective autophagy. In particular, it is not known if pathogens inhibit autophagy by modulation of upstream regulatory pathways. Cells infected with HIV-1 blocked rapamycin-induced autophagy and CD40-induced autophagic killing of Toxoplasma gondii in bystander (non-HIV-1 infected) macrophage/monocytic cells. Blockade of autophagy was dependent on Src-Akt and STAT3 triggered by HIV-1 Tat and IL-10. Neutralization of the upstream receptors VEGFR, beta-integrin or CXCR4, as well as of HIV-1 Tat or IL-10 restored autophagy in macrophage/monocytic cells exposed to HIV-1-infected cells. Defective autophagic killing of T. gondii was detected in monocyte-derived macrophages from a subset of HIV-1(+) patients. This defect was also reverted by neutralization of Tat or IL-10. These studies revealed that a pathogen can impair autophagy in non-infected cells by activating counter-regulatory pathways. The fact that pharmacologic manipulation of cell signaling restored autophagy in cells exposed to HIV-1-infected cells raises the possibility of therapeutic manipulation of cell signaling to restore autophagy in HIV-1 infection.

## *Supplemental Content*



Intervirology. 2007;50(3):224-8. Epub 2007 Mar 14.

# HIV Tat protein increases Bcl-2 expression in monocytes which inhibits monocyte apoptosis induced by tumor necrosis factor-alpha-related apoptosis-induced ligand.

Zheng L, Yang Y, Guocai L, Pauza CD, Salvato MS.

### Source

Department of Infectious Diseases, The First Affiliated Hospital, Medical School, Key Laboratory of Infectious Diseases of Chinese Ministry of Public Health, Zhejiang University, Hangzhou, Zhejiang, PR China.

### Abstract

### OBJECTIVE:

To investigate the effect of HIV Tat protein on Bcl-2 expression in human monocytes, and observe apoptosis of Tat-stimulated monocytes induced by TNF-alpha-related apoptosis-induced ligand (TRAIL).

## METHODS:

Western blot was used to detect Bcl-2 expression in monocytes stimulated by HIV Tat protein, and Annexin V and 7-AAD staining were used to detect apoptosis of monocytes induced by TRAIL.

## RESULTS:

HIV Tat protein increased Bcl-2 expression in human monocytes in a dose-dependent manner. Annexin V staining showed that 51.54% of monocytes underwent apoptosis after being treated with 100 ng/ml recombinant TRAIL. When monocytes were prestimulated with HIV Tat, only 15.46% of monocytes underwent apoptosis. This effect can be inhibited by polyclonal anti-Tat serum. 7-AAD staining showed similar results.

## CONCLUSION:

HIV Tat protein increases Bcl-2 expression in monocytes which inhibited apoptosis induced by TRAIL. HIV Tat protein may play an important role in the mechanisms of HIV-persistent infection in monocytes.

## *Supplemental Content*