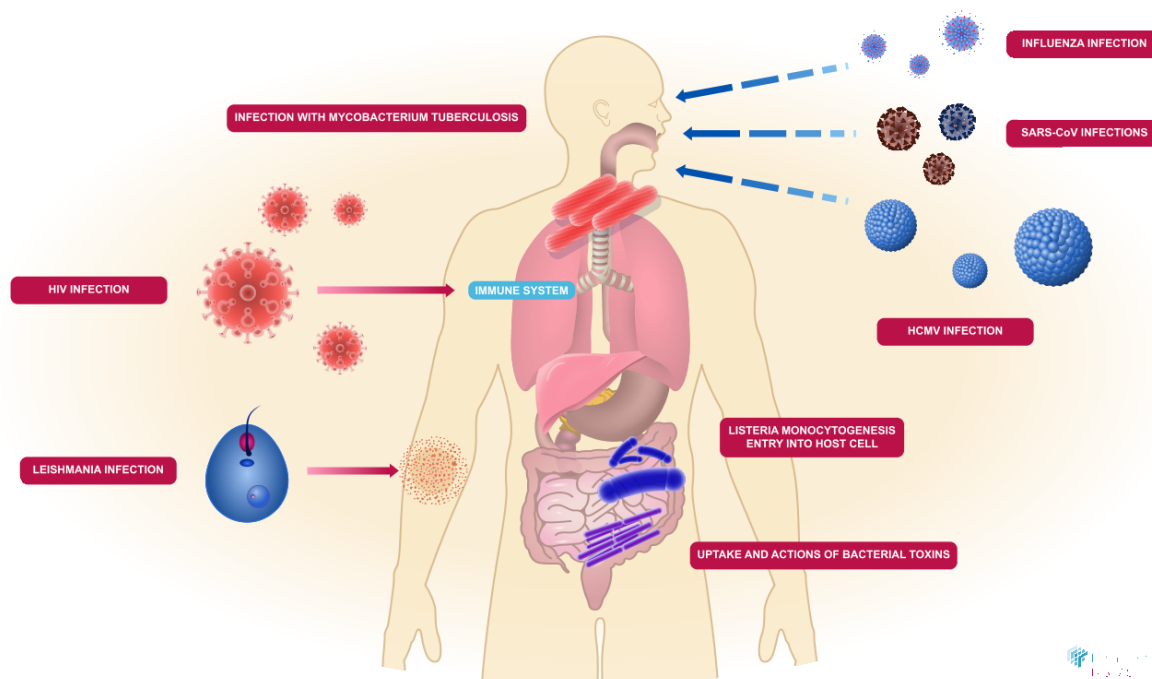# Infectious disease

Bukrinsky, M., Caposio, P., D'Eustachio, P., Deffur, A., Garcia-Sastre, A., Gillespie, ME., Gopinathrao, G., Gregory, DJ., Iordanskiy, S., Jassal, B., Luo, F., Matthews, L., Morrow, MP., Murillo, JI., Orlic-Milacic, M., Pardo, AM., Rice, AP., Rush, MG., Scheuermann, RH., Schwerk, C., Squires, B., Stephan, R., Streblow, DN., Wilkinson, RJ.

26/09/2021

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 77

This document contains 9 pathways (see Table of Contents)

Infectious disease ↗

Stable identifier: R-HSA-5663205

Diseases: disease by infectious agent
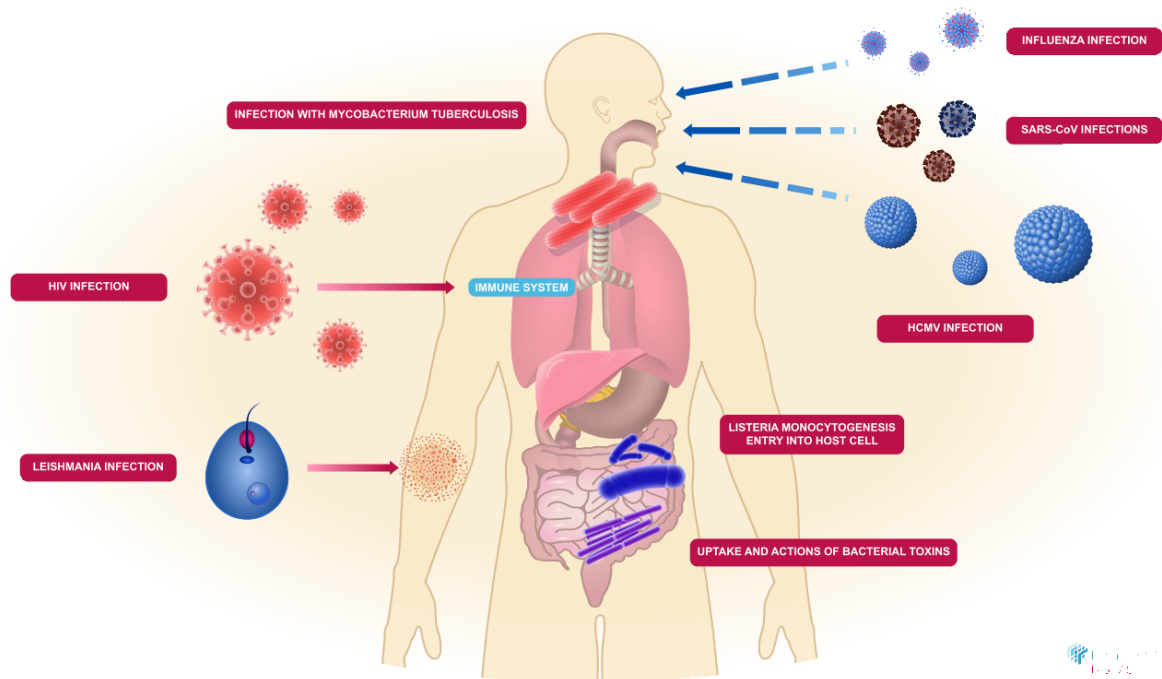
Infectious diseases are ones due to the presence of pathogenic microbial agents in human host cells. Processes annotated in this category include the life cycles of SARS-CoV viruses, influenza virus and HIV (human immunodeficiency virus), some metabolic processes mediated by intracellular Mycobacterium tuberculosis, the actions of clostridial, anthrax, and diphtheria toxins, and the entry of Listeria monocytogenes into human cells.

HIV Infection ↗
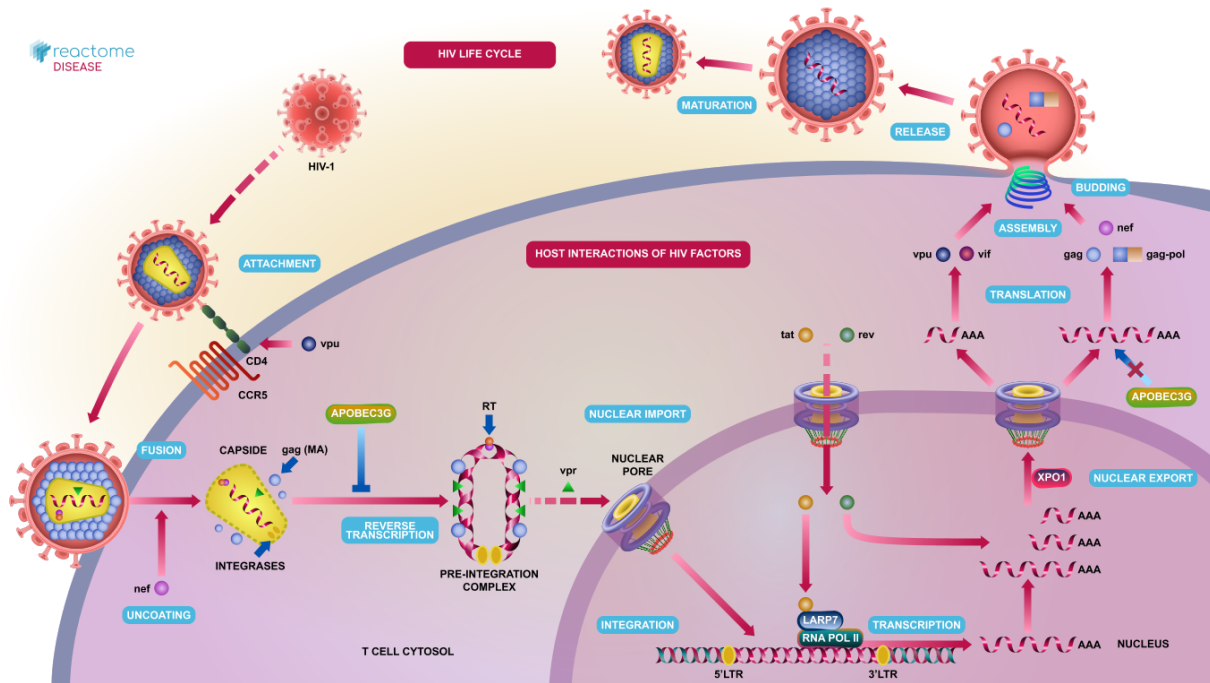
Location: Infectious disease

Stable identifier: R-HSA-162906

Diseases: Human immunodeficiency virus infectious disease

The global pandemic of Human Immunodeficiency Virus (HIV) infection has resulted in tens of millions of people infected by the virus and millions more affected. UNAIDS estimates around 40 million HIV/AIDS patients worldwide with 75% of them living in sub-Saharan Africa. The primary method of HIV infection is by sexual exposure while nonsexual HIV transmission also can occur through transfusion with contaminated blood products, injection drug use, occupational exposure,accidental needlesticks or mother-to-child transmission. HIV damages the immune system, leaving the infected person vulnerable to a variety of "opportunistic" infections arising from host immune impairment (Hare, 2004).

HIV-1 and the less common HIV-2 belong to the family of retroviruses. HIV-1 contains a single-stranded RNA genome that is 9 kilobases in length and contains 9 genes that encode 15 different proteins. These proteins are classified as: structural proteins (Gag, Pol, and Env), regulatory proteins (Tat and Rev), and accessory proteins (Vpu, Vpr, Vif, and Nef) (Frankel and Young,1998).

HIV infection cycle can be divided into two phases:

1. An **Early phase** consisting of early events occuring after HIV infection of a susceptible target cell and a

2. **Late phase** comprising the later events in the HIV-infected cell resulting in the assembly of new infectious virions. The section titled **HIV lifecycle** consists of annotations of events in these two phases.

The virus has developed various molecular strategies to suppress the antiviral immune responses (innate, cellular and humoral) of the host. HIV-1 viral auxiliary proteins (Tat, Rev, Nef, Vif, Vpr and Vpu) play important roles in these host-pathogen interactions (Li et al.,2005). The section titled **Host interactions of HIV factors** highlights these complex post-infection processes.

Literature references

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Frankel, AD., Young, JA. (1998). HIV-1: fifteen proteins and an RNA. *Annu Rev Biochem, 67*, 1-25. ↗

Li, L., Li, HS., Pauza, CD., Bukrinsky, M., Zhao, RY. (2005). Roles of HIV-1 auxiliary proteins in viral pathogenesis and host-pathogen interactions. *Cell Res, 15*, 923-34. ↗

Editions
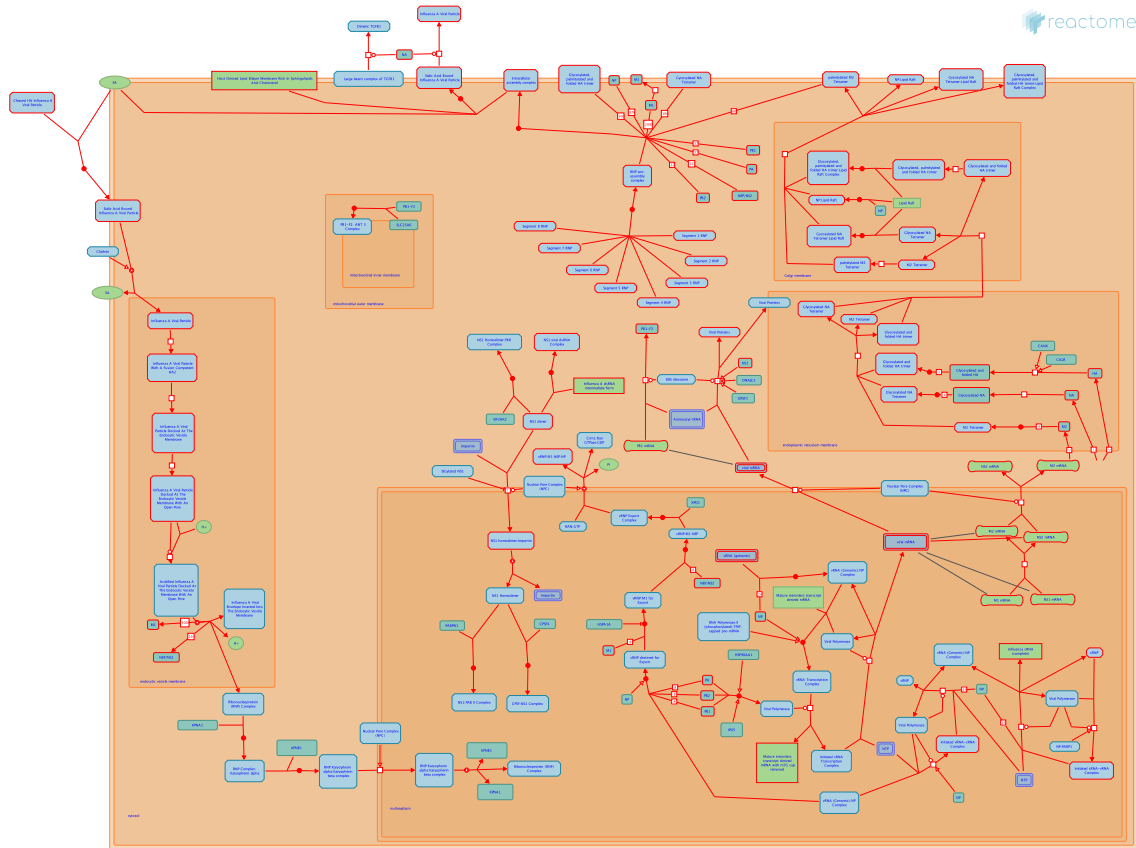
2015-01-13   Authored   Gillespie, ME., Gopinathrao, G., D'Eustachio, P., Matthews, L., Rice, AP., Morrow, MP. et al.

Hare, BC. (n.d.). Clinical Overview of HIV Disease. Retrieved from http://hivinsite.ucsf.edu/InSite?page=kb-03-01-01

Influenza Infection ↗

Location: Infectious disease

Stable identifier: R-HSA-168255

Diseases: influenza

For centuries influenza epidemics have plagued man; with influenza probably being the disease described by Hippocrates in 412 BC. Today it remains a major cause of morbidity and mortality worldwide with large segments of the human population affected every year. Many animal species can be infected by influenza viruses, often with catastrophic consequences. An influenza pandemic is a continuing global level threat. The 1918 influenza pandemic is a modern example of how devastating such an event could be with an estimated 50 million deaths worldwide.

Influenza viruses belong to the family of Orthomyxoviridae; viruses with segmented RNA genomes that are negative sense and single-stranded (Baltimore 1971). Influenza virus strains are named according to their type (A, B, or C), the species from which the virus was isolated (omitted if human), location of isolate, the number of the isolate, the year of isolation, and in the case of influenza A viruses, the hemagglutinin (H) and neuraminidase (N) subtype. For example, the virus of H5N1 subtype isolated from chickens in Hong Kong in 1997 is: influenza A/chicken/Hong Kong/220/97(H5N1) virus. Currently 16 different hemagglutinin (H1 to H16) subtypes and 9 different neuraminidase (N1 to N9) subtypes are known for influenza A viruses. Most human disease is due to influenza viruses of the A type. The events of influenza infection have been annotated in Reactome primarily use protein and genome references to the Influenza A virus A/Puerto Rico/8/1934 H1N1 strain.

The influenza virus particle initially associates with a human host cell by binding to sialic acid receptors on the host cell surface. Sialic acids are found on many vertebrate cells and numerous viruses make use of this ubiquitous receptor. The bound virus is endocytosed by one of four distinct mechanisms. Once endocytosed the low endosomal pH sets in motion a number of steps that lead to viral membrane fusion

mediated by the viral hemagglutinin (HA) protein, and the eventual release of the uncoated viral ribo-nucleoprotein complex into the cytosol of the host cell. The ribonucleoprotein complex is transported through the nuclear pore into the nucleus. Once in the nucleus, the incoming negative-sense viral RNA (vRNA) is transcribed into messenger RNA (mRNA) by a primer-dependent mechanism. Replication occurs via a two step process. A full-length complementary RNA (cRNA), a positive-sense copy of the vRNA, is first made and this in turn is used as a template to produce more vRNA. The viral proteins are expressed and processed and eventually assemble with vRNAs at what will become the budding sites on the host cell membrane. The viral protein and ribonucleoprotein complexes are assembled into complete viral particles and bud from the host cell, enveloped in the host cell's membrane.

Infection of a human host cell with influenza virus triggers an array of defensive host processes. This co-evolution has driven the development of host processes that interfere with viral replication, notably the production of type I interferon. At the some time the virus counters these responses with the viral NS1 protein playing a central role in the viral response to the host cells defense.

Literature references

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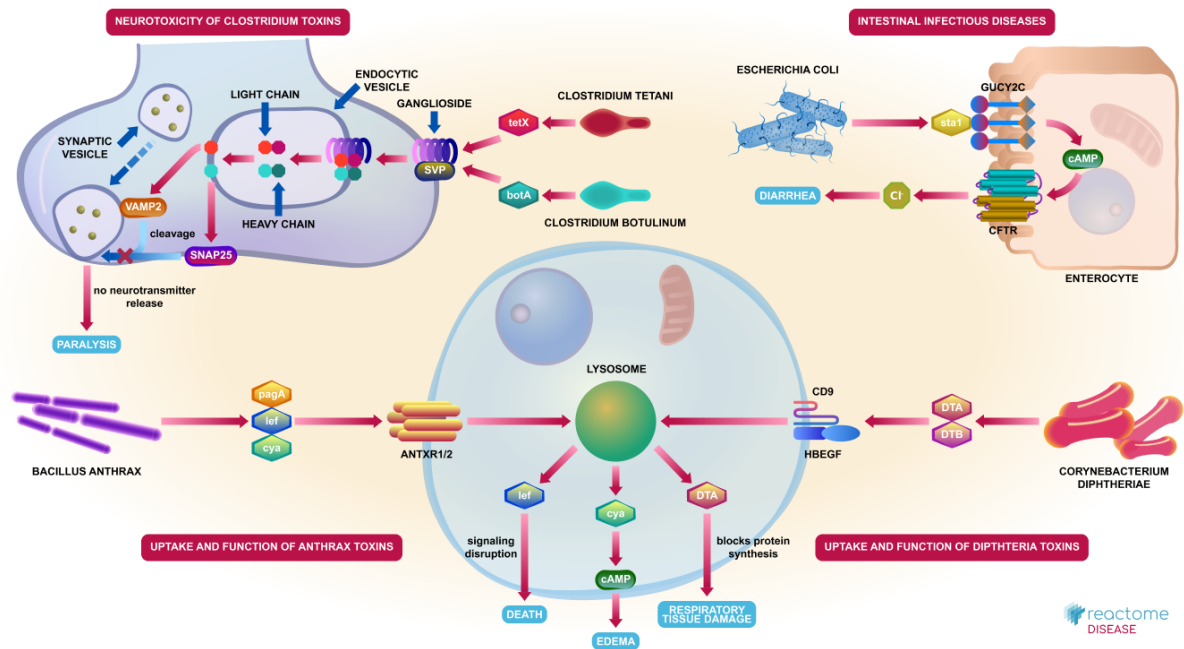
Editions

2004-05-12	Reviewed	Garcia-Sastre, A.
2006-01-05	Authored	Luo, F., Squires, B., Scheuermann, RH.
2006-10-31	Reviewed	Garcia-Sastre, A., Squires, B.
2007-05-01	Reviewed	Rush, MG., Squires, B.

Uptake and actions of bacterial toxins ↗

Location: Infectious disease

Stable identifier: R-HSA-5339562

Diseases: primary bacterial infectious disease

The toxic effects of many bacteria on their human hosts are mediated by proteins released from the bacteria that enter human cells and disrupt critical cellular functions (Henkel et al. 2010). All of the ones annotated here share a bipartiite mechanism of host intoxication: one moiety binds target cells and mediates the delivery of the other part to the intracellular compartment where it can function as an enzyme to degrade or derivatize and inactivate critical target cell proteins or to activate constitutive synthesis of high levels of cAMP.

Literature references

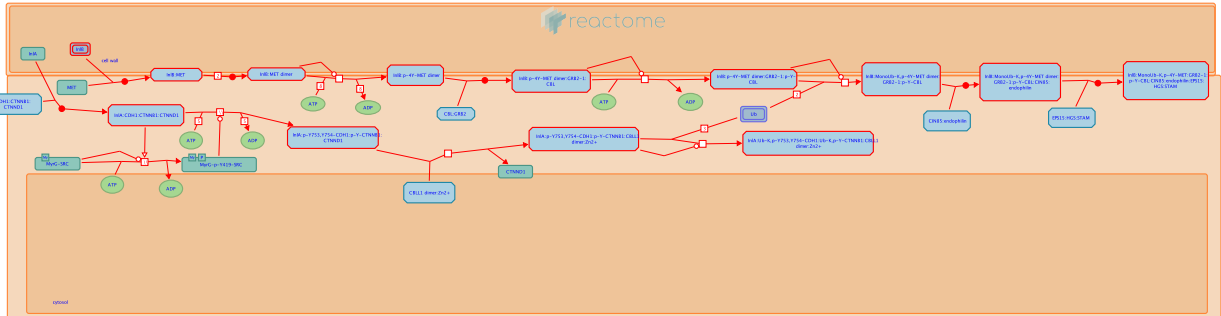Henkel, JS., Baldwin, MR., Barbieri, JT. (2010). Toxins from bacteria. *EXS, 100*, 1-29. ↗

Listeria monocytogenes entry into host cells ↗

Location: Infectious disease

Stable identifier: R-HSA-8876384

Diseases: listeriosis

Listeria monocytogenes is a short, gram-positive, nonspore-forming motile rod. Serotypes 1/2a, 1/2b and 4b make up more than 95% of isolates from humans, with serotype 4b causing most of the food-borne outbreaks. Listeria monocytogenes enters the body through the gastrointestinal tract after ingestion of contaminated food. The bacteria can survive food preservation procedures, such as refrigeration, low pH and high salt.

Listeria monocytogenes expresses several adhesin proteins at the cell surface that facilitate bacterial binding and entry to host cells. The bacteria can enter host cells through endocytosis mediated by binding of the bacterial InlA (internalin) protein to CDH1 (E-cadherin) at the host cell plasma membrane. Listeria monocytogenes can also enter host cells through endocytosis mediated by binding of the bacterial InlB protein to MET receptor tyrosine kinase at the host cell plasma membrane. Listeria monocytogenes proliferates inside the host cells and triggers formation of filopods, elongated protrusions of the host plasma membrane that contain bacteria. Filopods are ingested by adjacent cells, allowing Listeria monocytogenes to spread from cell to cell, invisible to the immune system of the host.

Listeria monocytogenes can cross the intestinal, blood-brain and placental barriers. In immunocompetent adults Listeria monocytogenes infection usually causes gastroenteritis. In infants infected in utero and in immunocompromised adults Listeria monocytogenes infection can result in meningoencephalitis and bacteremia (sepsis).

InlA is critical for crossing the intestinal barrier while both InlA and InlB are needed for crossing the placental barrier (Gessain et al. 2015) and, based on in vitro studies, the blood-cerebrospinal fluid barrier (Grundler et al. 2013). It seems that the intrinsic level of PI3K activity in Listeria-targeted host cells determines whether the entry depends on InlA only or InlA and InlB. The interaction of InlA with E-cadherin does not activate PI3K/AKT signaling while the interaction of InlB with the MET receptor activated the PI3K/AKT signal transduction cascade. Therefore, InlB-MET interaction may be important in tissues with low intrinsic PI3K activity (Gessain et al. 2015). Even if InlA-E-cadherin route is sufficient for bacterial entry, InlB may accelerate bacterial invasion (Pentecost et al. 2010). Cholesterol levels in host cell plasma membrane may also influence the preferred route for bacterial endocytosis (Seveau et al. 2004). In addition to InlA and InlB, many other virulence factors are involved in the Listeria monocytogenes infection cycle (Camejo et al. 2011) and will be annotated as mechanistic details become available.

For review, please refer to Bonazzi et al. 2009, Brooks et al. 2010, Camejo et al. 2011, Pizarro-Cerda et al. 2012.

Literature references

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Pentecost, M., Kumaran, J., Ghosh, P., Amieva, MR. (2010). Listeria monocytogenes internalin B activates junctional endocytosis to accelerate intestinal invasion. *PLoS Pathog., 6*, e1000900. ↗
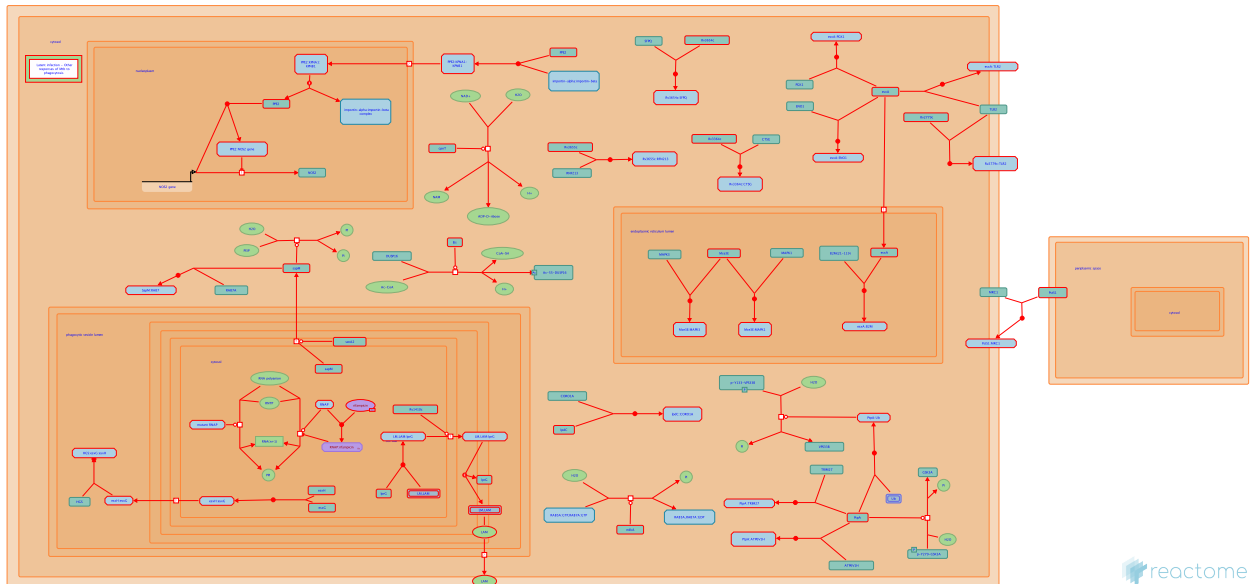
Editions

2016-06-14	Authored	Orlic-Milacic, M.
2016-10-25	Reviewed	Schwerk, C.
2016-10-26	Edited	Orlic-Milacic, M.

Infection with Mycobacterium tuberculosis ↗

Location: Infectious disease

Stable identifier: R-HSA-9635486

Diseases: tuberculosis

Infection with Mycobacterium tuberculosis (Mtb) is soon countered by the host's immune system, the organism is however almost never eradicated; ten per cent of infections will develop into "open tuberculosis", while the other ninety per cent become "latent", a state that can persist for decades until loss of immune control. Approximately 25% of the world's population is estimated to harbour latent tuberculosis. Latent infection involves the bacterium being internalized by phagocytes where it stops and counters the innate immune answer (Russell 2011, Russell et al. 2010). When a status-quo is reached, Mtb enters a non-replicating persistent state (Barry et al. 2009, Boshoff & Barry 2005). Weakening of the immune defense sooner or later enables the waking up and multiplication of the bacterium inside the phagocyte, necrosis of the cell, and escape, analogous to the burst of lytic viruses (Repasy 2013).

Literature references

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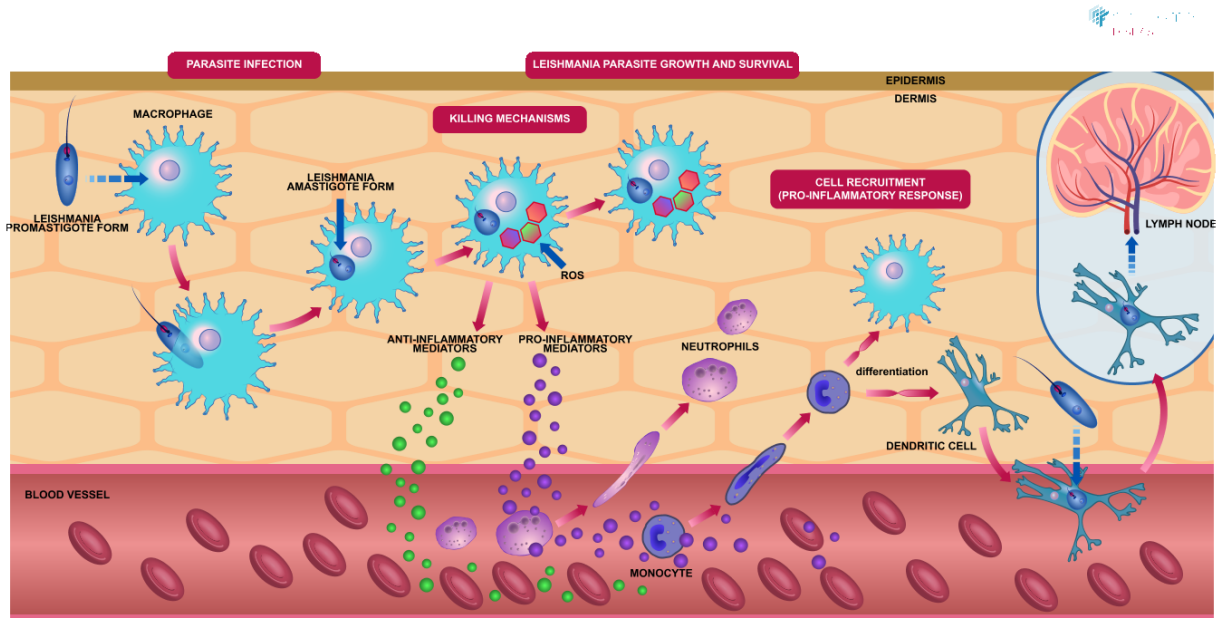
Editions

2019-02-05	Edited	Pardo, AM.
2019-02-06	Authored	Stephan, R.
2019-10-23	Reviewed	Wilkinson, RJ., Deffur, A.

Leishmania infection ↗

Location: Infectious disease

Stable identifier: R-HSA-9658195

Diseases: cutaneous leishmaniasis

Intracellular parasites of the genus Leishmania constitute the etiologic agent of a disease complex called Leishmaniasis. Leishmania parasites alternate between two distinct developmental stages: the insect-adapted, flagellated, extracellular "promastigote" and the mammal-adapted, non flagellated, intracellular "amastigote" form, where the later resides within phagolysosomal vesicles of the phagocytic cell (Liu et al. 2012a). Paradoxically, the macrophage, which is the main host cell where the parasite replicates and grows, is at the same time the main cell responsible for its elimination.

The uptake of Leishmania promastigotes by host cells is a receptor mediated process that initiates phagocytosis (Ueno et al. 2012). Some parasites differentiate and survive within the macrophage phagolysosomes; others are killed by the acidic and higher temperature environment (Rossi et al. 2018). In the end, it is the balance between the host and parasitic factors that control the activation/deactivation of macrophages that determines the fate of the parasites as well as the infection outcome (Liu et al. 2012b).

The pathways curated here summarize the major steps of parasite internalization by the macrophage, the defence mechanisms that are turned on and the mechanisms of evasion of the parasite to counteract them.

Literature references

Liu, D., Uzonna, JE. (2012). The early interaction of Leishmania with macrophages and dendritic cells and its influence on the host immune response. *Front Cell Infect Microbiol, 2*, 83. ↗

Ueno, N., Wilson, ME. (2012). Receptor-mediated phagocytosis of Leishmania: implications for intracellular survival. *Trends Parasitol., 28*, 335-44. ↗

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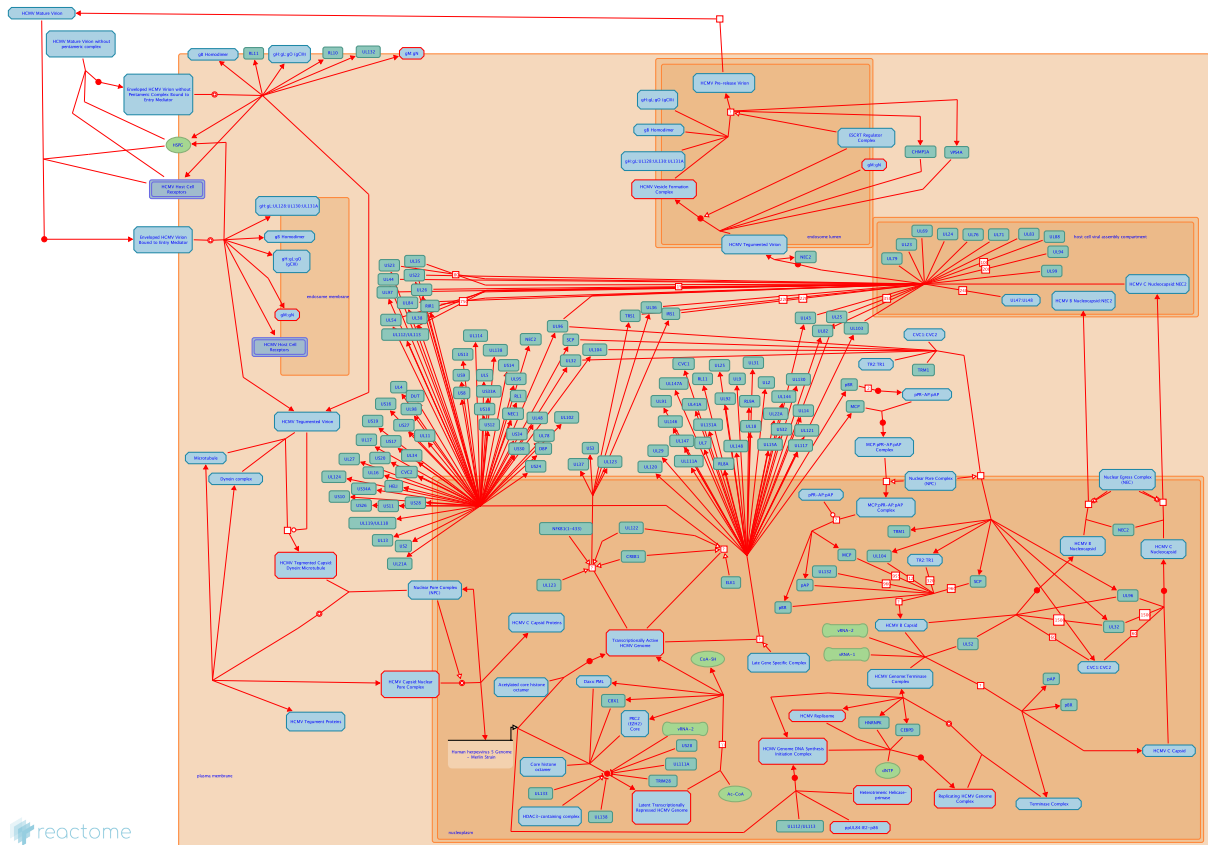
Editions

2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Authored, Edited	Jassal, B.
2020-02-05	Authored, Edited	Murillo, JI.

HCMV Infection ↗

Location: Infectious disease

Stable identifier: R-HSA-9609646

Diseases: viral infectious disease

Herpesviruses have a unique four-layered structure: a core containing the large, double-stranded DNA genome is enclosed by an icosapentahedral capsid which is composed of capsomers. The capsid is surrounded by an amorphous protein coat called the tegument. It is encased in a glycoprotein-bearing lipid bilayer envelope.

Herpesviruses are divided into three groups: alpha-herpesviruses, beta-herpesviruses, and gamma-herpesviruses. The beta herpesviruses have a restricted host range. Their reproductive life cycle is long (days), with infection progressing slowly in cell culture systems. These viruses cause their host cells to enlarge, as exemplified by a human cytomegalovirus (HCMV) infection. These viruses can establish latent infection in secretory glands, cells of the reticuloendothelial system, and the kidneys.

Human Cytomegalovirus, or HCMV, is a common virus that infects people of all ages. In the United States, nearly one in three children are already infected with HCMV by age 5 years. Over half of adults by age 40 have been infected with HCMV. Once HCMV is in a person's body, it stays there for life and can reactivate.

Cytomegalovirus causes three clinical syndromes:

(1) Congenital cytomegalovirus infection (when symptomatic) causes hepatosplenomegaly, retinitis, rash, and central nervous system involvement.

(2) In about 10 per cent of older children and adults, primary cytomegalovirus infection causes a mononucleosis syndrome with fever, malaise, atypical lymphocytosis, and pharyngitis.

(3) Immunocompromised hosts (transplant recipients and human immunodeficiency virus [HIV]-infected individuals) may develop life-threatening disseminated disease involving the lungs, gastrointestinal tract, liver, retina, and central nervous system.

Experimentally HCMV can be propagated in multiple cell lines. When propagated in human fibroblasts, HCMV clinical isolates acquire mutations in a manner that suggests a process of adaptation. Two strains of HCMV AD169 (grown from cultures of adenoid tissue taken from a 7-year-old girl) and Towne (developed as an attenuated vaccine by passaging 125 times in vitro) were initially used as the primary clinical strains. As only 26 % of HCMV canonical genes (45/171) are essential for viral replication in vitro it became important that a model strain be developed.

The Merlin BAC was derived for this use. Produced using a bacterial artificial chromosome (BAC) cloning system (to avoid adaptation/degradation of the genome with each passage) the Merlin strain contains a complete HCMV genome that is thought to accurately to represent the original clinical agent from which it was derived. It is also a reproducible source of clonal virus (via transfection) and is capable of reconstituting phenotypically wild-type virus.

The lifecycle represented here uses the Merlin strain where possible.Infectious Human Cytomegalovirus (HCMV) particles enter the cell through interaction with cellular receptors. Once in the cytoplasm capsid and tegument proteins are delivered to the cytosol. The capsid travels to the nucleus, where the genome is delivered and circularized. Tegument proteins regulate host cell responses and initiate the expression of viral I immediate early genes. This is followed by delayed early genes, which initiate viral genome replication, then late genes. Late gene expression initiates capsid assembly in the nucleus, followed by nuclear egress to the cytosol. Capsids associate with tegument proteins in the cytosol and are trafficked to the viral assembly complex that contains components from the endoplasmic reticulum, Golgi apparatus, and endosomal machinery. The capsids acquire additional tegument proteins and a viral envelope by budding into intracellular vesicles. These vesicles fuse with the plasma membrane to release enveloped infectious particles along with non-infectious dense bodies.

Literature references

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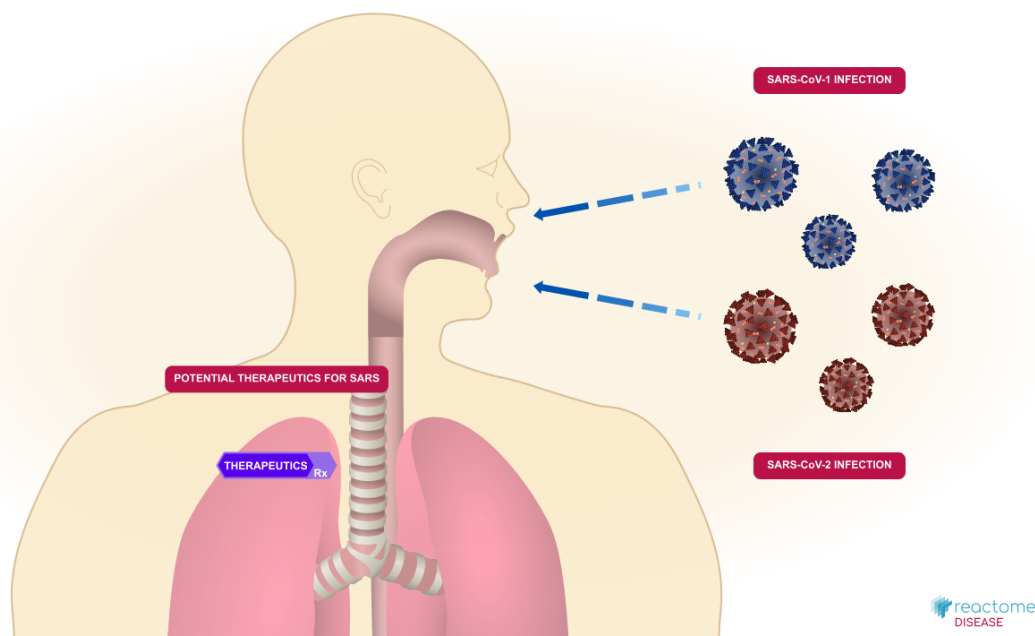
Editions

2018-05-26	Authored	Gillespie, ME.
2019-10-18	Reviewed	Streblow, DN., Caposio, P.

SARS-CoV Infections ↗

Location: Infectious disease

Stable identifier: R-HSA-9679506

Diseases: Coronavirus infection

Coronaviruses (CoVs) are large, enveloped, positive strand RNA viruses that can be classified into four genera: alpha, beta, delta, and gamma. Coronaviruses are ecologically diverse, infecting animals including camels, cattle, cats, and bats, with the greatest variety seen in bats, suggesting that bats are the reservoirs for many of these viruses. Rarely, A and B lineage beta coronaviruses of non-human origin can infect people and then spread directly between people. Four human coronaviruses (HCoVs), HCoV 229E, NL63, OC43, and HKU1, are endemic globally and account for 10% to 30% of upper respiratory tract infections in adults, typically presenting as common colds (van der Hoek 2007). However, in the 21st century, three highly pathogenic HCoVs - severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2003, Middle East Respiratory Syndrome coronavirus (MERS CoV) in 2012, and SARS-CoV-2 in 2019 - emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality (De Wit et al. 2016; Fung & Liu 2019; Marra et al. 2003; Paules et al. 2020).

During the 2003 outbreak of SARS-CoV-1, 8,098 people worldwide became sick. Of these, 774 died. In the United States, only eight people had laboratory evidence of SARS-CoV-1 infection. All of these people had traveled to other parts of the world where the disease was spreading. Community spread was not observed in the United States (De Wit et al. 2016; WHO - SARS). A second human coronavirus, MERS-CoV, first observed in 2012, has been identified in 2,494 patients with respiratory distress of whom 858 have died. Human-to-human transmission of the virus appears to be limited (De Wit et al. 2016; WHO – MERS).

In December 2019, yet another pathogenic HCoV, 2019 novel coronavirus (2019 nCoV), was recognized, initially in Wuhan, China. The World Health Organization has named the disease caused by the 2019 novel coronavirus COronaVIrus Disease 2019, or COVID-19. The disease has also been referred to as 2019 novel coronavirus or 2019 nCoV.

SARS-CoV-1 and SARS-CoV-2 viral infection pathways are annotated in this section, as are drugs that potentially modulate the infection processes. Many of the steps of SARS-CoV-1 infection have been characterized experimentally in the past 15 years (Fung & Liu 2019; Masters 2006), and this experimental work has allowed the annotation here of the infection process and interactions with host proteins in molecular detail. Less comparable data is yet available for SARS-CoV-2 infection, but the similarity in the genomes and predicted proteomes of the two viruses allows the inference of a detailed infection pathway for SARS-CoV-2 that has been manually annotated as well with experimental results published in the first half of 2020.

Literature references

Marra, MA., Jones, SJ., Astell, CR., Holt, RA., Brooks-Wilson, A., Butterfield, YS. et al. (2003). The Genome sequence of the SARS-associated coronavirus. *Science, 300*, 1399-404. ↗

Editions

2020-05-26	Authored, Edited	Gillespie, ME.

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