Infectious disease


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**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.

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**Literature references**


Reactome database release: 71

This document contains 7 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 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.
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 needle-sticks 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 occurring 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**

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


For centuries influenza epidemics have plagued man, and influenza was probably 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. A continuing threat is the possibility of a pandemic similar to that experienced in 1918, estimated to have been responsible for 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, so the events of Influenza infection have been annotated in Reactome with reference to this type.

Literature references


Editions

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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 bipartite 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

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.

**Literature references**


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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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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 host (transplant recipients and human immunodeficiency virus [HIV]-infe-
ted individuals) may develop life-threatening disseminated disease involving the lungs, gastrointesti-
nal 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 (d-
veloped as an attenuated vaccine by passaging 125 times in vitro) were initially used as the primary clin-
cial 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 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 reconsti-
tuting 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 rep-
lication, then late genes. Late gene expression initiates capsid assembly in the nucleus, followed by nu-
clear 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

(HCMV) - Revised. Transfus Med Hemother, 37, 365-375.


Editions

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