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Genes conferring immunity against viral infections

OUTLINE

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Viruses invade living cells and utilize the host's cell machinery for their survival, growth, and multiplication. This can kill, damage, or change cells and make the individual sick. Different viruses attack certain cells in the body such as those of the liver, respiratory system, or blood. When a body detects a viral infection, it responds accordingly. RNA interference is a process to degrade viral genetic material, thereby enabling cells to outlast the infection.

As already discussed in the earlier chapter on innate immunity (Chapter 5), the body has several defense mechanisms against such infections. During their entry into the body, viruses first encounter the skin as the primary physical barrier preventing their entry. Interferons are also important substances preventing the entry of viruses.

When the virus enters the body, it triggers the body's immune defense mechanism. White blood cells (WBCs), as monocytes and lymphocytes, are responsible for attacking invading viruses and in turn the destruction of the virus or infected cells. Once the viral infection exceeds that which WBCs memorize, the body's immune system can react more quickly and smartly to a further infection caused by the same virus. This is the basis for memory cells, and for vaccination. This response mechanism is called immunity.

Viral infection in vertebrates results in two general types of immune response:

1. The first is a rapid-onset "innate" response against the virus, which involves the synthesis of proteins called interferons and the stimulation of "natural killer" lymphocytes. In some cases, innate response may be enough to prevent a large-scale infection.
2. However, if the infection proceeds beyond the first few rounds of viral replication, "adaptive immune response" kicks into high gear. Adaptive immune response itself has two components:
 - ☛ humoral response (the synthesis of virus-specific antibodies by B lymphocytes)
 - ☛ cell-mediated response (the synthesis of specific cytotoxic T lymphocytes that kill infected cells)

Both components of adaptive immune response also result in the production of long-lived "*memory cells*" that allow for a much more rapid response (i.e., immunity) to subsequent infection with the same virus.

Viral infections can be classified into the following categories by the outcome of immune response with suitable examples from human beings:

1. acute (only)—smallpox, influenza, rhinovirus, rotavirus, Ebola, SARS
2. latent—herpes viruses
3. chronic or persistent—hepatitis B and C
4. progressive—human immunodeficiency virus (HIV)

All cases where the individual gets sick and then either dies or recovers completely, leading to the elimination of all virus from the body, are included in category 1.

For categories 1 to 4, initial infection may be acute or inapparent, but the body's immune response does not clear the virus completely and things proceed to a situation where there may be very little ("latent"), some ("chronic/persistent"), or abundant ("progressive") virus replication going on during the rest of the person's life.

During the early stages of the clonal selection process, immunoglobulin gene DNA rearrangements occur. "Antigen-presenting cells" lead to the activation and proliferation of T helper cells, which are required for the generation of humoral (clonally selected B cells secreting an antigen-specific antibody that binds to extracellular virus particles) and cell-mediated (clonally selected cytotoxic T cells recognizing antigen-displaying "altered self" cells and killing them) responses. A subset of these B and cytotoxic T cell populations become antigen-specific "memory" cells to provide long-lived immunity to reinfection.

Viral pathogenic mechanisms include implantation of the virus at a body site (the portal of entry), replication at that site, spread to and multiplication within sites and in target organs, and ultimately shedding of the virus into the environment. Most viral infections are subclinical, suggesting that the body's viral defenses arrest most infections before disease symptoms become manifested. It is difficult to assess subclinical infection through clinical manifestation; rather, it is confirmed through serologic studies through the detection of specific antibodies to viruses.

These inapparent infections have great epidemiologic importance—they constitute major sources for dissemination of viruses through the population and confer immunity.

Direct cell damage and death from viral infection may result from

- (1) diversion of cell energy,
- (2) shutoff of cell macromolecular synthesis,
- (3) competition of viral mRNA for cellular ribosomes,
- (4) inhibition of interferon defense mechanisms,
- (5) competition of viral promoters and transcriptional enhancers for cellular transcriptional factors such as RNA polymerases, and
- (6) damage of the cell due to integration of the viral genome, mutations in the host genome, inflammation, and host immune response.

Factors that determine the affinity for viruses for specific body tissues (tropism) are determined by

- (1) cell receptors for the virus,
- (2) cell transcription factors that recognize viral promoters and enhancer sequences,
- (3) ability of the cell to support virus replication,
- (4) physical barriers,
- (5) local temperature, pH, and oxygen tension enzymes and nonspecific factors in body secretions, and
- (6) digestive enzymes and bile in the gastrointestinal tract that may inactivate some viruses.

The peculiarity for viral infection is that after entry of the virus, infection occurs if the host cell is able to support viral replication. A receptor, a cell surface attachment site, is needed for the virions to bind. A convenient intracellular environment is needed for the replication and release of a virus. Even if a virus initiates infection in a susceptible organ, the replication of a sufficient amount of the virus to cause disease may be prevented by host defenses.

The body's immune system produces specific antibodies that are capable of binding to the viruses and thereby making them noninfectious. Apart from this, T cells are sent to demolish the virus.

Though most viral infections produce a protective response from the body's immune system, viruses such as HIV specialize in damaging the immune system through various techniques.

As the virus gains entry into the body, secondary lymphoid organs respond and the immune response is triggered followed by local inflammatory signaling. Innate immune reaction is initially activated by conserved pathogen-associated molecular patterns (PAMPs), pattern recognition receptors (PRRs), retinoic acid inducible gene I (RIG-I)-like receptors, and toll-like receptors (TLRs) (Daniels et al., 2015). Viral nucleic acid binds to these receptors expressed on macrophages, microglia, dendritic cells (DCs), and astrocytes and releases type I interferon (IFN-I) and causes the production of interferon-stimulated genes (ISGs). IFN-I upregulates antiviral proteins—peripheral immune cells are stimulated and alter endothelial tight junctions. It has been observed that the absence of IFN-I signaling leads to the prevention of microglial differentiation and a decrease in peripheral myeloid cell patrolling.

IFN-I signaling—after binding of viral nucleic acid with these receptors, IFN-I is released and ISGs are produced. IFN-I upregulates antiviral proteins, recruits peripheral immune cells, and decreases permeability by altering endothelial tight junction proteins. It has been observed that the absence of IFN-I signaling prevents microglia differentiation, decreases peripheral myeloid cells, and significantly increases the number of infected brain resident myeloid cells. IFN-I signaling was observed to control the entire immune program within the central nervous system.

IFN-I provides antiviral immunity that may be globally or regionally specific.

The role of chemokines in viral infection

In the case of viral meningitis due to coronavirus infection, meningeal endothelial cells and fibroblastic reticular cells release chemokines such as C–C motif ligands (CCLs) 19 and 21 and reactivate antiviral C–C chemokine receptor 7 (CCR7), CD4, and CD8 T cells in response to resident myeloid and neural cell infection. The entry of CCR7 T cells is aided by stromal cell reorganization after infection. Chemokines are the proteins responsible for stimulating the recruitment of WBCs (leukocytes). The peculiarity for chemokines is that they are low-molecular-weight proteins. They are secondary proinflammatory mediators induced by primary proinflammatory mediators such as interleukin 1 or tumor necrosis factor (TNF). Specificity is one of the most important criteria for chemokines.

Unlike classic leukocyte chemoattractants, which have little specificity, members of the chemokine family induce recruitment of well-defined leukocyte subsets. Chemokine expression may serve as a useful indicator for the presence of different types of leukocytes in healthy and diseased conditions.

The chemokine family comprises two major subfamilies based on the position of cysteine residues—C–X–C and C–C (or CXC, CC). All members of the CXC chemokine subfamily have an intervening amino acid between the first two cysteines; members of the CC chemokine subfamily have two adjacent cysteines. In general, CXC chemokines are chemotactic for neutrophils, and CC chemokines are chemotactic for monocytes and a small subset of lymphocytes.

Chemokines have the potential role in inflammation. The two best-characterized chemokines are observed to be

- monocyte chemoattractant protein 1 of the CC chemokine subfamily and
- interleukin 8, a member of the CXC chemokine subfamily.

Chemokines are generally low-molecular-weight cytokines (around 8 kDa, with a mature peptide comprising between 70 and 120 amino acids) whose major collective biological activity appears to be that of chemotaxis of leukocytes. They play a critical role in the directed movement of leukocytes from the bloodstream into tissue as well as localization of cells within tissues. These molecules act as extracellular messengers for the immune system. However, emerging data also show that various members of the chemokine gene superfamily exert a range of biological effects beyond chemotaxis including angiogenesis and hematopoiesis. All nucleated cells and tissues examined to date are capable of expressing at least some chemokines, and it seems likely that by the time all chemokines in the genome have been identified and all their biological functions elucidated, we will find that as a family, these molecules perform vital roles in all tissues of the body.

Gene products are assigned to the chemokine gene superfamily according to the organization of a characteristic cysteine signature in their predicted primary amino acid structure. Based on this cysteine motif, the various members can be subdivided into four families (two major and two minor) known interchangeably as either (1) CXC, CC, C, and CX₃C, or (2) α , β , γ , and δ . CXC chemokines can be further subdivided into glutamic acid/leucine/arginine (ELR)-containing and non-ELR-containing chemokines depending on the presence of an ELR motif just prior to the CXC signature. ELR-containing C–X–C chemokines attract neutrophils, whereas non-ELR-containing C–X–C chemokines attract lymphocytes. Recently, a new member of the CXC subfamily was identified. This chemokine, known as CXCL16, is unique among CXC chemokines in that it is significantly larger than the others (the CXCL16 gene encodes a 249-amino acid peptide) and is predicted to contain a mucin-like stalk, a transmembrane domain, and a short cytoplasmic tail with a six-cysteine-containing 88-amino acid chemokine module at the N-terminus. The second major branch of CC chemokines are chemoattractants for a wide range of cells including monocytes, granulocytes other than neutrophils, various subpopulations of lymphocytes including thymocytes, and DCs. The CC subfamily contains the largest number of chemokines. The only C chemokine cloned to date, XCL1/lymphotactin, has been reported to selectively attract CD8⁺T lymphocytes. This chemokine has only two cysteines in its primary amino acid sequence. Finally, CX₃CL1/fractalkine, the only member of the CX₃C subfamily, has a unique primary amino acid sequence with three intervening amino acids between its first two cysteines. Like CXCL16, it is an unusual chemokine in that it is also a large protein with a chemokine module positioned at the N-terminus and is predicted to comprise a mucin-like stalk, a transmembrane domain, and a cytoplasmic tail.

It was observed that CD4⁺ T cells use interferon gamma (IFN- γ) to help maintain immune populations during homeostasis by promoting the expression of adhesion, chemokine, and antigen-presenting molecules on the epithelium. Deletion of the IFN- γ receptor was shown to reduce steady state immune cell numbers as well as immune traffic. This process depends in part on nuclear factor kappa B subunit 1 (NF- κ B)/p65 signaling.

Herpes simplex virus (HSV-1) infection leads to better induction of microglia to utilize the cGAS-STRING cytosolic DNA sensing pathway to induce the release of IFN-I. This prevents viral spread and lethality by activation of the neural antiviral program. Even in dengue viral infection, microglial protection was observed.

Genes conferring immunity against viral infections

TLR7 is a member of the TLR family that recognizes single-stranded RNA in endosomes, which are a common feature of viral genomes. TLR7 can recognize GU-rich single-stranded RNA. It has an effect against viral infection in poultry. TLR7 is a vital component of antiviral immunity, particularly in ducks (Pal, A, 2017). 3D structure of TLR7 is represented in pymol view (Fig 10.2).

RIG-I (retinoic acid-inducible gene I) is a RIG-I-like receptor dsRNA helicase enzyme. RIG-I is part of the RIG-I-like receptor family, which also includes melanoma differentiation-associated protein 5 (MDA5) and laboratory of genetics and physiology 2 and functions as a PRR that is a sensor for viruses such as influenza A, Sendai virus, and flavivirus. RIG-I typically recognizes short 5' triphosphate uncapped double-stranded or single-stranded RNA. RIG-I and MDA5 are involved in activating MAVS and triggering an antiviral response. It is an important gene conferring antiviral immunity for ducks, particularly against avian influenza (Pal et al., 2017). The 3D structural representation of RIG I is presented in Fig 10.3.

TLR3 is a member of the TLR family that recognizes PAMPs expressed on infectious agents and mediates the production of cytokines necessary for the development of effective immunity. It recognizes dsRNA associated with viral infection and induces the activation of interferon regulatory factor 3 (IRF3), unlike all other TLRs, which activate NF- κ B. IRF3 ultimately induces the production of type I interferons. It may thus play a role in host defense against viruses. The 3D structural representation of TLR3 is represented in Fig 10.4.

Double-stranded RNA is also recognized by the cytoplasmic receptors RIG-I and MDA5. Table 10.1 lists a set of genes providing antiviral immunity in different livestock species.

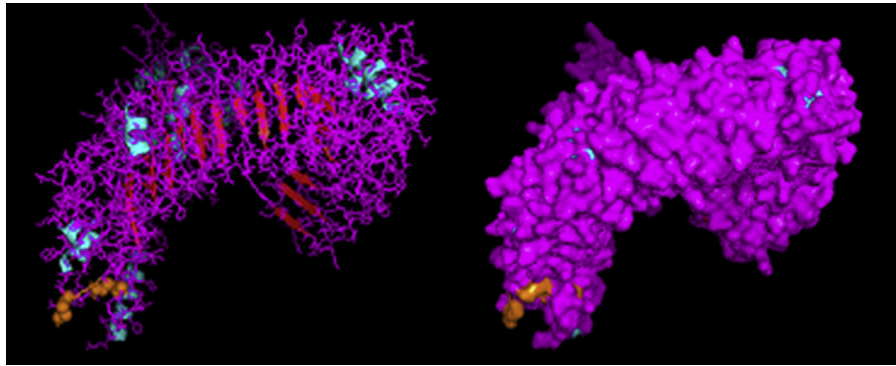


FIGURE 10.2 3-D structure of TLR7 based on secondary structure; helix-loop and sheet (left) and surface view (right).

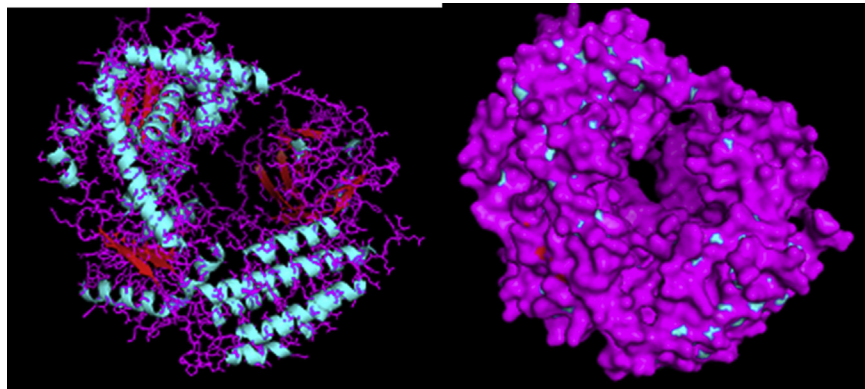


FIGURE 10.3 3-D structure of RIG-I based on secondary structure; helix-loop and sheet (left) and surface view (right).

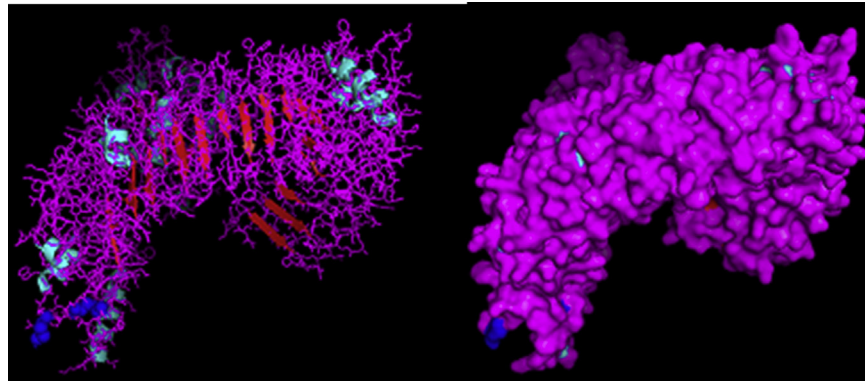


FIGURE 10.4 3-D structure of TLR3 based on secondary structure; helix-loop and sheet (left) and surface view (right).

TABLE 10.1 Important immune-response genes pertaining to antiviral immunity.

Sl. no	Immune response gene coding for cytokine	Gene bank accession no. (www.ncbi.nlm.nih.gov)	Protein ID	Species
1	RIG-I	KX687005		Sheep
2	RIG-I	KF517376	AGW84229	Buffalo
3	MDA5	KF517377	AGW84230	Buffalo
4	TNF- α	GU129693	ACY68103	Cattle
5	IFN- α	AY323970	AAQ00942	Cattle
6	ISG20	NM_001046217	NP_001039682	Cattle
7	CCL19	NM_001034345	NP_001029517	Cattle
8	TLR3	KX865108	ASW23003	Duck
9	TLR7	KX687004		Duck
10	IFN- γ	NM_205149	NP_990480	<i>Gallus gallus</i>
11	IFN- γ	NM_174086	NP_776511	Cattle
12	<i>Bos taurus</i> CCR7	AY834253	AAV97930	Cattle
13	MCP-1	EU276059	ABX72057	Cattle
14	IL-8	JN559767	AEO13897	Cattle
15	CXCL10	EU276062	ABX72060	Cattle
16	CXCL9	EU276061	ABX72059	Cattle
17	IFN- β	EU276065	ABX72063	Cattle
18	IRF3	KU641390	AQT40598	Cattle
19	NF- κ B	NM_001076409	NP_001069877	Cattle
20	LGP2	BT020952	AAX08969	Cattle

CCL19, C–C motif chemokine ligand 19; CCR7, C–C chemokine receptor 7; CXCL9, monokine induced by interferon gamma; CXCL10, gamma interferon-inducible protein 10; IFN- α , interferon alpha; IFN- β , interferon beta; IFN- γ , interferon gamma; IRF3, interferon regulatory factor 3; IL-8, interleukin 8; ISG20, interferon-stimulated exonuclease gene 20; LGP2, laboratory of genetics and physiology 2; MCP-1, monocyte chemoattractant protein 1; MDA5, melanoma differentiation-associated gene 5; NF- κ B, nuclear factor kappa B subunit 1; RIG-I, retinoic acid-inducible gene I; TNF- α , tumor necrosis factor alpha; TLR3, toll-like receptor 3; TLR7, toll-like receptor 7; TNF- α , tumor necrosis factor alpha

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