AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

BIOMOLECULAR MECHANISMS OF LIVER CELL DAMAGE IN HEPATITIS A VIRUS INFECTION

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ABSTRACT: This article examines the molecular mechanisms of the pathogenesis of viral hepatitis A (HAV), an infectious disease that causes acute liver inflammation. HAV is an RNA-containing virus transmitted by the fecal-oral route and is self-limiting in most cases. However, the molecular processes underlying the disease's pathogenesis include complex interactions between the virus and liver cells, activation of the immune response, and the development of inflammation.

This article examines the key stages of hepatocyte infection , the mechanisms of viral entry and viral genome replication, and the influence of viral proteins on cellular metabolism. Particular attention is paid to the body's immune response, including the activation of innate and adaptive immunity, as well as the role of cytokines in inflammation. Describe the molecular mechanisms of liver cell damage and inflammation, which contribute to a better understanding of the pathogenesis of viral hepatitis A and opens new horizons for the development of more effective methods for diagnosis, treatment, and prevention of the disease.

The article also highlights the importance of host genetic factors in the pathogenesis of HAV and examines the prospects for using molecular approaches in therapy and vaccination against the virus.

Keywords: Viral hepatitis A, molecular mechanisms, pathogenesis, viral replication, hepatocytes , immune response, liver inflammation, cytokines, diagnostics, vaccination.

БИОМОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ ПОВРЕЖДЕНИЯ КЛЕТОК ПЕЧЕНИ ПРИ ИНФЕКЦИИ ВИРУСА ГЕПАТИТА А

АННОТАЦИЯ: Статья посвящена молекулярным механизмам патогенеза вирусного гепатита А (ВГА), инфекционного заболевания, которое вызывает острое воспаление печени. Вирус гепатита А представляет собой РНК-содержащий вирус, который передается фекально-оральным путем и в большинстве случаев приводит к самоизлечению. Однако молекулярные процессы, лежащие в основе патогенеза заболевания, включают сложные взаимодействия вируса с клетками печени, активацию иммунного ответа и развитие воспаления.

В статье рассмотрены ключевые этапы инфицирования гепатоцитов, механизмы проникновения вируса в клетку и репликации вирусного генома, а также влияние вирусных белков на метаболизм клетки. Особое внимание уделено иммунному ответу

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

организма, включая активацию врожденного и адаптивного иммунитета, а также роли цитокинов в воспалении. Описание молекулярных механизмов повреждения клеток печени и воспаления способствует лучшему пониманию патогенеза вирусного гепатита А и открывает новые горизонты для разработки более эффективных методов диагностики, лечения и профилактики заболевания.

Статья также подчеркивает значимость генетических факторов хозяина в патогенезе ВГА и рассматривает перспективы использования молекулярных подходов в терапии и вакцинации против вируса.

Ключевые слова: вирусный гепатит А, молекулярные механизмы, патогенез, вирусная репликация, гепатоциты, иммунный ответ, воспаление печени, цитокины, диагностика, вакцинация.

RELEVANCE: The current relevance of research into the molecular mechanisms of viral hepatitis A (HAV) pathogenesis is driven by several important factors. Hepatitis A continues to be one of the most common infections worldwide, despite significant progress in vaccination and improved sanitation in some regions. In 2020, the World Health Organization (WHO) recorded over 1.4 million cases, highlighting the global relevance of the problem.

The molecular mechanisms underlying the pathogenesis of hepatitis A remain poorly understood, limiting the development of new diagnostic and therapeutic methods. The main characteristic of hepatitis A is its high contagiousness and acute course of the disease, which leads to a significant burden on healthcare systems, especially in developing countries with low vaccination rates and poor sanitation.

Therefore, research into the molecular aspects of viral replication, viral interactions with liver cells, and the role of the immune response in the development of liver inflammation is particularly important. A thorough understanding of these processes could not only aid in the development of more effective diagnostic and therapeutic methods but also contribute to improved vaccine strategies and disease prevention.

Furthermore, given the prevalence of HAV among travelers and in some countries with low immunity, it is necessary to consider the specific pathogenesis of the virus in different populations. This underscores the importance of a more detailed and comprehensive study of the molecular mechanisms of this disease, making the topic of this article extremely relevant in the context of global efforts to improve public health [1] .

MATERIALS AND METHODS:

1.1 Study design

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

To investigate the molecular mechanisms of viral hepatitis A pathogenesis, a retrospective review study was used. This study included an analysis of the available scientific literature and existing data on the molecular biology, virology, and immunology of HAV. This methodological approach allows us to systematize accumulated knowledge, identify research gaps, and propose potential directions for future experiments and clinical trials. Studies on the molecular identification of the virus, analysis of its interaction with liver cells, and the body's immune response were also reviewed.

1.2 Type of study

Study type: Review of scientific papers, articles, clinical reports, meta-analyses, and systematic reviews devoted to the molecular mechanisms of HAV pathogenesis, as well as studies on the molecular biology of the virus and immune response studies. An analysis of experiments aimed at studying viral replication and the role of specific molecules and pathways in liver cells was also conducted.

1.3 Duration of the study

The study lasted six months, during which a significant amount of information was collected and systematized from a database of scientific publications, including recent studies published in 2023–2024. This period was sufficient for a comprehensive analysis of existing studies and the formation of conclusions.

1.4 Inclusion and exclusion criteria

- Inclusion criteria:

- Articles published over the past 10 years, including studies of the molecular mechanisms of viral replication and immune response.

- Works that include both experimental and theoretical research.

- Research related to molecular diagnostic methods, therapy and vaccination of viral hepatitis A.

- Exclusion criteria:

- Articles not related to the topic of molecular pathogenesis of HAV.

- Works based only on clinical observations without molecular and experimental data.

- Publications that do not discuss the molecular mechanisms of viral infection.

1.5 Selection of subjects

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This study did not involve experiments on humans or animals. All data were obtained from existing publications, scientific databases, and available meta-analyses. Only studies that contained molecular analysis results meeting specific criteria were included.

2. Research methods

2.1 Data collection and processing

Databases of scientific articles such as PubMed , Scopus , Google were used to collect data. Scholar and other specialized resources. A systematic literature search was conducted, filtering by keywords such as "molecular mechanisms of viral hepatitis A," " HAV replication ," "immune response in viral hepatitis A," and "molecular diagnostics of the virus." Papers published in peer-reviewed journals and conference proceedings were also included.

2.2 Laboratory methods

No laboratory studies were conducted as part of this review, but the following methods described in the studies under review were used in the literature review process:

- PCR (polymerase chain reaction) – to detect viral RNA in biological samples.

- Genome sequencing – to determine the molecular characteristics of the virus, including its genetic variability.

- Enzyme-linked immunosorbent assay (ELISA) – to assess the immune response to infection.

- Microscopy and cell culture – to study the interaction of the virus with liver cells.

2.3 Statistical processing of data

Statistical processing of data within the review study involved a comparative analysis of existing literature sources. Meta-analysis methods were used to assess the reliability and significance of the data. The following statistical tests were used:

- A contrast analysis method to identify differences between molecular mechanisms described in different studies.

- Statistical justification for substantiating conclusions about the significance of molecular pathways in pathogenesis.

2.4 Quality of literary sources

To ensure high-quality analysis, only peer-reviewed studies published in high-impact journals were included . All data were critically assessed for sample representativeness and study quality.

3. Results and their analysis

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The results of the literature review will analyze the molecular pathways of HAV pathogenesis, including the interaction of the virus with liver cells, the mechanisms of viral replication, and the role of the immune system in the pathogenesis of the disease. Molecular aspects of diagnostics and new therapeutic approaches will also be considered.

RESULTS AND DISCUSSION: Viral hepatitis A (HAV) is an acute infectious disease caused by the hepatitis A virus, which belongs to the Picornaviridae family and the Hepatovirus genus . HAV is an important public health problem in many countries worldwide, particularly in developing regions with poor sanitation. It is characterized by acute inflammation of the liver, most often with a mild or moderate course of the disease, but in some cases can lead to serious complications, including acute liver failure and death. The virus is transmitted by the feco-oral route, which explains its high prevalence in countries with insufficient sanitation infrastructure and limited access to drinking water. Despite the existence of an effective vaccine against the virus, HAV remains a significant threat to public health, especially in countries with low vaccination and sanitation levels [2] .

Epidemiology and prevalence of viral hepatitis A

According to the World Health Organization (WHO), viral hepatitis A remains one of the most widespread viral diseases, causing over 1.4 million cases worldwide annually. In areas with poor sanitation infrastructure, the incidence of HAV remains high, especially among young children, who are more vulnerable to infection. In countries with developed healthcare systems and high sanitation standards, the incidence of HAV is significantly lower; however, cases still occasionally occur, especially in areas with limited access to water and poor living conditions. The incidence of viral hepatitis A also varies significantly depending on the socioeconomic status of the population and their level of awareness of preventive measures and vaccination [5,6,7] .

The primary mode of transmission is the fecal-oral route, which is explained by the high susceptibility of the population in conditions of poor sanitation, particularly in refugee camps, areas with migration, and emergency situations. Although the hepatitis A virus is less common in developed countries with high vaccination rates and good hygiene, epidemics and outbreaks still occur, especially among unvaccinated individuals or during international travel to endemic regions. Particularly high incidence rates are recorded in countries with limited access to clean water and unauthorized discharge of wastewater into water bodies, which facilitates the spread of the virus [3].

The importance of studying the molecular mechanisms of pathogenesis of viral hepatitis A

Understanding the molecular mechanisms of viral hepatitis A pathogenesis is crucial for better understanding the clinical course of the disease, as well as for developing new diagnostic, therapeutic, and preventative methods. Although HAV often has a favorable outcome, severe

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

forms of the disease, such as acute liver failure, can occur in rare cases. Understanding the molecular mechanisms underlying viral replication, viral interactions with liver cells, and the body's immune response can significantly improve our understanding of the disease and aid in the development of effective therapeutic and preventative approaches.

One of the key molecular mechanisms in the pathogenesis of viral hepatitis A is viral replication in the liver. The virus penetrates liver cells (hepatocytes) through specific receptors on the cell surface and begins replicating. This process is accompanied by inflammation, liver cell damage, and activation of the immune response, which can lead to varying degrees of organ damage. Understanding the molecular mechanisms that determine the nature of liver damage is crucial for predicting the course of the disease, as well as for developing more effective treatments, including antiviral drugs and therapeutic interventions [1,8,9] .

Furthermore, viral hepatitis A is associated with several important aspects of the immune system, including both the innate and adaptive immune responses. Studying the molecular interactions between the virus and immune cells allows for a more precise definition of the mechanisms underlying the development of inflammation and liver damage. Immune system activity in response to viral infection is an important component of HAV pathogenesis, which also opens up opportunities for the development of methods aimed at modulating the immune response to prevent or minimize liver damage [4] .

Finally, research into the molecular aspects of viral hepatitis A is essential for the development of new, more effective diagnostic methods. Modern molecular technologies, such as PCR (polymerase chain reaction), sequencing , and other methods, not only allow for rapid and accurate detection of the virus but also allow for the study of its genetic variability, which is essential for diagnosing and monitoring epidemic outbreaks.

Thus, research into the molecular mechanisms of viral hepatitis A pathogenesis is essential for improving diagnostics and developing new treatments. It also helps expand scientific knowledge about viral infections, which could impact global hepatitis control strategies, particularly in high-risk countries with limited diagnostic and treatment capabilities.

General description of the hepatitis A virus: family, genus, structure of the viral particle

The hepatitis A virus (HAV), which causes the disease of the same name, belongs to the Picornaviridae family , genus Hepatovirus . Viruses in this family are known for their small size, simple structure, and high resistance to external influences, which plays a significant role in their transmission and spread in the environment. HAV is one of five types of viruses that cause viral hepatitis, along with hepatitis B , C , D , and E.

Structure of the viral particle

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The hepatitis A virus is a non -contained , positive-stranded RNA virus. The structure of the viral particle (virion) has the following key features:

1. RNA genome: The hepatitis A virus has a genome consisting of a single-stranded RNA molecule, the length of which varies from 7 to 8 kilobases . The viral RNA encodes a single polypeptide, which then undergoes proteolytic cleavage, producing several proteins necessary for viral replication and the formation of viral particles.

2. Capsid : The hepatitis A virus is non-enveloped, its structure consists of a capsid that forms a spherical shell. The capsid is composed of 60 identical subunits , each containing several protein molecules. The major structural proteins of the hepatitis A virus include VP 1, VP 2, VP 3, and VP 4. These proteins form a capsid that protects the viral genome from environmental influences such as temperature, acidity, and enzymes, making the virus highly resistant to environmental conditions [10,11,12,13] .

3. Size and shape: Hepatitis A virus virions are approximately 27-30 nm in diameter , which is considered small for a virus. This compact shape and the lack of an outer membrane make the virus resistant to environmental influences and aggressive factors such as high temperatures, acidity, and chemicals.

4. Receptors and Cell Entry: The hepatitis A virus enters the host cell by interacting with receptors on the surface of liver cells (hepatocytes). Viral molecules bind to specific proteins on the cell surface, such as HAVCR 1 (or Tim-1), which facilitates entry of the virus into the cell through endocytosis .

5. Resistance to external influences: One of the characteristic features of the hepatitis A virus is its high resistance to physical and chemical influences. For example, it retains its infectivity in bodies of water at temperatures up to 60° C and in an acidic environment, which facilitates the spread of the virus through the feco-oral route, especially in countries with poor sanitation [5] .

Viral replication

After penetrating a cell, the hepatitis A virus utilizes cellular replication mechanisms, including the synthesis of viral RNA and proteins. Viral replication occurs in the cytoplasm of the infected cell. Viral RNA serves as a template for the synthesis of new copies of viral RNA and proteins, which later form new viral particles. These particles exit the cell, often destroying it, leading to inflammation and damage to liver tissue—the primary mechanism causing the symptoms of the disease [14] .

The genetic structure of the hepatitis A virus and the characteristics of its genome

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
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Hepatitis A virus (HAV) is a positive-sense, single-stranded RNA virus belonging to the Picornaviridae family , genus Hepatovirus . The genetic structure of HAV is determined by its RNA genome, which plays a key role in viral replication and disease pathogenesis.

The structure of the hepatitis A virus genome

The hepatitis A virus genome is a single-stranded , positive-sense RNA, ranging from 7.4 to 7.5 kilobases in length . It encodes several proteins essential for viral replication and the formation of viral particles. The hepatitis A virus genome includes several key regions:

1. 5' untranslated region (5' UTR): The beginning of the hepatitis A virus genome is the 5' untranslated region (UTR), which plays a key role in the initiation of viral replication and interaction with cellular factors. This region contains elements that ensure the binding of viral RNA to cellular structures to initiate the synthesis of viral proteins.

2. Coding region: The main part of the genome encodes one large polypeptide, which is then cleaved into several structural and nonstructural proteins. This process is called polycipiration . Structural proteins derived from the viral polypeptide include:

- VP 1, VP 2, VP 3, and VP 4 - these proteins form the viral capsid , which protects the viral genome.

- VP 4 - plays an important role in the formation of the capsid , while other proteins (VP 1, VP 2, and VP 3) make up the main structure of the virion.

3. 3' untranslated region (3' UTR): At the end of the genome is the 3' untranslated region, which is also important for regulating viral replication and interaction with cellular machinery. This region contains important elements for stabilizing RNA and its efficient use in the replication process [15] .

4. Polycistronic genome: The hepatitis A virus genome is polycistronic , meaning it encodes multiple proteins from a single RNA molecule. After viral RNA replication, long intermediate protein molecules are created, which are then cleaved by cellular enzymes into structural and non-structural proteins. These proteins are involved in the assembly of new viral particles and their release from the cell [6] .

Features of the hepatitis A virus genome

1. Absence of a viral envelope: The hepatitis A virus lacks a viral envelope, making it more resistant to external influences. This allows the virus to persist in the environment (for example, in water) for long periods and be transmitted via the fecal-oral route.

2. High RNA stability: The RNA of the hepatitis A virus is highly stable, which facilitates its persistence in unfavorable conditions. This also contributes to the virus's ability to spread

AMERICAN ACADEMIC PUBLISHER
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through contaminated water and food, causing widespread outbreaks in areas with poor sanitation.

3. Polycipylation and proteolytic cleavage: The process of polycipylation and subsequent cleavage of the polypeptide chain is an important feature of the hepatitis A virus. Proteins produced by cleavage of the viral polypeptide ensure the formation of new viral particles and the replication of viral RNA. This process is important for increasing the number of viral particles in an infected cell.

4. Genetic variability: The hepatitis A virus genome is characterized by a low mutation rate, making the virus relatively stable. However, within species, there are several genotypes of the hepatitis A virus, which may differ in their ability to adapt to different geographic regions. This underscores the importance of studying the virus's genetic variability for monitoring and predicting the spread of the disease.

5. Interference with cellular mechanisms: The hepatitis A virus RNA, being positively oriented, acts as mRNA , allowing the virus to quickly produce proteins necessary for replication. This ability to suppress normal cellular processes and trigger viral replication mechanisms is important for understanding the molecular mechanism of hepatitis A pathogenesis [2] .

Mechanisms of hepatitis A virus replication in cells

Hepatitis A virus (HAV) replication occurs in the cytoplasm of infected cells and involves several key stages, beginning with viral entry into the cell and ending with the assembly of new viral particles. Studying the molecular mechanisms of HAV replication allows for a deeper understanding of the pathogenesis of the disease and the development of strategies for the development of new antiviral therapeutics [16,17] .

1. Penetration of the virus into the cell

Replication of the hepatitis A virus begins with its entry into the cell. The virus, like other picornaviruses , lacks an outer envelope, which contributes to its high stability in the environment and resistance to external influences. However, to enter the cell, the virus uses cellular receptor molecules.

- Receptor binding: The process begins with the interaction of the virus with a cellular receptor located on the surface of liver cells, such as hepatocytes . The nature of this receptor for HAV remains a subject of research, but it is suggested that it may be associated with cell surface molecules involved in cell adhesion and endocytosis [18] .

- Endocytosis : After binding to the receptor, the virus enters the cell through endocytosis , forming a vesicle inside the cell containing viral particles [3].

2. Defrosting the virus and releasing the genome

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After the virus enters the cell, it undergoes further processing in endosomes , where the acidity decreases. This change in pH leads to conformational changes in the viral particle, resulting in the release of the viral genome from the capsid and into the cell's cytoplasm.

- Disassembly capsid : After penetrating the cytoplasm, the virus loses its outer protective shell (capsid), allowing the release of the viral RNA (positively oriented).

3. Synthesis of viral proteins and RNA replication

Once viral RNA enters the cytoplasm, it begins to function as mRNA for the synthesis of viral proteins. This is a key feature of picornaviruses , as their genomes can be directly translated by cellular ribosomes. Several important processes occur during this stage of replication:

- Translation of viral proteins: Viral RNA uses cellular ribosomes to synthesize viral proteins, including structural (VP 1, VP 2, VP 3, and VP 4) and nonstructural proteins required for genome replication. Structural proteins form the viral capsid , while nonstructural proteins are involved in RNA replication and other aspects of viral life [19,20] .

- Viral RNA Replication: Viral RNA, functioning as mRNA , begins synthesizing a polyprotein , which is then cleaved into several nonstructural proteins. Key proteins for viral RNA replication are viral RNA-dependent RNA polymerases, which copy the genome into additional RNA molecules. The HAV genome replicates, producing both positive- and negative-strand RNA. These intermediate molecules serve as templates for the synthesis of new positive-strand RNA, which are then used to synthesize mRNA and form new viral particles.

4. Assembly of viral particles

After synthesizing viral proteins and RNA, new viral particles begin to assemble in the cytoplasm. First, viral proteins such as VP 1, VP 2, VP 3, and VP 4 form a capsid , which then wraps around copies of the viral RNA, forming new virions.

- Genome packaging into a capsid : Inside the cell, viral RNA is packaged into a newly formed capsid . This process depends on the interaction of viral proteins and RNA, which facilitates the proper formation of mature viral particles.

5. Release of viral particles from the cell

After completing the synthesis and assembly of new viral particles, they exit the cell to begin infecting other cells. HAVs exit the cell through the cell membrane without disrupting the cell structure, a process known as noncellular exit. This process often occurs through exocytosis , a mechanism by which viral particles are transported to the cell membrane, where they are released into the extracellular space [21] .

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- Exocytosis : Viral particles collected in the cytoplasm pass through exocytic vesicles, fuse with the cell membrane and are released into the environment where they can infect new cells.

Interaction of the virus with liver cells (hepatocytes)

The hepatitis A virus (HAV) has a number of specific molecular and cellular targets in the body, with which it interacts for invasion, replication, and production of new viral particles. The liver is the primary organ affected by HAV infections , as hepatocytes —liver cells—play a key role in the pathogenesis of the disease. Studying the interactions between the virus and liver cells allows for a deeper understanding of the mechanisms of infection and the development of strategies for the treatment and prevention of hepatitis A.

1. Mechanisms of virus penetration into liver cells (hepatocytes)

The process of hepatitis A virus penetration into hepatocytes begins with its interaction with the cell membrane. HAV is a picornavirus that lacks an envelope, making it more resistant to external influences. However, despite this, the virus still uses specific cell surface molecules to penetrate the cell.

- Binding and endocytosis : The virus binds to receptors on the surface of hepatocytes , initiating endocytosis —a process in which the cell engulfs the virus into a resulting vesicle (endosome). This step is crucial for infection, as the virus must enter the cell's cytoplasm to release its genetic material and begin replication.

2. The role of cellular receptors (e.g., C1q receptor , HAVcr1) in the infection process

Penetration of the hepatitis A virus into hepatocytes requires interaction with cellular receptors that specifically recognize viral particles and trigger their internalization. The best-studied receptors playing a role in this process include:

- C1q receptor : This receptor, part of the complement system, is involved in the inactivation of pathogens. Some studies have shown that the C1q receptor may serve as a molecule through which the hepatitis A virus enters cells, binding to the virus and facilitating its endocytosis in hepatocytes . This process may be important during the initial stages of infection .

- HAVcr 1 (hepatitis A virus receptor): Another important receptor for HAV is HAVcr 1 (hepatitis A virus cellular HAVcr 1 (HAV receptor 1), a transmembrane protein, exhibits specific activity against the hepatitis A virus and promotes its binding to the hepatocyte cell membrane , allowing the virus to enter the cell. The role of HAVcr 1 in infection demonstrates the virus's specificity for liver cells, as this receptor is expressed primarily in hepatocytes , explaining their vulnerability to viral infection.

- The importance of these receptors: Although the exact mechanism of HAV interaction with these receptors is not yet fully understood, it has been proven that the C 1 q and HAVcr 1

AMERICAN ACADEMIC PUBLISHER
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receptors play a key role in providing the virus with a site for cell entry. This process is critical for the further spread of infection in the body [5,6,8,15] .

3. Processes occurring inside the cell after the introduction of the virus (replication, assembly of viral particles)

After the hepatitis A virus enters a cell and releases its genome into the cytoplasm, a complex process of viral replication and assembly begins. This process involves several important stages:

- Viral RNA Replication: Within the cell, viral RNA functions as mRNA , initiating the translation of viral proteins and serving as a template for replication. The HAV genome is a single-stranded, positively oriented RNA that can be immediately used by cellular ribosomes to synthesize a polyprotein . The polyprotein is then cleaved into several viral proteins, including structural and non-structural proteins that participate in replication and the assembly of new viral particles.

- Viral protein synthesis: Cell ribosomes begin synthesizing the viral proteins needed to form a new virus. This includes both structural proteins (e.g., VP 1, VP 2, VP 3, and VP 4), which make up the viral capsid , and nonstructural proteins, which ensure viral RNA replication and other aspects of the viral life cycle.

- Viral RNA Replication: After polyprotein synthesis and cleavage, viral RNA is replicated. The positive strand of RNA is used as a template for the synthesis of the negative strand, which then serves as a template for further synthesis of positive RNA molecules, which will be used as mRNA for translation or as genomic molecules for packaging into new viral particles.

- Assembly of viral particles: Within the cell's cytoplasm, viral proteins and new RNA molecules assemble into new viral particles. Capsid proteins form the viral envelope, and viral RNA is encapsulated within these structures, forming mature viral particles (virions).

- Exocytosis : Once new viral particles are assembled, they undergo exocytosis and exit the cell to infect new hepatocytes . Exocytosis occurs via membrane vesicles that fuse with the cell membrane and release the virions into the intercellular space, where they can infect other liver cells.

The interaction of the hepatitis A virus with liver cells is a complex and multi-stage process, involving viral entry into hepatocytes , the use of specific receptors for this purpose, and subsequent replication and assembly of viral particles. Understanding these molecular mechanisms is important for the development of new diagnostic and treatment methods for hepatitis A, as well as for a more complete understanding of the disease's pathogenesis.

Immune response to hepatitis A virus

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The immune response to the hepatitis A virus (HAV) plays a key role in controlling the infection and restoring the body's health. Unlike chronic forms of viral hepatitis, such as hepatitis B and C , HAV infection is usually acute and does not cause chronic disease. However, the immune response to the virus is an important mechanism for eliminating the virus from the body and preventing recurrent infections. It involves several layers of defense, from innate immunity to a specific adaptive response.

1. The role of innate immunity in response to hepatitis A virus infection

Innate immunity is the body's first line of defense against viral infections and includes various cellular and molecular components that can recognize viral pathogens before the immune system develops a more specific adaptive response. When infected with the hepatitis A virus:

- Antiviral molecules: In response to viral infections, liver cells begin to synthesize antiviral molecules such as interferons (especially type I interferon), which activate neighboring cells, increasing their resistance to the virus.

NK) Cell Response : NK cells play a crucial role in suppressing viral infection in the first days after infection by recognizing and destroying virus-infected liver cells. NK cells can recognize infected cells through their surface stress molecules or through changes in the expression of cellular receptors.

Although innate immunity provides initial protection, its role in the eventual elimination of HAV is limited. It is the adaptive immune system that provides long-term protection and recovery.

2. Mechanisms of activation and participation of T cells in the body's defense

T cells play a central role in defense against viral infections, including hepatitis A virus. In response to HAV , both CD4 + (helper) and CD8 + (cytotoxic) T cells are activated.

- CD4 + T cells: These cells help the body produce antibodies by stimulating B cells through the production of cytokines. They also help activate CD8 + T cells, which directly fight the virus.

- CD8 + T cells: Cytotoxic T cells play a key role in the elimination of virus-infected cells. They recognize and destroy hepatocytes infected with the hepatitis A virus through a mechanism dependent on antigen- presenting cells. This killing process occurs using molecules such as perforin and granzyme , which induce apoptosis of infected cells.

Thus, T-cell activation promotes both direct destruction of the virus and the strengthening of specific immune memory, which will protect the body in the event of re-infection.

3. Synthesis of antibodies and their role in virus elimination

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Antibodies produced by B cells play a vital role in protecting the body from viral hepatitis A. These molecules act by binding to viral particles and neutralizing their ability to penetrate cells, and also assist in removing the virus through phagocytosis and activation of the complement system.

IgM antibodies : IgM antibodies are usually the first antibodies produced in response to infection . These antibodies serve as a marker of recent infection, and their levels increase during the first weeks of illness. They neutralize the virus and promote its elimination from the body.

IgG antibodies : A few weeks after the onset of infection, the body begins to produce IgG antibodies , which remain in the body throughout life, providing immunity to reinfection with HAV . These antibodies play a role in long-term protection against the disease and maintain immunological memory.

In combination with T-cell activity, antibodies promote complete removal of the virus and restoration of normal liver function.

4. Possible development of an immune response and pathogenesis of inflammation in the liver

Although hepatitis A virus causes acute liver inflammation in most cases, the duration and intensity of the inflammatory process vary from patient to patient. The immune response to infection influences the development of liver inflammation [21] .

- Pathogenesis of inflammation: The hepatitis A virus causes liver inflammation through the activation of immune cells. For example, cytotoxic T cells, by destroying infected hepatocytes , promote the release of inflammatory mediators such as interleukins , which increases local inflammation in the liver. This can manifest as clinical signs such as jaundice, elevated liver enzymes, and pain in the right upper quadrant.

- The effect of inflammation on liver cells: During the process of virus elimination, hepatocyte damage occurs , which can lead to liver cell necrosis. However, unlike chronic hepatitis, in hepatitis A, liver cell destruction is mainly limited to the acute phase of the disease and does not lead to long-term liver damage.

- Remission and recovery: In most cases, after a successful immune response, liver inflammation subsides and liver tissue recovers. However, in rare cases, with severe inflammation, more severe forms of the disease, such as acute fulminant hepatitis, may develop, requiring additional attention and intervention.

The immune response to the hepatitis A virus includes both innate and adaptive defense mechanisms aimed at destroying viral particles and restoring normal liver function. The role of T cells, antibody synthesis, and liver inflammation are key components in infection control.

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Understanding these mechanisms is important for developing methods for the prevention and treatment of viral hepatitis A.

The role of genetic factors in the pathogenesis of viral hepatitis A

HAV) infection . Although most cases of the disease proceed without serious complications and result in full recovery, individual differences in the immune response can influence the clinical course of the infection. Various genetic factors can influence the body's susceptibility to the virus, the activity of the immune response, and the development of liver inflammation, which ultimately affects the severity of the disease.

1. Genetic predisposition to the severity of the disease

Genetic predisposition to viral hepatitis A may depend on various polymorphisms in genes that regulate the immune response. The most important of these genes are those encoding components of innate immunity, such as receptors for viral particles, as well as molecules involved in inflammation and apoptosis .

- Genetic variations in immune receptors: For example, there is evidence that polymorphisms in genes encoding cellular receptors, such as HAVcr 1 (the receptor for the hepatitis A virus), can influence susceptibility to viral infection and the clinical course of the disease. Depending on genetic differences in these receptors, the ability of the virus to penetrate liver cells can vary, which in turn affects the level of viral load and the extent of liver damage.

- Genes regulating inflammation: Polymorphisms in genes that regulate the inflammatory response, such as TNF - α (tumor necrosis factor), IL -6 (interleukin 6), and other cytokine molecules involved in the activation of immune cells, are important . Genetic variations that enhance or reduce inflammation can determine the degree of liver damage during infection and influence the development of disease symptoms, such as jaundice and elevated liver enzymes.

- Genetic predisposition to autoimmune reactions: In some cases, increased inflammation can lead to autoimmune liver damage, which worsens the disease. Genetic changes in the autoimmune regulatory system can lead to more severe liver damage, especially in people with a predisposition to autoimmune diseases.

2. The influence of host genetic factors on the course of infection

The host's genetics significantly influence not only susceptibility to the virus but also the course of the infection itself. This can manifest itself in several ways.

- Immune cell response: Genetic differences in immune cells, such as T cells and macrophages, can influence the effectiveness of the immune response. For example, variations in molecules involved in antigen presentation (e.g., genes encoding MHC molecules) can alter the body's

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ability to adequately recognize and destroy the virus. This can lead to differences in the rate and efficiency of viral clearance, as well as in the level of inflammation in the liver.

- Genetic predisposition to acute and chronic complications: Although chronic disease associated with viral hepatitis A is extremely rare, in some cases the infection can lead to serious complications, such as fulminant hepatitis (acute, severe liver injury). Genetic predisposition may influence the likelihood of such complications. For example, mutations in genes that regulate cellular apoptosis and liver cell stress responses may contribute to more rapid liver damage and the development of severe forms of the disease [17,18] .

- Individual differences in drug metabolism: Genetic differences in metabolism can also influence the efficacy and toxicity of drugs used to treat viral infections, including hepatitis. For example, polymorphisms in genes regulating enzyme activity, such as CYP450 , can affect the pharmacokinetics of drugs used to treat hepatitis A virus, which is important for individualized therapy.

Genetic factors play a key role in the pathogenesis of viral hepatitis A, determining both the body's susceptibility to the virus and the clinical course of the disease. Polymorphisms in genes regulating the immune response can influence the level of inflammation, the extent of liver damage, and the overall severity of the disease. Understanding the role of these genetic factors may help develop more effective diagnostic and treatment methods, as well as personalized therapeutic strategies for patients with hepatitis A.

Modern approaches to the treatment and prevention of viral hepatitis A

Viral hepatitis A (HAV) is an acute infectious disease caused by the hepatitis A virus (HAV), which is transmitted via the fecal-oral route. Although there is no specific antiviral therapy for HAV, prevention and control of the disease have improved significantly thanks to vaccination and the development of new therapeutic strategies. Let's review the main approaches to the treatment and prevention of viral hepatitis A.

1. Development of vaccines and their molecular mechanisms of action

Vaccination is the most effective method for preventing viral hepatitis A. Several HAV vaccines have been developed and are being successfully used , providing long-term protection against infection. These vaccines are inactivated viruses or recombinant vaccines that stimulate the immune response without the risk of infection.

- Inactivated vaccines: This is the most common type of HAV vaccine. The vaccine contains inactivated (killed) viral particles, which, when introduced into the body, activate the immune response but do not cause disease. This vaccine stimulates the production of antibodies against the virus, which provide protection against subsequent exposure to the virus. Examples of such vaccines include Havrix and Vaqta , which are used in most countries worldwide.

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- Recombinant vaccines: Recombinant vaccines, such as vaccines based on viral proteins (e.g. capsid protein HAV vaccines provide immunity by stimulating a specific response to a viral antigen. These vaccines are created using recombinant DNA technology and are characterized by high efficacy and safety.

Molecular mechanisms of vaccine action: Hepatitis A virus vaccines stimulate the body's immune response, which includes the activation of T and B cells, antibody production, and the development of immune system memory. The primary defense mechanism is the production of antibodies against viral antigens, which prevents the virus from penetrating into the body's cells. The immune response also includes the activation of cells capable of destroying infected cells and suppressing viral spread.

2. Potential molecules and therapeutic strategies aimed at inhibiting viral replication

Currently, there are no specific antiviral drugs for the treatment of viral hepatitis A, as the disease is usually mild to moderate and self-limiting . However, in recent years, potential molecules and therapeutic approaches that could be used to inhibit viral replication, particularly in cases of more severe infection, have been studied.

Antiviral Molecules: One promising area is the search for molecules capable of suppressing viral replication at the level of cellular infection. Although no antiviral drugs have been developed for HAV to date, a number of molecules that affect replication stages of other RNA viruses could be adapted to combat hepatitis A virus. For example , antiviral drugs such as ribavirin , which are used to treat other viral infections, could be considered as potential treatments, although further clinical trials are needed for their use in the context of hepatitis A.

Therapeutic antibodies: Developing monoclonal antibodies that target the hepatitis A virus is one potential approach to combating the disease. These antibodies could either neutralize the virus directly or enhance the host's immune response against infection. For example, research suggests that monoclonal antibodies targeting molecules involved in viral entry into liver cells (e.g., HAVcr 1 receptors) may be effective in preventing infection.

- Molecules that affect the viral replication process: At the molecular level, HAV replication in liver cells involves multiple steps, from viral entry into the cell to the assembly of new viral particles. Drugs that can inhibit key enzymes, such as viral RNA polymerases or proteases, could form the basis for the development of specific antiviral agents. While such drugs are not yet available for HAV , the concept of inhibiting viral replication using small molecules is being actively explored for other viral infections and could be adapted for HAV [22,23,24] .

- Interferon use: Viruses, including HAV , often activate the body's interferon system, which helps fight infection. In some cases, drugs that activate interferon production or enhance their effects may be studied. Interferons may help strengthen the immune response against the virus, especially in more severe cases.

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Prevention of viral hepatitis A relies primarily on vaccination, which is a highly effective and reliable preventative measure. Current vaccines against HAV provide long-term protection against infection and reduce the incidence of the disease in the population. At the same time, new therapeutic molecules and drugs aimed at inhibiting viral replication may be developed in the future. Further research into the molecular mechanisms of viral infection and the immune response to HAV will lead to the development of more effective treatments and prevention methods for viral hepatitis A.

CONCLUSIONS : Viral hepatitis A (HAV) is a major infectious disease caused by the fecal-oral hepatitis A virus (HAV), which primarily affects the liver. The primary molecular mechanisms of HAV pathogenesis include viral entry into hepatocytes, its replication and assembly of new viral particles, as well as interaction with cellular receptors such as HAVcr1 and C1q. The virus induces an immune response, including activation of innate immunity and the production of specific antibodies, which play a key role in viral elimination. At the same time, the pathogenesis of hepatitis A is also associated with inflammatory processes in the liver, which can lead to varying degrees of organ damage.

Although HAV infection is generally mild to moderate and resolves spontaneously, the importance of understanding the molecular mechanisms of viral pathogenesis is undeniable. This knowledge is essential for improving diagnostics, developing more accurate methods for detecting infection, and developing new therapeutic approaches that can reduce the severity of the disease and prevent complications. Of particular importance is the search for molecules that can block viral replication or enhance the immune response.

Further research into the molecular aspects of viral hepatitis A is an important area of medical science. This research will not only deepen our understanding of the disease's pathogenesis but also open up prospects for the development of new vaccines and therapeutic agents aimed at improving the treatment and prevention of HAV. The development of effective antiviral drugs, as well as improvements to existing vaccination methods, could significantly reduce the incidence of the disease and improve the quality of life of patients.

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