



MINI REVIEW

Alteration of cell junctions during viral infection

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Abstract

Cell junctions serve as a protective barrier for cells and provide an important channel for information transmission between cells and the surrounding environment. Viruses are parasites that invade and commandeer components of host cells in order to survive and replicate, and they have evolved various mechanisms to alter cell junctions to facilitate viral infection. In this review, we examined the current state of knowledge on the action of viruses on host cell junctions. The existing evidence suggests that targeting the molecules involved in the virus-cell junction interaction can prevent the spread of viral diseases.

Introduction

Emerging and re-emerging infectious diseases pose an increasing threat to global health.^{1–3} Clarifying the molecular mechanisms underlying viral infection can improve the detection, control, and treatment of viral diseases.^{4–8} Viruses are noncellular life forms composed of proteins and a DNA or RNA genome wrapped in a protective protein coat. As parasites, viruses infect an organism and self-replicate using host cellular components.^{9–11} The first step in this process is invasion of target cells in the host tissue, which typically comprises a layer of epithelial cells connected via intercellular junctions. These junctions allow the transmission of information between cells and the surrounding environment and serve as a protective barrier against noxious stimuli.¹² The attachment of a virus to the host cell membrane can alter or destroy junctional proteins, leading to cell infection.^{13–16}

Mammalian cell junctions are classified based on their function as tight junctions, anchoring junctions (adherens junctions, desmosomes, and hemidesmosomes), and communicating (gap) junctions.^{17,18} Tight junctions are present

in the gastrointestinal epithelium, bladder epithelium, brain capillary endothelium, and in testicular supporting cells, and form a branching network of sealing strands, each of which contains a row of transmembrane proteins that are inserted into the bilayers of the plasma membrane and are connected to other proteins through their extracellular domains.^{19–21} Tight junctions do not constitute a static barrier, and are highly dynamic structures whose components (eg, occludin) undergo continuous turnover.²² Anchoring junctions provide a mechanical connection between cells; they can be one of two types depending on their constituent cytoskeletal proteins.^{23–26} Desmosomes and hemidesmosomes are linked to intracellular filaments, whereas adherens junctions are linked to actin.²⁷ Adherens junctions serve as anchors that connect the actin cytoskeletons of adjacent cells via cadherin.²⁸ These different types of anchoring junctions form an epithelial barrier that controls paracellular transport. Gap junctions enable communication between adjacent cells by allowing the movement of small molecules and ions in the cytoplasm in response to various signals. They also play an important role in

regulating cell proliferation and differentiation during embryonic development.^{29–33}

The major functions of cell junctions are to strengthen mechanical connections and permit the exchange of materials between cells to maintain physiological homeostasis. In this review, we summarize recent studies investigating the action of viruses on host cell junctions (Fig 1) and suggest that the molecules involved in this interaction are potential therapeutic targets for the treatment of viral diseases.

Rotavirus (RV) and tight junctions

Rotavirus (RV) is the most common cause of severe vomiting and diarrhea in infants and young children.³⁴ RV is an enterovirus with a wheel-like structure that is assembled in the lumen of the endoplasmic reticulum (ER); sub-viral particles germinate until the cells are lysed, with the mature virus remaining in the ER. RV enters cells via receptor-mediated calcium-dependent endocytosis, which causes calcium ions (Ca^{2+}) to move from the endocytic vesicle to the cytoplasm.³⁵ Once the Ca^{2+} concentration in the endocytic vesicle decreases below a certain threshold, the coat proteins of endocytic vesicles are degraded and the virus enters the cytosol.³⁶

The tight junction protein occludin is distributed in the margins of adjacent cells under normal conditions.

However, this arrangement is perturbed upon RV infection.³⁷ For instance, in infantile diarrhea caused by RV, the structure and function of tight junctions are disrupted, leading to changes in cell membrane permeability that enable RV to invade host cells.³⁸ In Caco-2 cells, the distribution of the tight junction proteins occludin and claudin-1 was altered by incubation with RV.³⁹ Meanwhile, MDCKII cells were infected with RV through the basal surface, suggesting that this area harbors RV receptors.⁴⁰ The primary site of RV infection is along the edge of intestinal epithelial cells.^{41,42} The binding of the RV coat protein viral protein 8 to receptors located on the intestinal cell surface leads to the destruction of tight junctions by activating the host cell RhoA/ROCK / MLC signaling pathway, which stimulates the translocation of viral receptors from the basolateral to the apical surface and further increases RV invasion.^{43,44} RhoA and its downstream effector Rho kinase (ROCK) are key molecules that mediate destruction of tight junction when RV infection.⁴⁵ Thus, disruption of tight junctions may play an important role in the pathogenesis diarrhea caused by RV.⁴⁶

Hepatitis C virus (HCV) and tight junctions

Hepatitis C is an infectious disease caused by HCV that mainly affects the liver.⁴⁷ HCV is a small, enveloped, positive-strand RNA virus that spreads through tight

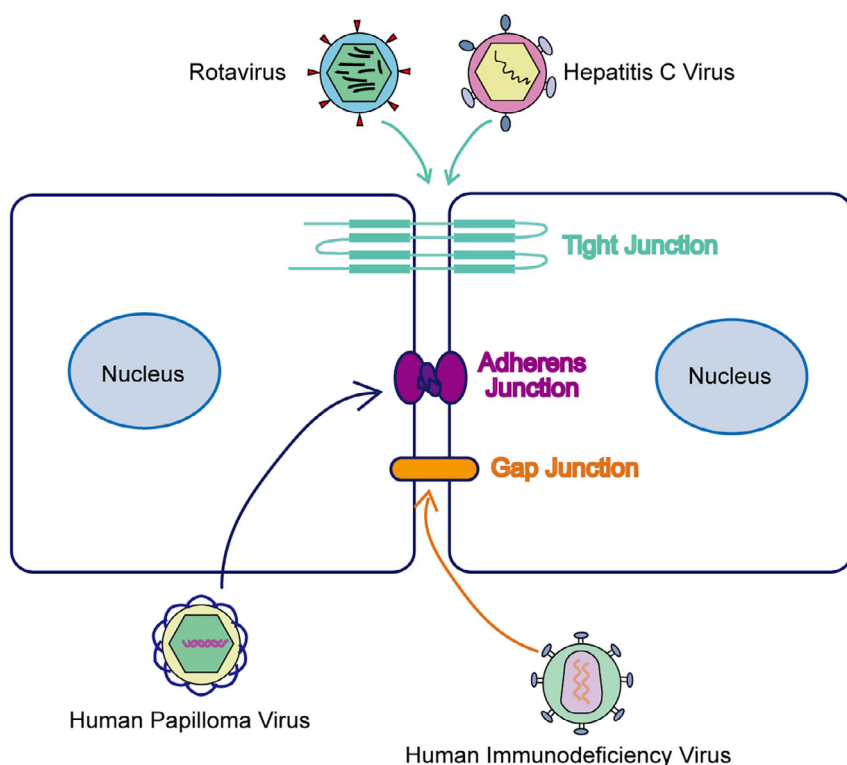


Figure 1 Different viruses invade host cells through specific cell junctions. Rotavirus and Hepatitis C virus disrupt the structure and function of tight junction. Human papilloma virus-induced changes in the organization of adherens junction proteins. Human immunodeficiency virus spread damaged signals to the adjacent cells through gap junction.

junctions and infects liver cells. Cellular entry of HCV is accomplished by its binding to tight junction-associated coreceptors on hepatocytes and subsequent endocytosis.⁴⁸ The tight junction proteins occludin and claudin-1 are the key molecules involved in this process. HCV was shown to readily infect and escape hepatocellular carcinoma (HCC) cells that were modified to express claudin-1 and occludin.⁴⁹ The GTPase protein dynamin II plays an important role in HCV internalization by forming a complex with occludin, which serves as a bridge between dynamin II and viral particles.⁵⁰

The tetraspanin molecule CD81 and human scavenger receptor class B member 1 are HCV receptors that cooperate with tight junction proteins to facilitate HCV entry into liver cells.⁵¹ Viral particles first bind to glycosaminoglycans or low-density lipoprotein receptor on the host cell.⁵² This is followed by interaction with claudin-1 at tight junctions and CD81 and the lateral migration of the virus through the plasma membrane, which continues until the virus has recruited a sufficient number of receptors to initiate the signaling required for internalization.⁵³ The combination of HCV and CD81 will promote the movement of the virus to tight junction associated proteins claudin-1 and occludin-1. Intracellular CD81 and claudin-1 are colocalized on the plasma membrane and transported on the plasma membrane. CD81 and claudin-1 containing vesicles fused to Rab5 expressing endosomes.^{54,55} However, it remains to be determined whether claudin or occludin protein mediate endocytosis of the virus.⁵⁶ Clarifying the precise role of tight junction proteins at different stages of HCV infection can inspire new strategies to prevent and treat hepatitis C.

Human papilloma virus (HPV) and adherens junctions

HPV is a spherical DNA virus that stimulates the proliferation of squamous epithelial cells of skin mucosa in humans.⁵⁷⁻⁶¹ Infection of cervical epithelial cells with HPV leads to cervical cancer in women.⁶² This is a result of a loss of cell adhesion and polarity, allowing the invasion and migration of tumor cells.⁶³⁻⁶⁵ This metastatic transformation involves alterations in adherens junction proteins that undermine epithelial cell structure.⁶⁶ During the epithelial-to-mesenchymal transition, epithelial cells lose polarity and their connection to adjacent cells and the basement membrane, which increases their migratory and invasive capacities.⁶⁷ At the molecular level, this process involves the rearrangement of adherens junction proteins including β -catenin, which links E-cadherin to the actin cytoskeleton and is involved in cancer-related signaling and inflammatory responses.⁶⁸⁻⁷¹ Thus, HPV-induced

changes in the organization of adherens junction proteins promotes infection.

Human immunodeficiency virus (HIV) and gap junctions

HIV is the causative agent of acquired immunodeficiency syndrome (AIDS).⁷²⁻⁷⁴ During infection, HIV targets the cytomembrane and penetrates the epithelial barrier by destroying cell junctions.⁷⁵ The blood-brain barrier (BBB) is a highly selective semi-permeable boundary that separates circulating blood from extracellular fluids in the brain and central nervous system (CNS).^{76,77} The pericytes and perivascular astrocytes that constitute the BBB differentially modulate neurovascular function in neuroAIDS pathogenesis.⁷⁸ Gap junctions, which are composed of connexin proteins, are abundant in the cells of the BBB and mediate intercellular communication in the CNS.

Astrocytes are the most widely distributed cells in the mammalian brain and the largest type of glial cell. Adjacent astrocytes are separated by a narrow space containing interstitial fluid. HIV uses channels containing connexins including connexin 43 in astrocytes to spread toxic factors to and induce apoptosis in uninfected cells, even in the absence of active viral replication.⁷⁹⁻⁸¹ Although the rate of viral replication in astrocytes is too low to be detected, disruption of connexin channels by HIV can exacerbate neurological pathophysiology.⁸² This opens the possibility of mitigating HIV-associated neurological dysfunction by targeting gap junctions in astrocytes.

Pericytes are located below the brain microvascular endothelial cells, covering approximately 30% of the abluminal surface.⁸³ Pericytes in the human brain express C-X-C chemokine receptor type (CXCR)4 and CCR5, which are the two major co-receptors participating in the HIV-1 infection process. CXCR4 and CXCR5 contribute to HIV-induced CNS impairment when the BBB is compromised, which is associated with increased microvascular permeability.⁸⁴ Thus, gap junctions in pericytes mediate HIV-induced loss of BBB integrity. Additionally, although HIV infects only a small fraction of pericytes, the damage that it inflicts is amplified by gap junctions that spread viral factors to adjacent uninfected cells (Fig 2).

HIV does not primarily disrupt the cell junction of the BBB. It also has a disruptive effect on the cell junction of other tissues. HIV-1 can damage the human retinal pigment epithelium (HRPE) barrier. HIV-1 particles can induce cells to release proinflammatory cytokines IL-6 and MCP-1, which down-regulate the expression of ZO-1 and claudin-1 in the HRPE barrier, leading to the destruction of HRPE cell junction and impaired cell monolayer integrity.⁸⁵⁻⁸⁷ HIV also disrupts cellular junctions in oral epithelial tissue. The long-term interaction between HIV

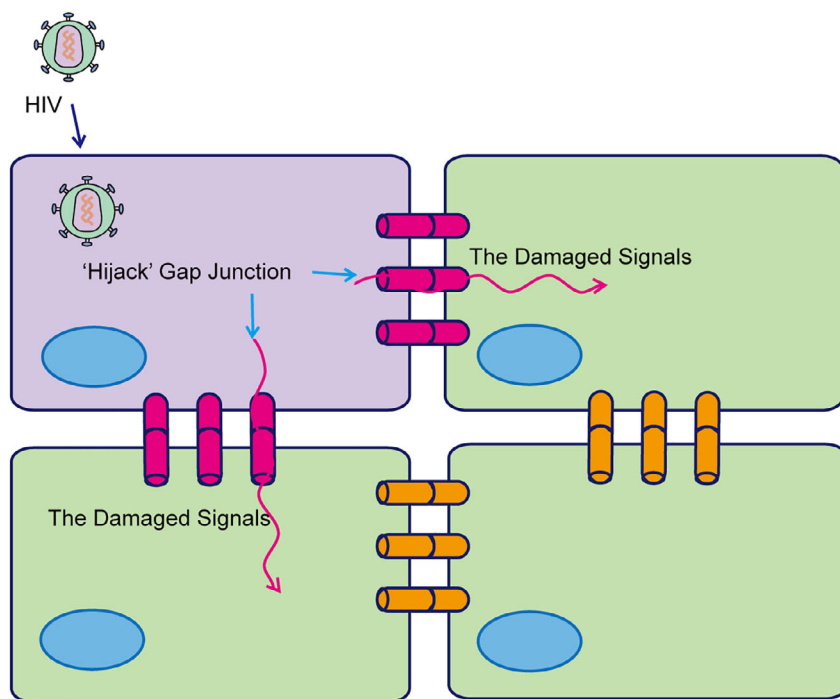


Figure 2 HIV hijack gap junction to spread toxic factors and damaged signals to the adjacent uninfected cells. In pericytes, although HIV only infects a small number of cells, the damage is amplified by the spread of viral factors to adjacent uninfected cells via the gap junction channel. (□The purple cell) HIV infected cell, (□The green cells) Uninfected cell, (□The yellow gap junctions) Normal gap junction, and (□The purple gap junctions) HIV “Hijacked” gap junction.

capsid protein and polarized oral epithelial cells destroys tight junctions and adherens junctions of epithelial cells through the mitogen-activated protein kinase signaling pathway.⁸⁸ HIV also infects intestinal epithelium, gastric epithelium and other tissues by affecting cell junctions. It is of great significance to study the key sites of cell junctions during HIV invasion.^{89,90}

Conclusions

Nonenveloped viruses initiate the infection cycle through binding of their capsid proteins to a viral receptor on the surface of target cells. This activates intracellular signaling pathways, which is often accompanied by the lateral translocation of the virus across the plasma membrane to cell junctions prior to their internalization via caveolar endocytosis. The interaction of the virus with specific cell junction proteins such as occludin, claudin, or connexin suggests the possibility that proteins at the precise point of cellular entry can be targeted by therapeutics. Blockers of these cell junction proteins can provide protection against viral infection. The mechanism by which cell junctions amplify viral invasion signals and dysfunctional signals increases the rates of viral amplification, so these cells with this particular mechanism should be detected and may be applied to the expansion and delivery of drug therapy signals.^{91–94} On the other hand, as-yet unidentified junctional proteins could contribute to the process of cell invasion by viruses. Elucidating the mechanisms by which viruses exploit host

cell junctions to propagate can provide a basis for the development of effective strategies to treat viral infectious diseases.

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Disclosure

The authors have no conflicts of interest to declare.

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