



## Review Article

## Exploring the Lifecycle, Pathophysiology, and Potential Therapeutic Applications of the Reovirus

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## ABSTRACT

The Reoviridae family of double-stranded RNA viruses includes Reovirus. Both humans and animals might become sick from it. Even though they are often benign, certain strains have been connected to significant illnesses. This review investigates the virus's structure, replication, pathogenesis, clinical significance, and potential therapies. Its unusual capsid form is made up of a segmented genome that encodes twelve proteins and two concentric protein shells. Replication involves uncoating, receptor binding, endocytosis, genome transcription, and cytoplasmic translation. Reovirus masterfully manipulates its host's cellular functions, inducing apoptosis and stress responses that help it spread and multiply. Recently, encephalitis, myocarditis, and maybe even certain cancers have been linked to reovirus, which often produces mild respiratory or gastrointestinal symptoms. To fully understand the viral-host interactions producing these illnesses, further research is necessary. Particularly, the reovirus has promise for oncolytic virotherapy. Whether used alone or in conjunction with other medicines, a range of cancer types have showed positive outcomes in clinical studies. In essence, reovirus is a versatile pathogen that has intimate relationships with its hosts. To realize its therapeutic potential and shed light on its pathogenesis, one must have a complete grasp of its molecular and cellular connections. Unlocking the virus's potential is necessary to predict how it will impact both human and animal health.

## INTRODUCTION

Several more intriguing viral illnesses share the Reoviridae family with reovirus. Since the virus was first identified in the respiratory and gastrointestinal systems and was not previously related with any disorders, it was given the moniker "respiratory enteric orphan virus," abbreviated to "reovirus" [1]. But recent evidence suggests Human Papillomavirus (HPV) may infect many other species and cause a wide variety of diseases in both people and animals [2]. Reoviruses are categorized as non-enveloped because they lack a lipid coat. Instead, a protein capsid that is robust and durable protects its DNA [3]. The segmented double-

stranded RNA (dsRNA) that makes up the viral genome of reoviruses sets them apart from other viruses. The genome segmentation produces several proteins necessary for viral replication, pathogenicity, and interactions with host cells [4]. Researchers first identified reovirus in the 1950s from human respiratory and intestinal samples. Reovirus was found to be a common pediatric virus that often caused minor respiratory and gastrointestinal symptoms, according to an early study. Recent advances in molecular techniques and research methodologies have improved our understanding of the

genetic diversity and clinical significance of reoviruses [5]. Reovirus may infect various hosts, including reptiles, birds, and mammals. It is pervasive in the environment, and susceptible creatures may take it up from surfaces including soil, water, and faces. Even while the majority of reovirus infections are self-limiting and recover without treatment, certain strains of the virus have been associated to more severe conditions such viral encephalitis, myocarditis, and even cancer [6, 7]. The virus penetrates host cells by receptor-mediated endocytosis, whereupon it releases its genetic material into the cytoplasm of the host cell. Reovirus depends on the host's machinery for genome replication, protein synthesis, and viral particle assembly when it enters a cell [8]. It possesses a number of mechanisms that enable it to influence host cell functions and evade immune system attacks in addition of effectively multiplying and spreading [9]. Recently, there has been a lot of discussion about the possible use of Reovirus in the treatment of cancer. Because of its natural ability to selectively infect and multiply within cancer cells while sparing normal ones, reovirus has been utilized in oncolytic virotherapy [10]. Therapeutic based on reovirus have shown promising results in clinical trials for treating a variety of cancer types, providing a foundation for further research and refinement of this treatment strategy [11]. Reovirus is an intriguing and versatile pathogen that can infect a wide range of hosts and manifest itself in a variety of ways within the body. Reovirus study offers the potential to revolutionize cancer treatment and provide a fresh perspective on viral pathogenesis [12]. If researchers continue to work on the complex issues raised by Reovirus and the animals it infects, this review paper may be about an intriguing virus and its effects on human and animal wellbeing.

### Lifecycle of Reovirus

Reoviruses carry out a series of precisely timed steps in the cytoplasm of their host cells in order to reproduce. The particles enter the host cell and attach to receptors there to begin the replication cycle (Figure 1) [13]. The properties of these receptors may be influenced by both the host species along with the kind of cell. After adhering, particles are internalized by the host cell by receptor-mediated endocytosis. Once absorbed, these particles undergo a process known as uncoating. Only the protein capsid around the viral DNA may be removed in order to access it. Two examples of situations that might start the uncoating process are low pH or the presence of proteolytic enzymes in the endosomes [14]. The transcription and translation of the viral genome take place once the viral DNA has been released into the cytoplasm of the host cell. The genome comprises double-stranded RNA (dsRNA) segments, each

of which codes for a unique viral protein [15]. The viral RNA-dependent RNA polymerase, a component of the viral core, creates messenger RNAs (mRNAs) from the dsRNA segments. These mRNAs are read by the host cell's machinery, which then converts them into viral proteins. Reovirus copies its DNA through "genome replication through a dsRNA intermediate" [16]. The production of a complimentary copy of each dsRNA segment by the viral RNA-dependent RNA polymerase results in a replication intermediate called "panhandle" or "tightly bound" dsRNA. This panhandle dsRNA serves as a template for synthesizing fresh genomic dsRNA segments. As replication progresses, newly generated genomic dsRNA segments and the viral proteins are combined to form viral particles. Piroplasmids are specialized cytoplasmic inclusions where assembly takes place [17]. Within these structures, the viral proteins and dsRNA segments come together to form contagious virus particles. Once assembled, reovirus particles break off from the host cell. Cell lysis, which includes rupturing the host cell membrane, or non-lytic processes like budding or exocytosis may be used in the release process. Different host cell types and reovirus strains may produce different release mechanisms [18]. The replication process's extraordinarily dynamic and tightly regulated character results from several intricate interactions between viral components and host cell factors. Reovirus has the ability to control cellular machinery and govern host cell functions, allowing it to easily multiply and propagate within its host (Figure 2) [19].

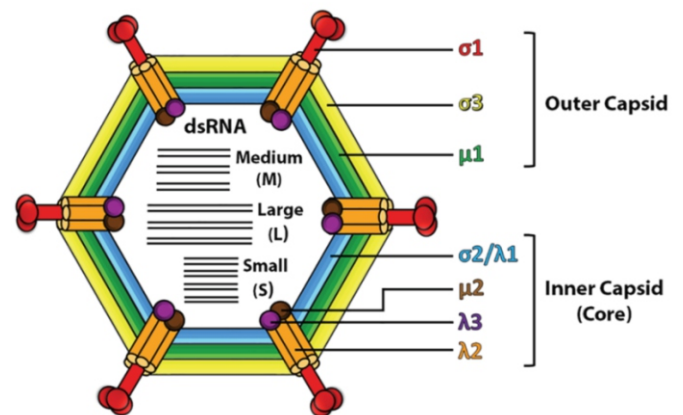
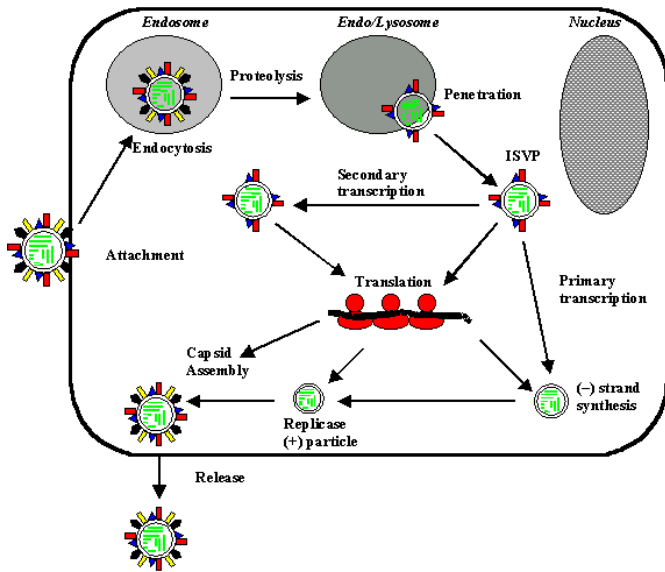


Figure 1: Structure of Reovirus [13]



**Figure 2:** Lifecycle of Reovirus [19]

### Clinical Prevalence of Reovirus

Reovirus is clinically relevant since it may infect both humans and animals. Despite reovirus infections often being regarded as mild and self-limiting, certain strains of the virus have been associated with more severe clinical signs [20]. Children typically have mild respiratory and gastrointestinal ailments from diseases of the digestive and respiratory systems. Possible side effects include fevers, coughs, runny noses, sore throats, diarrhea, and vomiting. Without the need for medical attention, many infections often go away on their own. Certain reovirus strains have been related to viral encephalitis, or brain inflammation [21]. Reovirus encephalitis may result in fever, headache, altered consciousness, convulsions, and localized neurological abnormalities. Although rare, reovirus encephalitis may be highly dangerous and need hospitalization and supportive care when it does happen. Myocarditis, an inflammation of the heart muscle, has been associated with this virus. Heart failure, shortness of breath, palpitations, and chest pain are all signs of reovirus myocarditis [22]. For serious cases, hospitalization and heart care experts may be required. Due to its emphasis on oncolytic virotherapy, reovirus has generated attention as a potential therapeutic agent. Oncolytic virotherapy employs reovirus because it has the potential to specifically infect and multiply within tumor cells, eventually destroying those cells. Clinical research evaluating reovirus-based therapy, either alone or in combination with other modalities, have shown promising responses in a variety of cancer types, including those of the head and neck, ovaries, and pancreas [23, 24]. It has been linked to various chronic diseases, including type 1 diabetes and celiac disease, according to recent research.

Although the precise mechanisms are not fully understood, reovirus infection may result in immune reactions that help in the development or progression of several illnesses [25].

### Various Therapeutic Uses of Reovirus

Reovirus has a wide range of prospective medical applications. One of its particular characteristics that makes it an attractive therapeutic target is its ability to infiltrate and proliferate primarily within cancer cells while sparing normal cells. As it has received substantial research as a possible oncolytic virus for the treatment of cancer [26]. In oncolytic virotherapy, viruses are utilized to specifically target and eradicate cancer cells. Reovirus finds it simple to replicate within tumor cells, lyse them, and release viral particles, which spreads the infection. Clinical investigations have shown that reovirus-based therapies are both safe and efficient against cancer. Reovirus-based therapies may be used alone or in conjunction with other approaches like chemotherapy or immunotherapy [27]. By inducing the release of tumor antigens, immunogenic cell death brought on by reovirus infection may lead to an immune response against tumors. This immune response may enhance the efficacy of therapies like chemotherapy and immunotherapy. Clinical studies are now looking at the possible additive advantages of combining Reovirus with other therapeutic modalities [28]. Reovirus-based vaccination research has shown promising outcomes in preventing viral infections and inducing protective immune responses. Because of its peculiar characteristics, such as its ability to trigger innate and adaptive immune responses, Reovirus is an intriguing vaccine candidate. In tests against viruses including rotavirus, HIV, and influenza, vaccines created utilizing Reovirus have showed promise. Reovirus vectors may be used to provide immune responses against specific infections or tumor antigens [29]. Its ability to infect and multiply within target cells makes it a potential vehicle for the delivery of therapeutic genes to tumors or specific organs. Research into the delivery of therapeutic genes to target cells for the treatment of cancer, immunological regulation, and other disorders has focused on reovirus vectors. This virus has shown potential as an antiviral treatment for a variety of viral diseases. (Table 1)[30]. RSV, HPV, and HSV are among them. Reovirus may stop the spread of these viruses by inducing a strong immune response. Reovirus may be employed as a therapeutic agent in the treatment of cancer, the creation of vaccines, gene therapy, and antiviral therapy, among other conditions. It is predicted that continued research and clinical investigations will contribute to a better knowledge of the efficacy, safety, and appropriate use of reovirus-based therapies in a variety of disorders [31].

**Table 1:** Overall prevalence of human toxoplasmosis in district Gujranwala, Punjab, Pakistan

Reovirus Therapeutic Applications	Description	References
Cancer Treatment with Oncolytics	Selectively locating and eliminating cancer cells	[3]
Immunotherapy Immune Stimulation	The immune system's responses against tumors are activated	[11]
Chemotherapy and Combination Therapy	Increased chemotherapeutic sensitivity of tumor cells	[15]
Viral infection treatment	Effects that might be antiviral against certain viruses	[21]
Examining Autoimmunity Conditions	Study of virus-host interactions in autoimmune disease	[27]
Vector for Vaccines and Gene Therapy	Therapeutic genes or vaccination antigens delivery	[32]

### Manipulation of apoptosis

Apoptosis, a process of programmed cell death in the host cell, may be used by reovirus to spread and survive. These may actively suppress apoptosis by avoiding premature cell death in order to limit viral multiplication. To stop apoptotic signaling and the activation of pro-apoptotic proteins, the virus employs a number of strategies [32]. By inhibiting the activation of Bcl-2 family members that promote apoptosis or by preventing the release of cytochrome c from mitochondria, reovirus, for example, may obstruct the intrinsic apoptosis pathway. By blocking apoptosis, the host cell's normal dying process, reovirus ensures host cell survival and continued infection. In response to apoptotic signals, reovirus may increase its ability to reproduce by activating a number of cellular survival pathways. One technique activates the PI3K/Akt signaling pathway, which promotes cell survival and anti-apoptosis. This also encourages cell survival by inhibiting the phosphorylation and subsequent inactivation of pro-apoptotic proteins including Bad and caspase-9 by increasing PI3K/Akt signaling. It may interact with death receptors, such as tumor necrosis factor receptor 1 (TNFR1), to modify apoptotic signaling. Reovirus infection has been demonstrated to enhance the number of cancer cells undergoing apoptosis when TRAIL is present [34]. When a reovirus infection activates TRAIL 9, these cells may experience caspase activation and death. For example, reovirus infection may trigger apoptosis in certain cancer cells by triggering internal and extrinsic apoptotic pathways. The strain of Reovirus used to cause apoptosis may interact with the genetic and molecular characteristics of the host cell. When within a host cell, reovirus may alter apoptotic pathways to guarantee its survival and propagation [35].

### Therapeutic agent in oncolytic virotherapy

Reovirus has become a potent therapeutic tool in oncolytic

virotherapy, which utilizes viruses to specifically infect and kill cancer cells. Its ability to proliferate inside cancer cells while sparing healthy ones is a big advantage since invasive cancer cells reproduce selectively [36]. The virus prefers cancer cells as its primary host for infection and reproduction because these cells often contain an active Ras signaling pathway. This kind of focused replication leads to oncolysis, the death of cancer cells without damaging healthy tissue. When the virus multiplies within cancer cells, destroying them and releasing their progeny, direct oncolysis is induced. The viral particles that are produced when tumor cells are lysed may infect surrounding cancer cells, spreading the infection and enhancing the anti-tumor effect [37]. Another outcome of reovirus infection is the immunogenic death of infected cells, which causes the release of tumor antigens and the activation of the immune system to fight cancer cells. It has been shown that reovirus infection stimulates the immune system, triggering anti-tumor immunological responses. It activates innate immunity cells including dendritic and natural killer (NK) cells to start and direct immune responses against tumors. Reovirus infection may enhance the presentation of tumor antigen to immune cells, activating T lymphocytes specific to the tumor [38]. This immune activation assists in eliminating cancerous tumor cells, both infected and uninfected, and may leave a lasting memory of the disease. Reovirus, when combined with other drugs, may enhance the efficacy of cancer therapy. When used with other medications like chemotherapy, radiation treatment, or immunotherapies, it has shown to have synergistic effects. Combining Reovirus with other cancer treatment options may improve immune responses, tumor cell eradication, and resistance mechanisms. Clinical research employing Reovirus has shown a favorable safety profile. Experts have concluded that Reovirus is a naturally occurring virus in humans since the majority of individuals have been exposed to it throughout infancy without experiencing any severe symptoms [39]. Due to its low toxicity, reovirus is a desirable candidate for use in therapeutic settings. Reovirus-based anticancer drug development requires a number of processes designed to maximize the virus's therapeutic potential and harness its oncolytic capabilities (Table 2)[40].



**Table 2:** Agents Used in Oncolytic Virotherapy, Virus types, Mechanism and mode of action

Therapeutic Agent	Virus Type	Mechanism of Action	Clinical Trials	Status	References
T-VEC (Melanoma)	Herpes Simplex	Direct lysis of cancer cells	Phase III	Approved	[2]
ONCOS-102	Adenovirus	Immunostimulation and cell lysis	Phase I/II	Clinical Trials	[5]
Reolysin	Reovirus	Disruption of signaling pathways	Phase II/III	Clinical Trials	[18]
CVA21	Coxsackievirus	CAR-dependent cell killing	Phase I/II	Clinical Trials	[21]
Pexa-Vec	Vaccinia	Viral replication and immune response	Phase I/II	Discontinued	[15]
Rigvir	Echovirus	Induction of apoptosis	In Use (Latvia)	In Use (Latvia)	[11]

## CONCLUSIONS

Reovirus is an intriguing and flexible viral pathogen that affects a wide variety of hosts and exhibits a wide range of clinical signs. Reovirus replication requires intricate interactions between viral and host cell components and is a highly dynamic and regulated process. The pathophysiology of reovirus infections is complex and involves interactions between viral replication, host immune responses, tissue lysis, and clinical manifestations. In a number of medical fields, including the treatment of cancer, the development of vaccines, gene therapy, and antiviral therapy, reovirus has great potential as a therapeutic agent. It is predicted that recent research and clinical trials will provide more insight on the efficacy, security, and ideal use of reovirus-based therapies for a range of disorders. It is critical to keep in mind that the development of reovirus-based anticancer drugs is ongoing and dynamic. The therapeutic effectiveness of Reovirus in the treatment of different forms of cancer is anticipated to be improved by further research into its mechanisms of action, improvement of therapeutic approaches, and development of predictive biomarkers.

## Authors Contribution

Conceptualization: AI, RF, MA, ZG, MM

Writing-review and editing: UM, HK, MA, RM, SH, MM, AA

All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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