Reovirus oncolysis: a brief insight on molecular mechanism and immunological aspect

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Abstract : Reovirus (respiratory enteric orphan virus), a naturally occurring benign human pathogen, has an inherent ability to target transformed and cancerous cells and cause their lysis, while leaving non-transformed cells relatively unaffected. The efficiency of this innate oncolytic activity of reovirus correlates with expression of the *ras* oncogene. Cells expressing activated Ras and the related Ras/RalGEF/p38 pathway are more permissive to the reovirus infection than that of untransformed counterparts. *Ras*-transformation orchestrates selective oncolysis of cancerous cells by mediating efficient virus uncoating as well as by enhancing infectivity and subsequent apoptosis-dependent release of nascent virus particles. Different human and murine cell lines derived from naturally occurring tumors also display similar activation of the *ras* pathway, and thus present selective susceptibility to reovirus oncolysis under *in vitro* as well as *in vivo* conditions. This ability of reovirus to selectively target a wide variety of tumors offers a novel anti-cancer therapeutic option. However, the efficiency of reovirus virotherapy in immunocompetent hosts is compromised due to the presence of anti-viral innate and adaptive immune responses. Hence, the success of this highly promising reovirus oncolytic therapy will likely be enhanced by modulating host immunity.

Key words: ❺reovirus ❺cancer ❺virotherapy ❺oncolysis ❺ras oncogene

INTRODUCTION

For more than a century, pathogens have been believed to poses an ability to infect and destroy the cancer cells selectively. Retrospectively, the concept of viruses as anti-cancer agents was originated following the historical observ-ations suggesting that the infections of leukemic patient (16) with certain pathogens had beneficial anti-cancer effects, even inducing the remission of the cancer in some cases (43). Such a potential of infectious agents to selectively target and destroy cancerous cells was further supported by the sporadic reports documenting tumor regression in patients with coincidental viral infections such as measles (21, 42, reviewed in 28), viral hepatitis (25, 50), chicken pox (8), mumps virus (4, 47) and many others (reviewed in 28). These observations led to the foundation of modern day cancer virotherapy. In 1949, for the first time, sera and tissue containing hepatitis virus were intentionally administered in the patients with Hodgkin's disease as a oncolytic therapeutic agent (25). Since then, many viruses have been identified as potential oncolytic agents, including adenovirus, herpes simplex virus (HSV), vesicular stomatitis virus (VSV), varicella virus and reovirus (reviewed in 28, 32, 49).

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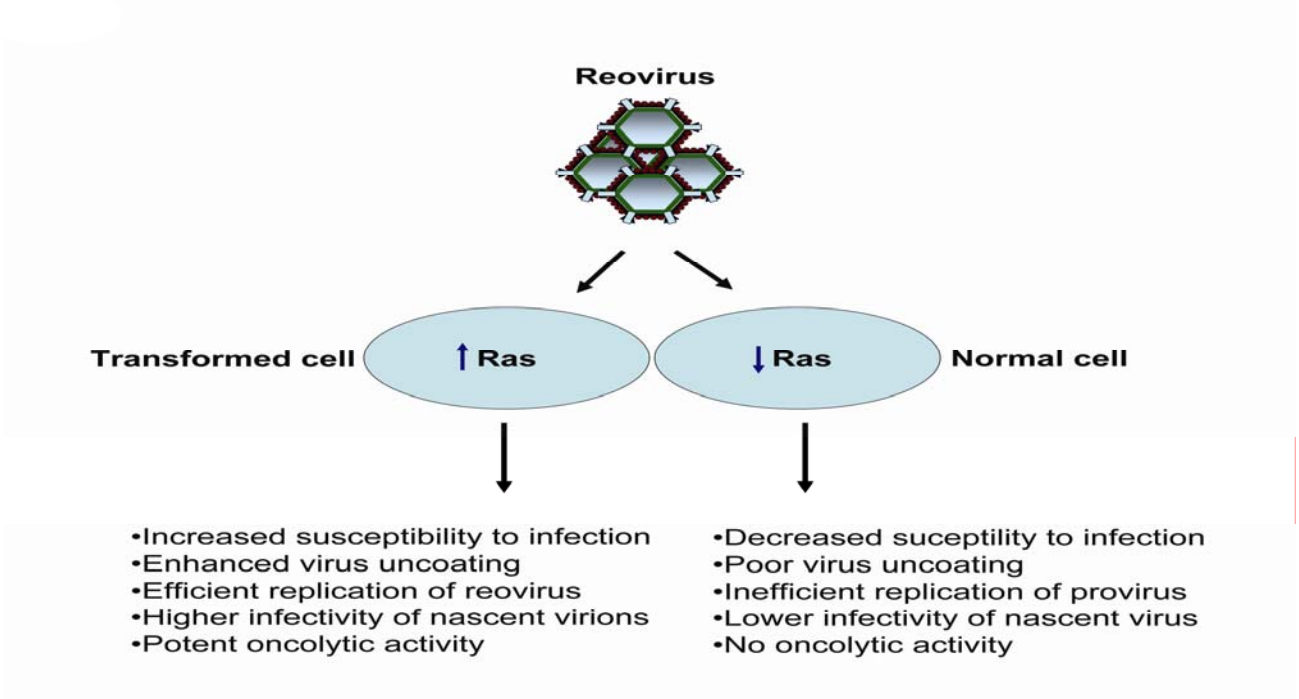

Fig. 1. Association between reovirus oncolytic ability and expression of *ras* oncogene. The *ras* transformation of cells endows them with higher susceptibility to reovirus infection. After uptake of virus, *ras*-transformed cells show enhanced uncoating and replication of virus, and produce nascent virions with higher infectivity which are released more efficiently through apoptosis-dependent mechanism leading to cytolysis, than that of non-transformed cells.

Reoviruses (respiratory enteric orphan viruses), first identified in 1959, are double-stranded RNA (dsRNA) viruses that belong to *Reoviridae* family and infect invertebrates, vertebrates and plants (39, 55). Reoviruses that infect humans are classified under genus *orthoreoviridae* and constitute a characteristic segmented genome. The segments of genome are grouped into three classes as large (L), medium (M) and small (S) depending on their sizes, which encode for λ, μ, σ viral proteins, respectively (39, 55). These viruses are non-enveloped and made up of double layered proteinaceous icossahedral capsid, composed of outer and inner capsid, that contains the viral genome.

Infection of reovirus is initiated by viral entry through receptor-mediated endocyto-sis, when virions first bind to low affinity sialic acid that is followed by high affinity interaction with junctional adhesion molecules 1 (JAM1) present on cell surface (6, 7). This endoc-ytosed reovirus present in endosomes is further uncoated to form infectious subvirion particles (ISVPs), which are further processed to generate transcriptionally active core particles (39, 55). Fusion of endosomal membrane with ISVP facilitates the delivery of core particles into the cytoplasm (12). In the cytoplasm, viral transcription ensues inside the core particles and is followed by viral replication and protein expression. Finally, newly assembled mature virions are released, and this process is accompanied by cell death and disruption of plasma membrane (reviewed in 14).

Reovirus causes mild gastrointestinal and respiratory tract infections in immuno-competent individuals and is considered as a benign human pathogen, since it is not associated with any severe disease pathology and has been shown to cause only minor illness in human volunteers (45). Infection with reovirus is a common global occurrence, with estimated 50-100% of the population showing the presence of antibodies to different reovirus antigens in sera, indicating previous exposure to the virus (36, 37).

Reovirus-mediated oncolysis

The oncolytic potential of the reovirus was first noticed in 1977, when reovirus type 2 was shown to cause selective cytolysis of transformed human and murine cell lines, while leaving normal cells unaffected (22). This finding was followed by similar studies including the one that showed that apparently reovirus-resistant mouse cell lines NR6

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and B82 (51) or NIH-3T3 (53) can be rendered highly susceptible to reovirus infection and subsequent cytolysis by transfecting them with epidermal growth factor receptor (EGFR) or v-erbB oncogenes, respectively. Trans-formation of reovirus-resistant cells with other signaling molecules such as the guanine nucleotide-exchange factor (GEF) Sos and the small G protein Ras, which are downstream from EGFR, also endowed cells with permissiveness to reovirus infection (48). In subsequent studies, constitutive activation of *ras* oncogene was shown to be pivotal in mediating reovirus oncolysis (33, 52, reviewed in 49). These hallmark studies recognized the oncolytic potential of reovirus and promoted its implication in animal models. Thus far, reovirus has been shown to replicate and cause oncolysis in cancer cell lines derived from breast, brain, colon, lymphoma, ovarian, spinal cord and bladder tissues (2, 15, 23, 24, 29, 41, 57, reviewed in 32, 49).

In 1998, the ability of reovirus to cause cytolysis of cancer cells *in vivo* was first evaluated in mouse model. In this study, a single intra-tumoral injection of reovirus was able to induce tumor regression in 65-80% of the severe combined immune deficient (SCID) mice bearing tumors established with v-erbB-transformed murine NIH 3T3 cells or human U87 glioblastoma cells (15). The oncolytic ability of reovirus was further extended in imunnocompetent C3H mice, wherein repeated injections of reovirus were able to destroy *ras*-transformed C3H-10T1/2 cells-induced tumors. These observations confirmed the oncolytic potential of reovirus under *in vivo* conditions, and initiated testing of this virotherapy against tumors of varied origin in different animal models. Through these studies, the solid tumors generated with human glioma (57), medulloblastoma (58), ovarian and colon cancer (23), bladder cancer (29), pancreatic cancer (19) cell lines as well as metastatic breast cancer (41) and lymphoma tissues (2) have shown the susceptibility to the cytolytic effects of reovirus virotherapy, confirming that the oncolytic ability of reovirus can target naturally occurring tumors and is not limited to artificially transformed or *in vitro* propagated cell lines only. These promising findings about reovirus virotheray in animal models have led to the currently undergoing human clinical trials (11, 59).

Molecular mechanism of reovirus oncolysis

The exact mechanism by which reovirus mediates the cytolysis of cancerous cells is not completely elucidated yet. What is clear is that, reovirus displays inherent preference towards transformed cells with an activated Ras signaling pathway (40,

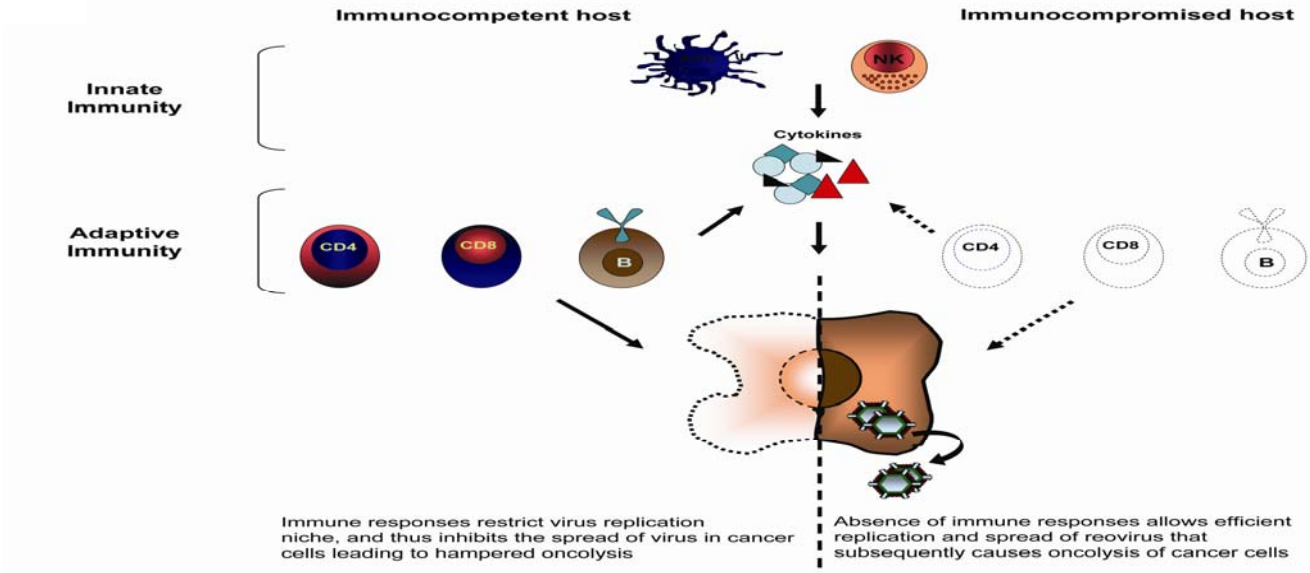

Fig . 2. Proposed effects of host immune responses on reovirus-mediated oncolysis. The exposure of immunocompetent host to reovirus has a potential to induce innate immune responses that include activation of DCs, macrophages, NK and NKT cells, and production of antiviral cytokines such as type I and II interferons and TNF-α. Activated innate responses could further initiate the reovirus-specific adaptive T (CD4+ and CD8+) and B cell (antibody) responses. The innate as well as adaptive responses developed this way could hamper the replication and subsequent spread of reovirus in tumor cells, leading to incomplete oncolysis. In absence of such immune responses, as observed in SCID mice or animals treated with immunosuppressive agents, reovirus displays potent oncolysis of tumor cells.

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52, reviewed in 49).

Association between *ras* oncogene and reovirus oncolysis

Ras proteins and its constituent signaling pathways are involved in the regulation of varied cellular processes such as differentiation, development, proliferation and apoptosis, and their anomalous expression is associated with tumorigenesis (reviewed in 49 and see figure 1). *Ras*-transformed NIH-3T3 cells are more permissive to the reovirus replication and cytolysis than that observed in non-transformed NIH-3T3 cells (52, reviewed in 49). Although the exact role of *ras* oncogene in mediating reovirus oncolysis is not fully understood, we have recently shown that *ras*-transformation not only endows the cell with higher susceptibility to infection with reo-virus, but also is required for the uncoating of reovirus after its entry into transformed cells (33). Further, similar study also showed that *ras*-transformation mediates the production of infectious progeny and is essential for the release of reovirus virions through apoptosis-dependent mechanism. The reovirus produced from *ras*-transformed cells was 3 times more infectious and generated 200 times higher viral titers than that of non-transformed cells, suggesting the pivotal role of *ras* oncogene in reovirus mediated oncolysis (33).

The aberrant expression of other downstream molecules from *ras* signaling cascade including phosphatidylinositol 3-kinase (P13K), Raf/Erk and Ral guanine nucleotide-exchange factors (RalGEFs) is also associated with *ras*-dependent transformation and has been observed in different human cancers. Considering these facts, studies were also focused on dissecting the precise role of these molecules during reovius oncolysis. In these studies, it was observed that *ras*-transformed NIH-3T3 cells which expressed activated RalGEF, in the presence of mutated P13K or Raf/Erk, were still permissive to reovirus infection. Further, inhibition studies with downstream molecules of RalGEF, such as p38 and JNK pathway, showed that reovirus requires an intact Ras/RalGEF/p38 cascade for its efficient replication and cytolysis (40). Such a constitutive activation of *ras* and *ras*-related proteins is observed in more than 80% of human cancers, making them suitable targets that can be possibly eradicated with reovirus oncolytic therapy.

Association of PKR with reovirus oncolysis

Another molecule that is implicated in defining the potency of reovirus oncolysis is dsRNA-dependent protein kinase (PKR) that is involved in regulation of cell differentiation, growth and proliferation (13, 30). However, its role in reovirus infection remains controversial (26, 35, 38, 52). We previously proposed that in untransformed NIH-3T3 cells, dsRNA structures within the reovirus transcripts likely cause PKR activation (phosphorylation), leading to the subsequent shutoff of viral protein synthesis (52). Since enhanced PKR phosphorylation was not observed in *ras*-transformed cells, we rationalized that Ras likely negatively regulates PKR, thereby allowing viral protein synthesis to ensue. This view was corroborated by the demonstration that cells in which PKR is inhibited or not expressed showed enhanced viral protein synthesis (26, 38). We have since found that the overall reduction in viral protein synthesis in untransformed cells is due to the reduced viral spread in these cells, as viral protein synthesis during the first cycle of infection is comparable between untrans-formed and *ras*-transformed cells (40). Whether inhibition of PKR activation in *ras*-transformed cells is linked to enhanced viral spread remains to be determined; the precise role of PKR in reovirus oncolysis will therefore need to be re-evaluated.

IMMUNOLOGICAL ASPECTS OF REO-VIRUS ONCOLYSIS

Although reovirus displays highly efficient cytolytic effects on transformed *in vitro*, its implementation *in vivo* in animal models or in patient studies has encountered a mixed success. It is hypothesized that the main factor that determines the efficiency of reovirus oncolysis under *in vivo* conditions is the status of anti-viral immune responses. Historically, it has been observed that the remission of cancers after coincidental viral infection was more efficient in the cancers affecting the immune system e.g., lymphoma (reviewed in 28), suggesting that the compromised immune responses are associated with higher oncolytic efficiency of the viruses (figure 2).

In general, infection with virus stimulates different arms of innate and adaptive immune responses in immunocompetent hosts. After virus invasion, the molecular pattern recognition receptors (PRRs), e.g., TLRs, present on the immune cells recognize the pathogen and induce an immediate anti-viral response. One of the major components of this early innate response is initiation of the interferon alpha/beta (IFN-α/β) pathway that can directly

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inhibit viral replication and induce an antiviral state in adjacent healthy cells, limiting the spread of infection (27).Activation of innate response also initiates the production of other cytokines, e.g., tumor necrosis factor-alpha (TNF-α), IFN-gamma (IFN-γ) and chemokines, e.g., interleukin-18 (IL-18) (9, 10, 44). These soluble mediators of immune response constitute inflammatory response that not only restrict the spread and replication of virus during early phase of infection, but also activate antigen presenting cells (APCs), e.g., dendritic cells (DCs), and natural killer (NK) cells, which subsequently initiate adaptive immunity (3, 5, 9, 10, 20). The adaptive immune response comprises activation of virus-specific T and B lymphocytes, which then establish virus-specific immunity that comprises activated cytotoxic T lymphocytes (CTLs) and antibody producing B cells (3, 46). These innate and adaptive immune responses constitute different layers of safeguard mechanisms that protect the host against viral infection, and ironically, hamper the efficiency of reovirus-mediated oncolysis in cancer-bearing immunocompetent hosts.

Our knowledge of the immune responses induced after reovirus infection is inadequate since these responses are only scantily characterized so far. Nonetheless, the genome of reovirus is comprised of dsRNA, which is known to be a potent activator of NFkB through its recognition by TLR3 (reviewed in 1, 34, 54). In TLR3 (-/-) mice, dsRNA derived from reovirus fail to induce type I interferon, interferon-inducible genes and proinflammatory cytokines unlike in TLR3 (+/+) mice, suggesting its recognition through TLR3 as well as its ability to induce innate responses. The dsDNA genome of reovirus also induces the expression of retinoic acid-inducible gene I (RIG-I) and melanoma differentia-tion-associated gene 5 (MDA5) which are involved in driving type I interferon production (31). Further, recent report studying the reovirus-induced immune responses during clinical trials showed increased number of CD3-CD56+ NK cells in the peripheral bloood mononuclear cells (PBMC) of the reovirus-treated patients (56). After culture with reovirus type 3 Dearing strain, human myeloid DC generated from PBMC get activated, produce proinfla-mmatory cytokines, e.g., IFN-α/β, TNF-α, IL-12 and IL-6, and further enhance the anti-tumor cytotoxic potential of NK as well as T cells (18). These studies have confirmed the ability of reovirus to stimulate different components of innate immunity. Although the contribution of these innate responses in limiting or complimenting the reovirus oncolytic potential is still a under investigated paradigm. The activated APCs and NK cells, along with anti-viral cytokines, can greatly influence the spread and subsequent oncolysis mediated by reovirus. Their potential in orchestrating in the outcome of virotherapy demands that the role of these innate responses after reovirus infection should be further dissected.

Even though innate immunity controls viral replication during early phase of infection, adaptive immune responses mediate the long-term control over the spread of virus. Unfortunately, the precise analysis of CD4+ or CD8+ T cell responses directed against different reovirus antigens and their involvement in determining the outcome of reovirus oncolysis have not completely defined yet. Nonetheless, the studies from immuno-compromised mice have suggested that absence of this adaptive arm of immune response can allow the reovirus to induce complete oncolysis of solid as well as metastatic tumors *in vivo* (24). It is interesting to note that, in SCID mice single injection of reovirus is sufficient to induce desirable oncolysis of transformed NIH-3T3 cells, while multiple injections of same virus are required in immunocompetent mice to achieve similar results. These observations suggested that existence of uncompromised adaptive immune.

IMMUNOLOGICAL CONSTRAINTS ON REOVIRUS VIROTHERAPY

responses are capable of hindering the reovirus-mediated oncolysis. This hypothesis was further supported in the study performed by Hirasawa et al., who assessed the ability of systemically administered reovirus to cause cytolysis of distally located or metastatic tumors (24). This report showed that intravenously administered reovirus could indeed target distal tumors, but its efficacy was severely hindered in the presence of ongoinganti-viral immune responses. The inhibition of these anti-reovirus adaptive immune responses using either cyclosporin-A (CyA) or anti-CD4/anti-CD8 antibodies dramatical-ly improved the survival in animals with metastatic cancer and enhanced the regression of solid tumors (24). Thus,

our understanding about of reovirus virotherapy so far has implied that the efficiency of this anti-cancer regimen is greatly influenced by anti-viral innate and adaptive immune responses. The cancer patients undergoing chemotherapy or radiation treatment are believed to have debilitating immune

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system and hence, are anticipated to experience similar oncolytic effects of reovirus treatment as those observed in SCID or immune-suppressed mice.

Although, the intact immune responses in remaining patients pose major constraint on the implication of reovirus virotherapy. More importantly, most of the humans are infected with reovirus at some point in their lifetime and thus carry anti-reovirus antibodies and most probably reovirus-specific memory T cells. Recently, different reovirus serotypes have been shown to mount distinctive recall immune responses in humans (17). The presence of such a anti-viral adaptive responses can inhibit the reovirus replication and spread in tumors and terminate the viral infection before it induces complete oncolysis. Thus, the compromised success of reovirus anti-cancer treatment in humans is mostly attributed to the detrimental effects of host immune responses on reovirus infection. None the less, the mice previously exposed to reovirus, and thus carrying active anti-reovirus immunity, have been shown to display efficient oncolytic effects of reovirus following CyA or anti-CD4/anti-CD8 treatment suggesting that the harmful effects of immune responses on reovirus oncolysis are avoidable. These findings provide a hope that the efficiency of reovirus virotherapy in immune competent humans could be enhanced to optimal levels by managing anti-reovirus immune responses.

CONCLUDING REMARKS

Reovirus has a ability to infect and induce apoptosis in transformed as well as cancerous cells. This ability of reovirus to specifically target cancer cells, while leaving normal or Ahealthy@ cells unaffected provides a promising therapeutic option to be used as oncolytic agent. Apart from. the tremendous success of this anti-cancer therapy in animal models, the use of such a oncolytic virotherapy in humans has been confronted with mixed success pertaining to anti-viral immune responses. Ultimately, the successful implementation of reovirus oncolytic therapy in the clinical settings will need the fine tuning of factors affecting the efficiency of this approach, including the modulation of host immune responses.

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