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REVIEW

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Defects in interferon pathways as potential biomarkers of sensitivity to oncolytic viruses

Olga V. Matveeva[1] | Peter M. Chumakov[2,3]

[1] Biopolymer Design LLC, Acton, MA, USA

[2] Engelhardt Institute of Molecular Biology, Moscow, Russia

[3] Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products, Moscow, Russia

Correspondence
Olga V. Matveeva, Biopolymer Design LLC, 23 Nylander Way, Acton, MA, USA.
Email: olga.matveeva@gmail.com

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Summary

Increased sensitivity of cancer cells to viruses is a prerequisite for the success of oncolytic virotherapy. One of the major causes of such a phenotype is the disruption of innate antiviral defenses associated with dysfunction of type 1 interferons (IFNs) that permits unlimited replication of viruses in cancer cells. Defects in IFN pathways help cancer progression by providing additional advantages to tumor cells. However, while these defects promote the survival and accelerated proliferation of malignant cells, they facilitate viral replication and thus enhance the efficiency of viral oncolysis. This review describes a broad spectrum of defects in genes that participate in IFN induction and IFN response pathways. Expression levels and/or functional activities of these genes are frequently low or absent in cancer cells, making them sensitive to virus infection. Therefore, certain specific defects in IFN signaling cascades might serve as potential biomarkers to help in identifying individual cancer patients who are likely to benefit from oncolytic virotherapy.

KEYWORDS

biomarkers, defects in IFN pathways, defects in IFN induction, defects in IFN response, IFN defects in cancer cell, malfunction of IFN signaling cascade, oncolytic viruses, oncolytic virotherapy, viral oncolysis

1 | INTRODUCTION

Oncolytic viruses represent a promising new addition to existing approaches to cancer therapy. However, despite impressive examples of occasional long-term remissions or even cures, clinical trials with oncolytic virotherapy still demonstrate rather modest results: A significant percentage of patients may not show any response at all. The difference in response to viruses highlights the tremendous variability of cancer cells in different patients. Analysis of the underlying roots of the difference forms an active area of research that can potentially lead to identification of reliable biomarkers, which would identify patients, who are most likely to respond to virotherapy.

Abbreviations: cGAS, cyclic GMP-AMP synthase; ERK, extracellular signal-regulated kinase (also known as mitogen-activated protein kinase 1 [MAPK1] or p42MAPK); GBP-1, guanylate binding protein 1; HSV, herpes simplex virus; IRF, interferon regulatory factor; ISG, interferon stimulated gene; JAK, Janus kinase; LGP2, laboratory of genetics and physiology 2 (also known as RIG-I-like receptor 3 [RLR-3] or RIG-I-like receptor LGP2); MDA5, melanoma differentiation-associated protein 5; MEK, mitogen-activated protein kinase (also known as MAP kinase); MV, measles virus; Mx, myxovirus resistance proteins; NDV, Newcastle disease virus; OAS, oligoadenylate synthetase; PAMP, pathogen-associated molecular pattern; PKR, protein kinase R; PRR, pattern recognition receptor; PTEN, phosphatase and tensin homolog tumor suppressor gene; RAF, serine/threonine-specific protein kinase; RIG-I, retinoic acid-inducible gene-1; RLR, RIG-I-like receptor; RNase L, ribonuclease L; RSV, respiratory syncytial virus; STAT, signal transducer and activator of transcription protein; STING, stimulator of IFN genes (also known as transmembrane protein [TMEM173]); TLR, toll-like receptor; TYK, tyrosine kinase; VSV, vesicular stomatitis virus

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Normal cells have a variety of mechanisms that protect them from pathogens. Key players in cellular antiviral defenses are type 1 interferons (IFNs). In response to initial virus intrusion, IFNs signal surrounding cells and stimulate them to enter an antiviral state that includes restricted proliferation, downregulated metabolism, and other specific changes that restrict viral replication.[1,2] Interferons also play an important role in immune surveillance, which reduces the probability of malignant transformation.[3] A malignant cell with dysfunctional IFN induction or response has numerous survival and growth advantages. Thus, accumulation of genetic defects in IFN signaling cascades and cancerogenesis go hand in hand.[4]

Half of the silencing epigenetic changes associated with immortalization of cells belong to genes involved in IFN pathways.[5] The deletion of such genes is often observed in gliomas,[6] leukemias,[7] and bladder cancer.[8] Low expression of IFN receptors is characteristic of hepatocellular,[9,10] pancreatic,[11] gastric,[12] colon rectal,[13] and many other cancers.[4] Moreover, immune cells of cancer patients often have impaired IFN signaling.[14]

Thus, along with the importance of IFN pathways for cellular defense against viruses, defects in these pathways promote viral oncolysis. The purpose of this review is to describe the broad range of these defects along with their role in promotion of malignant cell sensitivity to oncolytic viruses.

2 | DEFECTIVE INDUCTION OF TYPE 1 IFNs IN CANCER CELLS

In normal cells, virus infection triggers an antiviral mechanism which consists of 2 phases. First, as a result of recognition of viral components, expression and secretion of type 1 IFNs are initiated. Interferons then interact with specific receptors and stimulate a second phase, the IFN response. During the second phase, the secretion of IFNs is additionally stimulated by a positive regulatory feedback loop. The induction of IFN production is triggered by a set of molecular events that includes the interaction of viral components with specific cellular receptors and their activation. The activated receptors form a complex with adaptor proteins, and this complex promotes phosphorylation of transcription factors. Finally, the phosphorylated transcription factors move to the nucleus and initiate the transcription of IFN mRNAs, leading to production and secretion of IFNs. In cancer cells, this chain of molecular events might be broken at different levels and by a variety of mechanisms.

The genes of the IFN induction pathway whose defects have been shown to be associated with sensitivity to viruses are described below and listed in Table 1.

3 | PATTERN RECOGNITION RECEPTORS FOR VIRAL NUCLEIC ACIDS

Pattern recognition receptors (PRRs; also called innate immune receptors) are proteins that initiate induction pathways for IFNs and proinflammatory cytokines. Pattern recognition receptors are activated by pathogen-associated molecular patterns (PAMPs), molecular features of pathogens that are absent in host organisms. Viral nucleic acids are among the PAMPs, and their sensing by PRRs forms the first line of host defense against viral infection. Viruses are highly diverse pathogens, and correspondingly, cells evolved multiple types of PRRs with different functions and cellular locations. Some of these PRRs recognize only viral DNA and some only viral RNA. Some PRRs recognize viral nucleic acids at the cell surface, even before the virus enters the cell, while others recognize viral components inside the cell.[33]

3.1 | Membrane-associated PRRs

Toll-like receptors (TLRs) are membrane-bound PRRs that initiate pathways for induction of IFNs and proinflammatory cytokines (Figure 1). Toll-like receptors become activated after interaction with

TABLE 1 Biomarkers related to the IFN induction pathway

Category		Gene/Protein Name	Sensor of Viral	Type of Defect	Sensitivity to	Ref
Membrane-associated pattern recognition receptors (PRRs)	Toll-like receptors (TLRs)	TLR2	DNA	Absent	Adenovirus	15
		TLR9		Dislocated		
		TLR3	RNA	Low expression	Sendai virus	16
		TLR7				
Cytosolic pattern recognition receptors (PRRs)	Cyclic GMP-AMP synthase	cGAS	DNA	Epigenetic silencing	HSV1 vaccinia virus	17
	RIG-I like receptors (RLRs)	RIG-I	RNA	Downstream signaling is blocked	Reovirus	18
				Low expression	Measles virus	19
		MDA5		Experimental knockdown or low natural expression	Sindbis virus	20
	Protein kinase	PKR		Deletion	NDV	21
				Experimental inhibition	VSV	22
	RNase	RNase L		Experimental inhibition	VSV	22
	OAS gene family	OAS2		Low expression	VSV	23
Adaptor protein	STING			Loss of function	HSV1	24
				Epigenetic silencing	HSV1, vaccinia virus	17
Interferon regulating factors		IRF1		MEK activation suppresses IRF1 binding to RIG-I promoter	VSV	25-27
					Reovirus	18
		IRF3		Aberrant splicing	VSV	28
		IRF3/7		Low basal expression	NDV	29
		IRF5/7		Hyper-methylated promoters	VSV	30
		IFN-regulatory factor 9 (P48)		Expression is low or absent	VSV	31
Tumor suppressor, promoter of IRF3 nuclear import		PTEN		Deletion	VSV	32

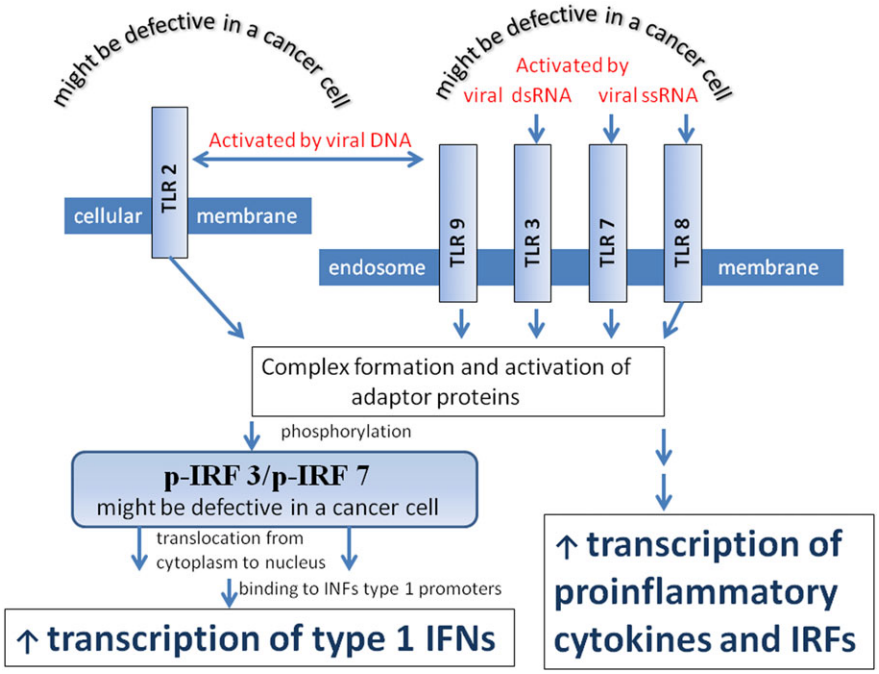

FIGURE 1 Toll-like receptors (TLRs) and their downstream signaling. Toll-like receptors are membrane attached pattern recognition receptors (PRRs) that initiate pathways that produce IFN and proinflammatory cytokines. TLR 2 and TLR9 are activated by viral DNA, TLR3 by viral double stranded RNA, and TLR7/8 by single-stranded RNA. Toll-like receptor 2 is located on the outer membrane of the cell, while TLR 3, TLR7/8, and TLR9 are associated with an endosome membrane. After activation by viral nucleic acids, TLRs engage adapter proteins and activate them. The complexes of TLRs with activated adaptor proteins phosphorylate interferon regulatory factors 3 and/or 7 (IRF3 and/or IRF7). Phosphorylated IRF3 and IRF7 relocate from the cytoplasm to the nucleus, where they trigger type 1 IFN production. Through an alternative pathway, the TLR/adaptor protein complexes trigger proinflammatory cytokine production. Malfunction of TLR receptors or IRFs disrupts downstream pathways, making cancer cells vulnerable to oncolytic virus infection

PAMPs, which might be viral nucleic acids or other pathogen-derived molecules.[34] Particular types of PAMPs activate particular types of TLRs that in turn recruit TLR type-specific adaptors for further signal transduction.[34] Thus, some TLRs (TLR2 and TLR9) recognize viral DNA, some (TLR7 and TLR8) recognize single-stranded viral RNA, and some (TLR3) recognize double-stranded viral RNA.[34] Toll-like receptor 2/7/8 and TLR9 use the MYD88 protein as adaptor, while TLR3 instead uses TRIF protein.[34] Toll-like receptors have various cellular locations: TLR2 is present at the cell surface, while TLR3, TLR7/8, and TLR9 are associated with endosomal membranes.[34,35]

3.2 | Cytosolic PRRs

Cytosolic PRRs are represented by viral RNA and DNA sensing proteins. The RNA sensing proteins include retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), protein kinase R (PKR), ribonuclease L (RNase L), and the oligoadenylate synthetase (OAS) enzyme family. RIG-I-like receptors include 3 proteins, RIG-I, LGP2 (also known as RLR-3), and melanoma differentiation-associated protein 5 (MDA5). The DNA sensors include GMP-AMP synthase (cGAS), gamma-interferon-inducible protein (IFI16), HIN200, DAI, AIM-2, LRRFIP1, RNA polymerase III, and some other proteins.[36-39] It is interesting that cytosolic viral RNA can also serve as cGAS activating ligand by forming DNA: RNA hybrid.[40] In general, it should be noted that some viral RNA intermediately transcribed from the cytoplasmic genome of a DNA virus can be also be recognized by cytosolic RNA sensors.[41-43] Moreover, DNA reverse transcribed from genomic RNA of retroviruses can be recognized by cytosolic DNA sensors.[44]

3.3 | A type 1 interferon autocrine-paracrine signal amplification loop

Receptors that recognize viral nucleic acids initiate signaling cascades that lead to the induction of IFNs and some other proinflammatory cytokines. In particular, some TLRs[34] and RLRs,[45] along with PKR[46] and cGAS,[47] trigger signaling events that lead to increased transcription of type 1 IFNs. In turn, type 1 IFNs stimulate production of virus-sensing proteins. For example, IFN-beta promotes transcription of RIG-I,[48] MDA5,[49] and PKR[50,51] by increasing binding of interferon regulatory factor (IRF) 1 to the promoters of these genes. Increased transcription from these genes results in increased production of the corresponding proteins (Figure 2). Thus, RIG-I, MDA5, and PKR are functionally activated by viral RNA, but their transcription is activated by IFN-beta via a positive feedback loop.[48,52] This autocrine or paracrine signal amplification cycle is crucial for the antiviral protection of cells, but it can be disrupted in cancer cells by various mechanisms.

3.4 | Sensors of viral DNA

Among PRRs that sense viral DNA, TLR2 is located in the surface membranes of cells, TLR9 is located in endosomal membranes,[34,35] and cGAS is a cytosolic PRR.[47] Any serious defect in the TLR receptor circuit disrupts the IFN induction pathway and increases susceptibility to viral infection. For example, in some breast cancer stem cells, the TLR2 receptor is not detectable, whereas TLR9 is associated with endoplasmic reticulum (ER) and Golgi-like structures instead of endosomes. Consequently, in such cells, the virus is unable to induce expression of IFN-alpha, IFN-beta, or signal transducer and activator of transcription protein 1 (STAT1). Deficiency of these components promotes sensitivity of cells to adenovirus infection.[15]

Type 1 IFN response is triggered by cGAS though activation of secondary messengers (Figure 3).[47] Epigenetic silencing of the cGAS gene was found in some melanoma cell lines. These cell lines were highly susceptible to herpes simplex virus 1 (HSV1) and vaccinia virus.[17]

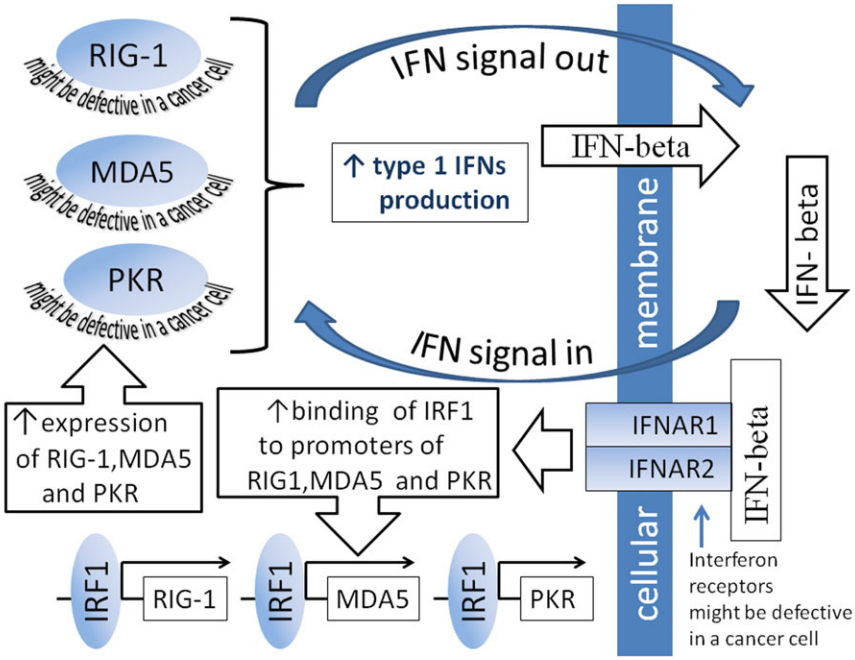

FIGURE 2 Interferon (IFN) signal amplification loop. RIG-I, MDA5, and PKR are functionally activated by viral RNAs. After activation, they trigger signaling cascades that result in increased production and secretion of type 1 IFNs. In turn, secreted IFN-beta interacts with intramembrane receptors of the cell in which it was produced or of another cell. Such interaction initiates autocrine or paracrine downstream signaling pathways, resulting in increased binding of IRF1 to promoters of RIG-I, MDA5, and PKR. Such binding stimulates transcription of these genes and ultimately increases production of the relevant proteins

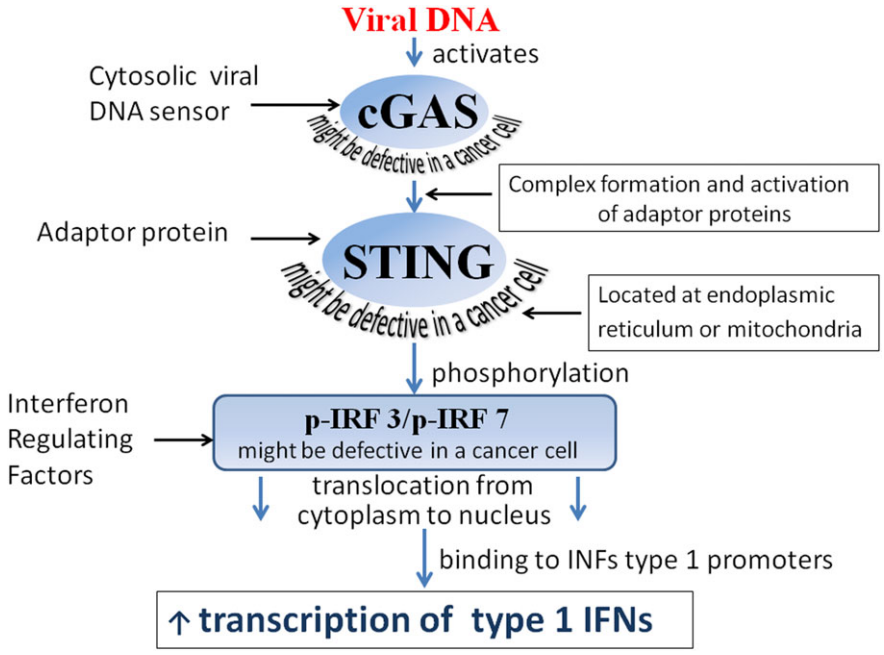

FIGURE 3 cGAS viral DNA sensor and its downstream signaling. GMP-AMP synthase (cGAS) is a cytosolic sensor of viral DNA that, after activation by foreign DNA, triggers a type 1 IFN response. cGAS forms a complex with adaptor protein STING, which promotes phosphorylation of interferon regulatory factors 3 and/or 7 (IRF3 and/or IRF7). Phosphorylated IRF3 and IRF7 relocate from the cytoplasm to the nucleus, where they trigger type 1 IFN production. Malfunction of cGAS, STING, IRF3, or IRF7 disrupts downstream IFN production pathways, making cancer cells vulnerable to oncolytic virus infection

3.5 | Sensors of viral RNA

Among PRRs that sense viral RNA are TLR3, TLR7/8,[34] RLRs,[53-55] PKR,[33] RNase L,[56] and representatives of the 2′-5′-OAS enzyme family.[41] All of these proteins are functionally activated by viral RNAs and initiate signaling cascades (Figure 4) that trigger type 1 IFN production and limit virus spread.

Toll-like receptors that recognize viral RNAs might be located in cell surface membranes (TLR3) or in endosomal membranes (TLR7/8). Sensitivity of primary prostatic adenocarcinoma cell lines to Sendai virus inversely correlates with expression levels of TLR3 and TLR7 mRNA. Cell lines with lower expression levels of these TLRs were more sensitive to virus infection.[16]

Retinoic acid-inducible gene-I-like receptors include protein products of RIG-I and MDA5 genes. These proteins are RNA helicases that are ubiquitously expressed in most tissues.[53-55]

Retinoic acid-inducible gene-I is a cytosolic viral RNA-sensing protein that is functionally activated after its interaction with ssRNAs containing 5′-triphosphate or with dsRNAs shorter than 1 kb[57,58] (Figure 4). Several studies suggest a contribution of RIG-I deficiency to virus-mediated oncolysis. In multiple myeloma, glioblastoma, and astrocytoma derived cells, the ability of Newcastle disease virus (NDV) to induce the expression of RIG-I is critical for resistance to viral infection.[59] Similar results were obtained in another study, in which normal cells were compared with sarcoma, breast adenocarcinoma, and macrophage-derived tumor cells. A negative correlation

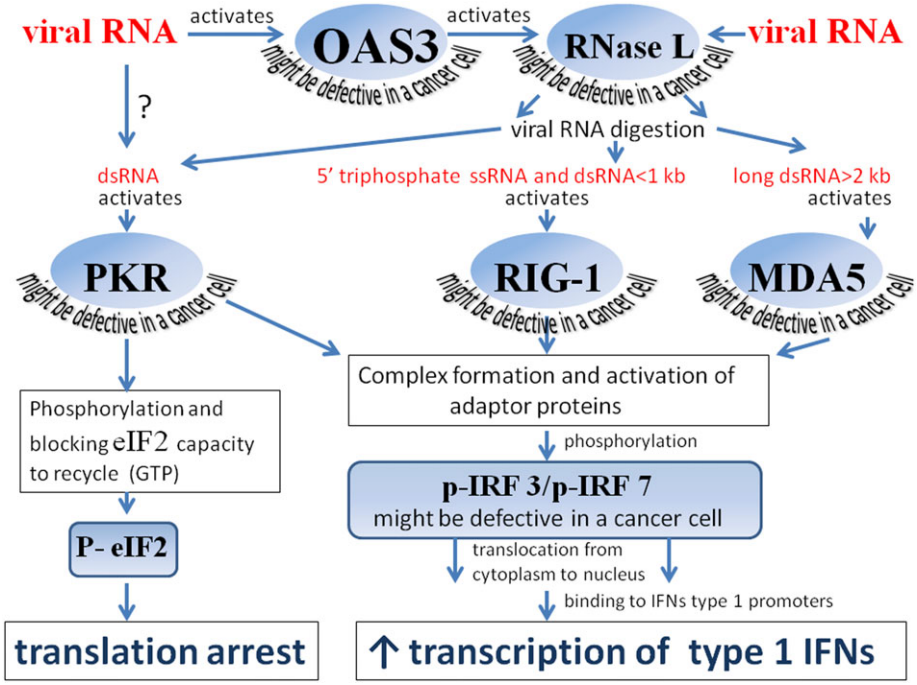

FIGURE 4 Viral RNA sensing proteins and their downstream signaling. Viral RNA activates the protein product of the OAS3 gene, which in turn activates RNase L that cleaves cytosolic viral RNA. RNA digestion products activate protein kinase PKR and the 2 helicases RIG1 and MDA5. After activation, PKR undergoes autophosphorylation and phosphorylates the translation initiation factor eIF2α. The phosphorylation of the initiation factor leads to translational arrests of both cellular and viral mRNAs, and these arrests promote apoptosis. Protein kinase R, RIG1, and MDA5 also participate in a signal transduction pathway that triggers IFN-beta transcription and limits viral spread. Protein kinase R, RIG1, and MDA5 form complexes with adaptor proteins that trigger phosphorylation of interferon regulatory factors 3 and/or 7 (IRF3 and/or IRF7). After phosphorylation, IRF3 and IRF7 relocate from the cytoplasm to the nucleus, where they trigger type 1 IFN transcription. Malfunction of OAS3, RNase L, PKR, RIG-I, MDA5, IRF3, or IRF7 disrupts downstream IFN induction pathways, making cancer cells vulnerable to oncolytic virus infection

was found between the efficiency of viral oncolysis and constitutive or NDV-stimulated expression of RIG-I.[29,60] Retinoic acid-inducible gene-I downstream signaling is blocked in some RAS transformed cells. The block causes susceptibility to reovirus infection, whereas overexpression of RIG-I restores virus resistance.[18] It has also been demonstrated that resistance to measles virus positively correlates with viral ability to initiate the expression of RIG-I in sarcoma cell lines. This expression was strong in resistant and weak in susceptible cell lines.[19]

Melanoma differentiation-associated protein 5 is a cytosolic viral RNA sensing protein that is activated after interaction with dsRNAs larger than 1 kb[55] (Figure 4). Impaired expression of the MDA5 gene leads to inhibition of type 1 IFN transcription that contributes to viral oncolysis. Although in normal cells treatment with an artificial analog of dsRNAs, poly (I:C), stimulates IFN-beta production, in hepatocellular carcinoma and some other forms of cancer in which there is weak, if any, expression of the MDA5 gene, similar treatment does not affect IFN-beta expression. Such lack of IFN-beta induction renders these cells sensitive to Sindbis virus. However, forced expression of MDA5 restores both cellular ability to produce IFN-beta and resistance to the virus.[20]

Protein kinase R is a cytosolic RNA-sensing protein that is activated by viral dsRNAs of variable length. During the activation process, PKR undergoes autophosphorylation and then phosphorylates the translation initiation factor eIF2α (Figure 4), leading to arrested translation of both cellular and viral mRNAs and even to apoptosis.[42,43] Protein kinase R also participates in a signal transduction pathway that further upregulates IFN-beta transcription[46] (Figure 4). By these mechanisms, the activated PKR restrains virus replication. Similar to RIG-I and MDA5 genes, the transcription of PKR mRNA is activated by type 1 IFNs, forming a self-activation regulatory loop.[50,51]

Malignant progression often leads to impaired PKR function.[61] Truncations of the PKR gene have been observed in many leukemia cell lines.[62] Moreover, in most of the leukocyte samples from patients with chronic B-cell leukemia, PKR enzymatic activity was undetectable, despite the presence of a full-length PKR gene.[62] Decreased levels of PKR expression were found in samples obtained from patients with chronic lymphocytic leukemia[63] and nonsmall cell lung cancer.[64-66] Low levels of PKR expression were also associated with higher incidence of disease relapse and reduced overall survival of patients with rectal cancers.[67] In breast cancer samples, substantial decrease in PKR functional activity was also observed, despite an increase in its expression.[68] In response to viral infection, cancer cells with low or absent PKR activity could not induce eIF2α phosphorylation and IFN-beta transcription, resulting in increased NDV replication.[21]

Ribonuclease L is another cytosolic sensor of viral RNAs.[56] After activation by interaction with viral dsRNA, it cleaves both viral and cellular RNAs. The RNA digestion products activate other viral RNA sensors, such as RIG-I, MDA5, and PKR (Figure 4), which in turn trigger IFN production[53] and/or promote apoptosis.[69] Some evidence suggests a relationship between tumor progression and RNase L dysfunction. Disabling mutations or deletions of RNAse L have been found in

prostate cancer samples[70-72] and are also associated with a predisposition to prostate cancer.[73] A decrease in RNase L activity was also observed in lung cancer.[74] There is some evidence that impaired RNase L function affects the sensitivity of cancer cells to oncolytic viruses. It was shown that the chemical compound sunitinib promotes infection with vesicular stomatitis virus (VSV) and negatively affects the functions of PKR and RNase L. In ovarian, prostate, and renal cell carcinoma cell lines, sunitinib inhibited RNase L enzymatic activity. In a mouse model, simultaneous sunitinib and VSV treatments led to complete elimination of prostate, breast, and kidney tumors, followed by the animals' recovery.[22]

The family of OAS enzymes is represented by 3 genes: OAS1, OAS2, and OAS3. All members of the family are cytosolic viral RNA sensors that are functionally activated by viral dsRNAs[41] and transcriptionally activated by type 1 IFNs.[50,51] During viral infection, OAS3 activates latent RNase L (Figure 4), whereas OAS 1 and OAS2 have other antiviral functions.[41] Without OAS3 activation, RNase L does not sense viral RNAs.[41] Oligoadenylate synthetase dysfunction is connected with carcinogenesis: Polymorphism of OAS1 is associated with prostate cancer[75]; low or absent OAS2 expression characterizes some pancreatic cancers[23]; and polymorphism of OAS3, which decreases its gene expression level, is associated with risk of chronic lymphocytic leukemia.[76] It has been shown that defective expression of members of the OAS family causes cellular susceptibility to viral oncolysis. Thus, pancreatic malignant cells with low or absent levels of OAS2 are often sensitive to VSV. In contrast, similar cells with constitutive expression of OAS2 are virus resistant.[23]

4 | ADAPTOR PROTEINS FOR PRRs

After activation with viral nucleic acid, PRRs recruit adapter proteins and form PRR-adaptor protein pairs that further facilitate downstream antiviral signaling (Figure 4). The PRR-adapter protein pairs initiate phosphorylation of transcription factors IRF3 and IRF7 via a mediator protein kinase. Phosphorylated IRFs activate transcription of type I IFN genes[77,78] (Figure 4).

The pairing adaptor for cGAS is the stimulator of IFN genes (STING) protein, also known as transmembrane protein TMEM173 or MITA (Figure 3). Stimulator of IFN genes is located on the ER and/or the mitochondria-associated ER membranes.[79] In some tumors, immune adaptor proteins' expression and/or activity is deregulated. Thus, STING function is disabled in numerous colorectal adenocarcinomas. This loss of function is highly predictive of HSV1-mediated oncolytic activity.[24] Melanoma cells often lose STING signaling through the epigenetic silencing of either STING or cGAS genes. Because of this loss, these cells are unable to produce type 1 IFNs in response to DNA viruses and are highly susceptible to HSV1 and vaccinia virus.[17]

5 | ANTIVIRAL IRFs

Antiviral IRFs belong to a family of transcription factors that control many cellular processes, including the induction of antiviral cytokines and type I IFNs. Viral nucleic acid sensors such as TLR3/7/8/9,[34] RLRs,[55] PKR,[46] and cGAS,[47] by interacting with adaptor proteins, initiate phosphorylation of IRF3 and/or IRF7 (Figures 3 and 4).[80] This phosphorylation promotes IRF3 and/or IRF7 translocation from cytoplasm to nucleus. In the nucleus, these phosphorylated IRFs trigger transcription of type 1 IFNs, which initiate autocrine and paracrine loops of signal amplification. Interferon-beta stimulates transcription of viral RNA sensors such as RIG-I,[48] MDA5,[49] and PKR[51] by increasing the binding of IRF1 to promoter regions of these genes. Thus, on the one hand, IRFs could be activated by virus-sensing proteins; on the other hand, IRFs promote the signal amplification process, leading to the activation of transcription from the genes encoding the virus-sensing proteins (Figure 2). As documented below, aberrant expression of IRFs, which characterizes many cancers,[81] contributes to viral oncolysis.

Interferon regulatory factor 1 is a transcription factor that activates transcription of the genes containing IFN-stimulated response elements. Viral nucleic acid-sensing proteins such as RIG-I, MDA5, and PKR are among these genes. Interferon regulatory factor 1 also participates in the upregulation of many genes that restrain cell proliferation and exert antitumor effects.[82] In cancer cells, the transcription activation function of IRF1 is often disabled. So, in acute myeloid leukemias[83] and gastric cancers,[84] the IRF1 gene is frequently deleted or silent; in many breast[85,86] and invasive hepatocellular carcinomas,[87] its expression is low or absent.

In cancer cells, IRF1 function can be suppressed by an activated Ras-Raf-MEK-ERK pathway. Specifically, activated MEK inhibits IRF1 binding to target promoter binding sites and suppresses transcription of viral RNA sensing genes. This inhibition often occurs in malignant cells, which on the one hand eliminates the antiproliferative constraints of IRF1-controlled genes, and on the other makes the cells vulnerable to viral infection. MEK inhibitors restore transcription of IRF1-controlled genes.[82] It was also shown that a permanently activated Ras-Raf-MEK-ERK pathway not only suppresses IRF1 transcriptional activity but also inhibits the function of IRF1 as such, whereas MEK inhibitors restore it.[82] Dysfunctional activation of MEK increases susceptibility of Ras-transformed malignant cells to VSV infection. In contrast, inhibition of MEK restores their VSV resistance.[25-27,88] Similar observations were made on another Ras-transformed cell line, which has defects in the MEK/ERK pathway and is vulnerable to reovirus infection. In these cells, activation of MEK suppressed the binding of IRF1 to RIG-I promoter and thus blocked RIG-I transcription and downstream signaling. Overexpression of RIG-I restored downstream signaling and resistance to reovirus.[18] However, malignant cells displaying an activated Ras-Raf-MEK-ERK pathway are not necessarily susceptible to virus infection. For instance, fibrosarcoma cells with constitutively activated RAS may develop reovirus resistance associated with suppression of some factors required for effective viral entry into cells.[89]

In normal cells, viruses induce activation of IRF3, IRF5, and IRF7 and thereby trigger production of type 1 IFNs. However, in cancer cells, activation may be impaired, leading to virus sensitivity. For example, in normal hepatocytes, VSV infection induces IEF3 expression accompanied by type 1 IFN production and the acquisition of virus resistance. In contrast, in hepatocellular carcinoma cells, VSV does not activate IRF3 expression due to IRF3 mRNA's aberrant

splicing. This defective splicing, which causes low IRF3 expression levels, prevents activation of IFN-beta transcription and leads to virus sensitivity.[28]

The comparison of normal and malignant macrophage derived cells demonstrated that basal and NDV-induced expression levels of IRF3 and IRF7 were reduced in cancer cells. Because the IRF3-IRF7 complex triggers transcription of type 1 IFNs, reduced levels of the complex are associated with low levels of type 1 IFNs, which are insufficient for protection against viruses. In cancer cells, a negative correlation was found between NDV sensitivity and the basal expression levels of IRF3, IRF7, and IFN-beta.[29] In lung cancer cell lines, IRF7 and/or IRF5 epigenetic silencing were associated with high VSV sensitivity. In cells that were the most sensitive to VSV, promoters of both IRF5 and IRF7 were hypermethylated. Moreover, experimental knockdown of IRF5 and IRF7 by siRNAs increased cell susceptibility to viral infection. In contrast, IRF5 and IRF7 overexpression reduced this susceptibility.[30]

The phosphatase and tensin homolog (PTEN) acts as a tumor suppressor gene and participates in IRF3 import into the nucleus, which is required for the transcription activation of IFN genes.[41] Therefore, it plays a critical role in antiviral innate immunity.[90] Phosphatase and tensin homolog tumor suppressor gene is commonly inactivated by mutations or deletions in human cancers,[91] resulting in VSV sensitivity.[32]

6 | DEFECTIVE IFN RESPONSE IN MALIGNANT CELLS

The type 1 IFN response pathway, schematically shown in Figure 5, is triggered by interaction of either IFN-alpha or IFN-beta with a receptor on the cell surface. The receptor consists of a complex of 2 transmembrane subunits, the products of the IFNAR1 and IFNAR2 genes.[92] After the interaction, the complex activates receptor-associated Janus kinase (JAK) 1 and tyrosine kinase 2. The kinases phosphorylate the STAT1 and STAT2 proteins, which form a dimer and interact with IFN-regulatory factor 9 (also known as p48) to form a trimolecular complex called IFN-stimulated gene factor 3. IFN-stimulated gene factor 3 moves to the nucleus and activates the transcription of interferon-stimulated genes[92] (Figure 5). Interferon-stimulated genes encode a family of proteins that inhibit multiple stages of a viral infection, including virus entry, translation, replication, assembly, and dissemination.[93] Other types of IFNs employ different receptor molecules, although their signal transduction pathways utilize similar JAK kinase and STAT proteins. Janus kinase 1 participates in type 1 and type 3 IFN signaling, while JAK2 participates only in the type 2 IFN signaling cascade.[94,95]

An impaired IFN response pathway is a common defect in cancer cells. The genes that belong to the pathway whose defects were shown to be associated with sensitivity to viral oncolysis are described below and listed in Table 2.

7 | IFN RECEPTORS

Low expression levels of IFNAR1 and/or IFNAR2 protein and/or mRNA are characteristic of different malignancies, including melanomas,[104] mesotheliomas,[31] and carcinomas of hepatocellular,[9,10] pancreatic,[11] and gastric[12] origin. IFNAR1 expression was also missing in approximately 25% of 48 mesothelioma tumor biopsies.[31] In addition, low IFNAR protein levels are common in various bladder cancer cell lines and in clinical samples of bladder tumors. IFNAR expression level

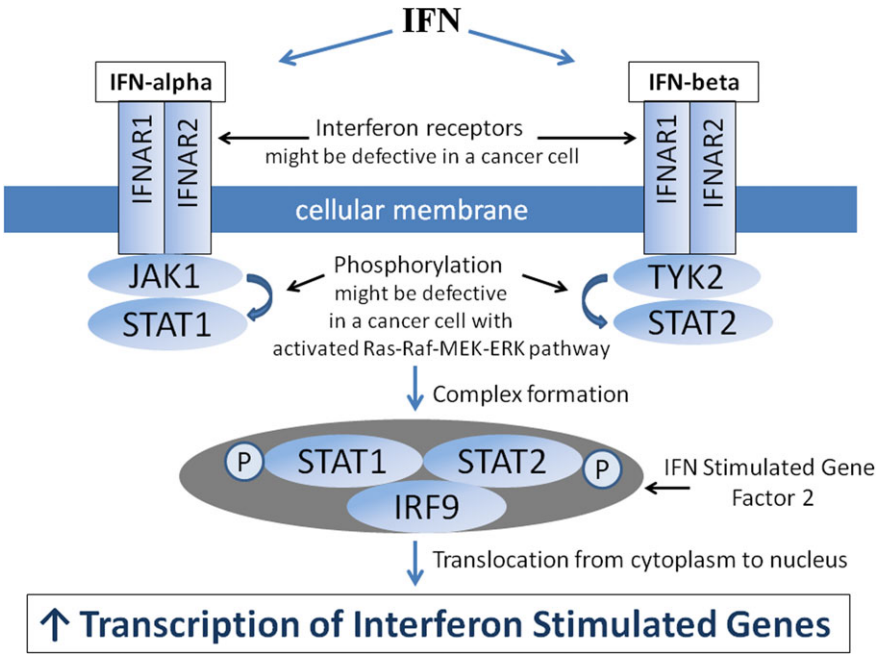

FIGURE 5 IFN-alpha and IFN-beta response pathways. Type 1 IFN response is triggered by a cell surface receptor represented by a complex of 2 transmembrane subunits IFNAR1 and IFNAR2. After interaction with IFN-alpha or IFN-beta, the complex activates receptor-associated Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK 2). The kinases phosphorylate the signal transducer and activator of transcription 1 (STAT1) and STAT2 proteins. These phosphorylated proteins (STAT1 and STAT2), in the form of a dimer, interact with IFN-regulatory factor 9 (IRF9, also known as p48) and form a trimolecular complex called IFN-stimulated gene factor 3. Interferon-stimulated gene factor 3 relocates from the cytoplasm to the nucleus, where it activates transcription of interferon stimulated genes. Interferon stimulated genes encode a family of proteins that inhibit multiple stages of viral infection, including virus entry, translation, replication, assembly, and spread. Malfunction of IFNAR1, IFNAR2, JAK1, STAT1, STAT2, and/or IRF9 disrupts transcription of IFN-stimulated genes, making cancer cells vulnerable to oncolytic virus infection

TABLE 2 Biomarkers related to the IFN response pathway

Category		Gene/Protein Name	Type of Defect	Sensitivity to	Reference
Interferon receptors		IFNAR1	Deletion	NDV	60
		IFNAR1/2	Expression is low or absent	VSV	31
		IFNAR2		VSV	96
Genes of JAK/STAT pathway		JAK1	Expression is low or absent	VSV	31
		JAK1/2	Experimental inhibition	VSV	23,97
		Tyrosine kinase 2	Expression is low or absent	VSV	31
		STAT1	Transcription is absent	Respiratory syncytial virus	98
		STAT1	Experimental knockdown	Sindbis virus	20
		STAT1	Delayed and low phosphorylation	Measles virus (MV)	19
		STAT1, STAT2	Low expression, absent phosphorylation	NDV	99
		STAT1, STAT2	Expression is low or absent	VSV	31
		STAT1, STAT2	Low phosphorylation	VSV	100
		STAT2	Expression is low		100
Genes of Ras, Raf, MEK, and ERK pathway		MEK2	Dysfunctionally activated	VSV	88
		B-RAF			101
Interferon stimulated genes (ISGs)	GTPase	GBP-1	Expression is absent	VSV	102
	Apoptosis inducer	XAF1			
	Anti-apoptotic protein	EPSTI1			
	Proteins with tetratricopeptide repeats	IFN-induced protein with tetratricopeptide repeats 1	Expression is low or absent	MV	19
	GTPase	MX1/MxA	Low expression	VSV	23
			Experimental knockdown		102
			Low expression	Adenovirus 5 and adeno-associated viruses 5 and 6	103

correlated with tumor grade: The content of IFNAR was relatively high in more differentiated tumors and relatively low in less differentiated tumors.[96]

IFNAR expression levels also correlated with cell sensitivity to viral infection. It was shown that in primary macrophages, deletion of the IFNAR1 gene was associated with NDV susceptibility.[60] In mesothelioma cell lines, which were sensitive to VSV, IFNAR1 and/or IFNAR2 expression were significantly downregulated or undetectable.[31] In bladder carcinoma cell lines, an inverse correlation was found between the inhibition of cellular proliferation induced by type 1 IFN treatment and VSV susceptibility. Cells that most actively proliferated despite IFN treatment were most sensitive to the virus. It has been suggested that VSV sensitivity can be caused by decreased IFNAR expression. This assumption was confirmed by the experimental knockdown of IFNAR either by siRNA or by neutralizing antibodies, both of which led to sensitization of the bladder carcinoma cells to VSV.[96]

IFNAR1 protein expression in clinical tumor samples can be conveniently and inexpensively evaluated by immunochemistry. Therefore, such easily measurable proteins as IFNAR1 can be particularly useful markers for the selection of cancer patients who are most likely to benefit from oncolytic virotherapy.

8 | JAK/STAT PATHWAY

Alterations in the JAK/STAT pathway were found in a number of malignancies. In some lymphomas,[105,106] myeloid leukemias,[107] and prostate cancers,[98] there was no expression or functional activation of STAT1. In chronic lymphocytic leukemia, STAT1 and STAT3 phosphorylation was impaired.[108] In some prostate cancers, JAK1 expression was not detected,[109] while in some leukemias and lymphomas, disabling mutations or chromosomal rearrangements of JAK 1 and/or JAK2 have been observed.[110-113]

There is a relation between JAK/STAT pathway dysfunction and virus sensitivity. Janus kinase 1/2 inhibitors make cancer cells sensitive to VSV infection. Treatment of virus-resistant head and neck cancer cells with these inhibitors before or simultaneously with administration of VSV enhanced the spread of infection and increased the virus progeny yield by few orders of magnitude.[97] Similarly, treatment of VSV-resistant pancreatic ductal adenocarcinoma cells with JAK1/2 inhibitor promoted VSV sensitivity.[23]

In fibrosarcoma cells, a defect in the IFN response pathway at the level of STAT protein promotes the cells' NDV sensitivity. Phosphorylation of STAT1 and STAT2 that occurs in normal fibroblasts in response to IFN treatment was not detected in these cells. Moreover, pretreatment of these cells with IFN-beta induced a much smaller number of IFN-stimulated genes and did not inhibit NDV spread.[99]

Similar observations were made in prostate cancer cells with respect to their susceptibility to respiratory syncytial virus. Unlike normal prostate cells, prostate cancer cells could not activate STAT1 transcription, despite their ability to induce IFN production in response to respiratory syncytial virus. It was concluded that a defect in the IFN response pathway at the level of STAT1 protein led to VSV sensitivity.[98] Similarly, STAT1 experimental knockdown rendered hepatocellular carcinoma cells susceptible to Sindbis virus.[20]

More examples of the relationship between a deficient JAK/STAT pathway and viral oncolysis were found in studies with mesothelioma and sarcoma cells. Vesicular stomatitis virus-sensitive mesothelioma cells, in addition to reduced expression levels of IFNAR1 and/or IFNAR2 mRNA, also displayed downregulation of one or several transcripts of STAT1, STAT2, JAK1, tyrosine kinase 2, PKR, and IFN-regulatory factor 9 (p48).[31] It also has been shown that measles virus-sensitive sarcoma cells exhibit weak, delayed, or only transient phosphorylation of STAT1 and weak or undetectable expression of IFN-induced protein with tetratricopeptide repeats 1.[19]

In another study, a decrease in IFN-induced phosphorylation of STAT1 and STAT2 proteins was observed when the Ras-Raf-MEK-ERK pathway was activated. Moreover, in cells with the activated pathway, the total amount of STAT2 was reduced. However, STAT2 overexpression partially restored the transcription of IFN-induced genes along with VSV resistance.[100]

It is sometimes difficult to distinguish whether cancer cell sensitivity to viruses is caused by defects in the IFN induction or IFN-response pathways. For example, it was found that differences in the sensitivity of melanoma cell lines to VSV were associated with a mutation in the B-RAF gene, a representative of the RAF serine/threonine specific protein kinase family and a participant in the Ras-Raf-MEK-ERK pathway.[101] The mechanism that underlies this sensitivity is not yet known, and it is not clear if the mutation is associated with downregulation of genes involved in type 1 IFN induction or response pathways.

9 | IFN STIMULATED GENES

The products of the MX genes are proteins with a protective function against both RNA and DNA viruses. Most mammals have two MX genes, MX1 and MX2, whose protein products are called MxA and MxB.[114] Mx proteins bind GTP and act as GTPases.[115] MX genes belong to a family of IFN stimulated genes; upregulation of their expression in response to viruses depends on the production of type 1 or type 3 IFNs.

Constitutive expression of Mx1 in normal and malignant pancreatic cells correlates with VSV resistance. Cell lines with particularly low or absent Mx1 and OAS gene expression are often sensitive to VSV.[23] Moreover, shRNA-mediated knockdown of Mx1 promotes VSV replication in virus-resistant cells.[102] Low expression of Mx1 mRNA and MxA protein in primary or established cell lines of pancreatic adenocarcinoma is associated with sensitivity to adenovirus 5 and adeno-associated viruses 5 and 6.[103]

In the pleural mesothelioma cell lines that were most VSV sensitive, neither basal nor IFN-beta stimulated expression of MxA, PKR, and OAS was detected. However, in cell lines that were less sensitive to VSV, IFN-beta treatment stimulated, to various degrees, transcription from these genes.[31] Thus, IFN-beta treatment response, in the form of induction of MxA, PKR, and OAS transcription, correlates with VSV sensitivity.

A relationship was also found between the expression of GBP1, XAF1, and/or EPSTI1 genes and viral oncolysis in pancreatic ductal adenocarcinoma cells. These genes were constitutively expressed in VSV resistant cells and were not expressed at all in VSV-sensitive cells.[102]

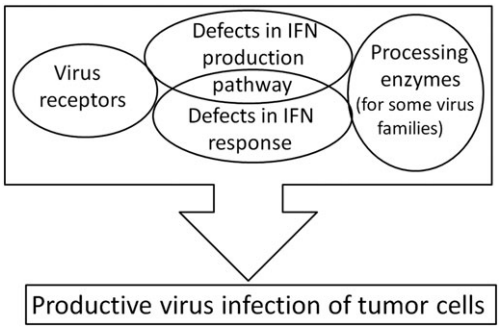

FIGURE 6 Host requirements for viral infection of tumor cells. For productive infection, viruses require cell to express virus receptors and to have a malfunctioning IFN pathway. Some virus families also require cells to express processing enzymes, without which infective virions cannot be formed

10 | DIRECTIONS FOR FUTURE RESEARCH

There are genes that are not involved in the IFN signaling pathway, whose expression is necessary for a productive viral infection of tumor cells (Figure 6). The virus replication cycle is a multistep process that involves the virus initial entry into the host cell, synthesis of viral proteins and nucleic acids, the assembly of progeny virions, and their release from the cell. Host cells must provide all the necessary conditions for this process. Viruses require that host cells express on their surface virus receptors, which control the efficiency of virus entry into the cell. Some viruses additionally require cells to express processing enzymes that perform modifications or cleavage of viral proteins necessary for the formation of mature infectious virions.

Expression levels of the viral receptors, processing enzymes and other genes needed for productive viral infection can vary considerably in different cancer cells. This variation along with variations in expression and functional activity of the genes involved in the IFN signaling pathways cause differences in cancer cell sensitivity to a particular virus. Therefore, all these genes could potentially serve as predictive biomarkers for identifying individual cancer patients who can most likely benefit from oncolytic virotherapy. Until now, relationships between the efficacy of viral oncolysis and the expression levels or functional abilities of these genes have been poorly understood, but future research should fill this gap.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

ORCID

Olga V. Matveeva http://orcid.org/0000-0001-8555-9847
Peter M. Chumakov http://orcid.org/0000-0002-8078-2908

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