Published in final edited form as:

Crit Rev Oncog. 2014 ; 19(0): 107–119.

NK Cells and Virus-Related Cancers

Rabinarayan Mishra, Raymond M. Welsh*, and Eva Szomolanyi-Tsuda

Department of Pathology, University of Massachusetts Medical School, 368 Plantation Street, AS9-2051, Worcester, MA 01605

Abstract

Natural killer (NK) cells become activated during viral infections and can play roles in such infections by attacking virus-infected cells or by regulating adaptive immune responses. Experimental models suggest that NK cells may also have the capacity to restrain virus-induced cancers. Here, we discuss the seven viruses linked to human cancers and the evidence of NK cell involvement in these systems.

Keywords

NK cells; virus; cancer

I. INTRODUCTION

Natural killer (NK) cells are effector and regulatory lymphocytes rapidly mobilized into the host response to viral infections. They are cytotoxic, interferon gamma (IFN- γ)-producing cells whose activities are regulated by cytokines and by stochastically expressed positive- and negative-signaling NK cell receptors (NKR) that recognize cellular stress-related molecules, adhesion molecules, and major histocompatibility complex (MHC) proteins.^{1,2} Some NKR have evolved to directly recognize certain viral proteins.^{3–6} NK cells patrol the host at a moderate state of activation and at a relatively high frequency (i.e., 15% of peripheral blood lymphocytes), but they proliferate and become even more active during a viral infection.^{7,8} Innate cytokines such as the type 1 IFNs and IL-15 are rapidly induced during viral infections and can stimulate the activation and proliferation of NK cells and augment the proliferation of T cells.⁹ The dynamics of this process follow the innate and adaptive immune-response paradigm first described in the 1970s: an early cytokine-driven activated NK cell innate response followed by a peak in virus-specific T cells.^{8,10,11} Notably, Ron Herberman, to whom this volume is dedicated, was among the first to report the activation of NK cells during viral infection. NK cells control infections by direct cytotoxic mechanisms or by the production of anti-viral cytokines, such as IFN- γ . Recognition of virus-infected cells may occur if the NK cells become positively activated by the up-regulation of stress-related proteins in virus-infected cells or if they fail to respond to negative signals driven, for example, by the down-regulation of class 1 MHC antigens on

virus-infected cells.^{2,12} To counter these effects, viruses may encode proteins that interact with these negative- and positive-signaling NKR and their ligands to alter the dynamics of this process.

The murine cytomegalovirus (MCMV) infection of C57BL/6 mice is the most well-studied model for the control of viral infections by NK cells and demonstrates the complexity of a multi-component process. Genetics of resistance to MCMV maps on chromosome 6 to the NK cell complex,¹³ which encodes a series of relevant proteins, including the positive-signaling NKR NKR-P1c (NK1.1) and NKG2D. It also encodes CD94 and NKG2A, B, C, and E proteins, which interact to form negative- or positive-signaling heterodimers, and the Ly49 series of c-type lectin molecules that deliver negative or positive signals when engaging their cognate MHC molecules.¹⁴ The NKG2 and CD94 molecules have human homologues, as does NKp46, a positive-signaling receptor encoded on mouse chromosome 7.¹⁵ Genetic resistance to MCMV maps to Ly49H, a positive-signaling NKR that reacts with the MCMV-encoded glycoprotein m157.^{3,4,5,16,17} The Ly49 molecules lack human homologues, but human killer cell immunoglobulin-like receptors (KIRs) perform similar functions by recognizing MHC molecules.¹⁸ MCMV also encodes a decoy class I MHC antigens¹⁹ and ligands for NKG2D.²⁰ Human CMV is similar with regard to its complex relationship with its host.¹ Less is known about the control of other viral infections by NK cells, but many mouse and human viruses encode proteins that alter expression of IFN, MHC, and NKR and their ligands, suggesting that NK cells are important in their pathogenesis. Whether NK cells play a role in the regulation of virus-induced tumors can be inferred from these capacities, though direct evidence is limited. Certainly, NK cells can be shown to reject virus-transformed cells implanted into mice,²¹ but definitive evidence that they control the natural progression of a virus-induced cancer *in vivo* is much more limited.

Recent work has revealed that NK cells may also mediate a profound immunoregulatory role in viral infections distinct from their direct targeting of virus-infected cells.^{22–31} NK cells can regulate the anti-viral T-cell response by virtue of the abilities of IFN-activated NK cells to directly lyse activated T cells. As a consequence of this activity, NK cells may serve as rheostats regulating the T cells that control whether an infection is cleared, becomes persistent, or becomes lethal. The fact that this immunoregulatory activity can play a role in persistent infections may have implications for the development of tumors associated with persistent infections in humans.

II. EVIDENCE FOR THE NK CELL CONTROL OF VIRUS-INDUCED TUMORS IN EXPERIMENTAL MODELS

Many tumors in humans and in various animals, including mice, are induced by viral infections. These tumors express viral proteins and are thought to be mainly controlled by cytotoxic CD8 T lymphocytes (CTL) specific for viral peptides. The role of NK cells in the resistance to virus-induced tumor formation is still not well understood. However, NK cells restrict the growth of syngeneic tumors implanted into mice, and acute virus infections that activate NK cells can enhance the rejection of implanted tumors.²¹ The role of NK cells in

the control of transgenic viral oncogene-induced mouse tumors has been suggested. Guerra et al. showed that TRAMP mice, which express SV40 T antigens in the prostate epithelium and are used as a model of prostate adenocarcinoma development, developed tumors early if they lacked NKG2D NKR. Similarly, NKG2D was essential for the control of myc transgenic B cell lymphomas in Eμ-myc transgenic mice.³² The contribution of NK cells to tumor resistance in hosts chronically infected with tumor viruses and spontaneously developing virus-induced tumors, however, is much less understood, although this knowledge would be highly relevant to human diseases.

Members of the polyomavirus family are small DNA tumor viruses that cause persistent infection in the host and harbor powerful oncogenes. Mouse polyomavirus (PyV) is ubiquitous in nature but induces tumors only in immunocompromised hosts, similarly to most human tumor viruses. PyV has provided an excellent mouse model to dissect the components of the host immune system that regulate persistent virus infection and tumor development. CD8 T cells specific for PyV epitopes greatly reduce the persisting virus load and consequently prevent tumor development, as a high virus load is prerequisite of tumor induction.³³ Unexpectedly, however, mice which are defective in αβ T cells (including CD4 and CD8 T lymphocytes) and have a high persisting virus load also show resistance to PyV-induced tumors.

NK cells and γδT cells can efficiently kill PyV-transformed tumor cells *in vitro* in cytotoxicity assays, and these two cell types *in vivo* also contribute to the control of PyV tumor outgrowth. Experimental PyV infections, which left practically all PyV-infected TCRβ KO (αβ T-cell deficient) mice tumor-free, induced tumors in ~80% of mice that lacked both αβ and γδT cells, indicating that γδ T cells could provide effective tumor surveillance. Although both T-cell-deficient NK-cell-sufficient and T- and NK-cell-deficient mice had close to 80% tumor incidence, the tumors appeared faster, with significantly shorter latency in mice that lacked both NK cells and T cells compared to animals with functional NK cells.³⁴ Thus, NK cells also contributed to *in vivo* tumor resistance. Notably, γδ T cells and NK cells did not act by reducing the PyV load, as there was no difference in the persisting viral load between mice which had or lacked NK cells or γδ T cells, respectively. Thus, NK cells (and also γδ T cells) have an anti-tumor activity in this naturally occurring virus-induced tumor model.³⁴

PyV-induced tumor cell lines express Rae-1, a stress molecule often found on virus-infected or transformed cells that serves as ligand for NKG2D, an activating NKR, and NK cells kill PyV-induced tumor cells *in vitro* in a NKG2D-dependent manner. Blocking or eliminating the NKG2D-Rae-1 interaction prevents this *in vitro* cytotoxicity. *In vivo* studies showed that in the absence of all T cells, NK cells delayed tumor development, but they could not prevent it, suggesting that the PyV-induced tumors developed an immune-escape mechanism.³⁵ Possible ways for the tumors to escape the control of NK cells would be to prevent NK cell migration to the tumors, to make NK cells dysfunctional, or to block the recognition of the tumors. Investigation of advanced PyV-induced tumors showed that the tumors contained NK-cell infiltrates, and the tumor-infiltrating NK cells were functionally competent, in that they could produce IFN-γ, granzyme B, and were able to degranulate. However, the expression of Rae-1, the NKG2D ligand involved in the recognition of tumor

cells by NK cells, was down-modulated by pro-inflammatory cytokines secreted into the tumor environment, mostly by inflammatory macrophages. IL-1, IL-33, and TNF each could suppress Rae-1 protein expression on PyV-induced tumor cells by a post-transcriptional mechanism. These findings implicated the inflammatory microenvironment of a virus-induced tumor in escape from NK cell surveillance.³⁵ More recent experiments showing earlier tumor development in PyV-infected NKG2D KO T-cell-deficient mice compared to T-cell-deficient mice (Mishra, unpublished) demonstrated that the role of NK cells in tumor resistance is mostly mediated by NKG2D.

III. EVIDENCE FOR A ROLE FOR NK CELLS IN VIRUS-ASSOCIATED TUMORS IN HUMANS

Seven viruses have been associated with cancers in humans: Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human papilloma virus (HPV), human T-cell leukemia virus (HTLV), Kaposi sarcoma virus (KSHV), and Merkel cell polyomavirus (MCV).^{36,37} The evidence that NK cells may be involved in control of these virus-induced tumors is indirect. In general, these virus-induced tumors are more likely to appear in globally immune-suppressed individuals, who have deficiencies in NK cell activity as well as in other components of the immune system, and co-infection with the immunosuppressive HIV promotes the tumorigenic potential of EBV, HPV, HTLV, KSHV, and MPV. Here, we discuss the evidence for NK cell control in these virus-associated human cancers.

A. Epstein-Barr Virus

Epstein-Barr virus (EBV) a γ herpesvirus, is one of the most commonly occurring human viruses; by the age of 35 years ~95% of people are seropositive for EBV, indicating past infection.³⁸ Infection is usually asymptomatic in young children, but in adolescents and young adults it often (35–50% of the cases) leads to infectious mononucleosis.³⁹ After the acute phase of infection, EBV, like many other herpesviruses, persists lifelong in a latent form, with periodic reactivations. In some individuals, EBV infection is associated with tumor development, specifically Burkitt's lymphomas, Hodgkin's lymphomas, nasopharyngeal cancers of epithelial origin, leiomyomas, NK, T and T and other B-cell lymphomas, and gastric carcinomas.^{40,41} The role of CD8 T cells in immune responses to EBV is well established and has been studied in detail, but there are several lines of evidence indicating that NK cells may play an additional, significant role in the control of EBV infection, and thereby indirectly contribute to the resistance to EBV-induced tumors.³⁸

A report from the early 1980s described the occurrence of severe-to-fatal EBV infections in patients with inherited, non-X-linked defects in their cellular immune responses, which were likely defects in NK cell function,⁴² although T-cell defects were not excluded. Moreover, a rare X-linked hereditary defect in SAP (X-linked lymphoproliferative syndrome (XLP)) with defective NK, T, and NKT responses and hypogammaglobulinemia was characterized by high susceptibility to EBV infections, manifested by fulminant infectious mononucleosis, high levels of EBV-infected B cells, and high incidence of lymphomas, which suggests a role for NK cells among other effectors in EBV control.⁴³ Acute infectious mononucleosis patients were reported to have NK cells in elevated numbers in the blood for at least a

month, a higher percentage of their NK cells exhibited a CD56^{bright} CD16- phenotype,³⁹ and these NK cells had increased ability to kill EBV-infected cell lines *in vitro* compared with NK cells from healthy individuals. Moreover, an inverse relationship was seen between the percentages of CD56^{bright} NK cells in the blood and EBV viral load in infectious mononucleosis patients, suggesting that the CD56^{bright} NK cells contribute to EBV clearance in the acute phase of infection.³⁹ NK cells taken from tonsils, the site of primary EBV infection, produced more IFN- γ upon stimulation by activated DC than NK cells from the blood, and tonsillar NK cells greatly reduced B-cell transformation by EBV when cultured together with EBV-infected B cells *in vitro*. Together, these data argue for a protective role of NK cells against lymphomas by limiting the extent of the initial EBV infection.³⁸ Reactivation of EBV by switching from latent to lytic viral gene expression increases the sensitivity of the cells to NK-cell-mediated killing because of down-regulation of MHC class I molecules that act on inhibitory NKR, in addition to up-regulation of ULBP-1 and CD112, that engage the activating NKR, NKG2D, and DNAM-1, respectively.⁴⁴

Studies on patients with life-threatening post-transplantation lymphoproliferative disorders caused by EBV showed that these patients had lower numbers of CD56^{bright} NK cells. Moreover, the expression of NKG2D and NKp46 activating receptors was lower and PD-1 expression was higher on their NK cells, and these phenotypic changes were associated with decreased NK cell function, consistent with NK cell exhaustion. Although the severely immunocompromised patients of this study also had T-cell dysfunctions, these data are consistent with NK cells playing a role in controlling EBV persistence.⁴⁵

An X-linked genetic defect in the magnesium transporter, MAGT1, results in decreased free intracellular magnesium and is associated with high levels of EBV and EBV-infected B cells and high incidence of EBV-induced lymphomas. A recent report demonstrated that the lack of free magnesium caused a decreased expression of NKG2D on NK and T cells, and impaired the cytolytic elimination of EBV-infected cells. Remarkably, magnesium therapy of the patients increased the NKG2D levels on NK and T cells and corrected the defect in EBV control. This is the first account that directly links cytotoxicity mediated by NKG2D-NKG2D ligand interactions to EBV clearance in patients.⁴⁶

A strong argument for the role of NK cells preventing EBV-induced tumor formation is a recent report of a young patient suffering from a rare, isolated NK cell deficiency (with normal NKT cells and adaptive immunity), who developed EBV-related smooth muscle tumors.⁴⁷ Smooth muscle tumors induced by EBV had been reported previously in severely immunocompromised people after transplantation or with HIV infection.⁴⁸

EBV utilizes several mechanisms to escape from NK-cell-mediated control. The expression of the NKG2D ligand MICB is down-modulated by an EBV-encoded microRNA, miR-BART-2-5p. This microRNA blocks the translation of MICB by binding to the 3'UTR of the message; neutralization of this effect by applying a microRNA antagonist "sponge" increases MICB on the cells and renders them more susceptible to NK-cell-mediated killing.⁴⁹ EBV-infected B cells also employ another way of preventing NK-cell-mediated

control, as they down-regulate NKG2D on NK cells in their proximity by secreting indoleamine 2,3 dioxygenase (IDO) metabolites.⁵⁰

B. Hepatitis B and Hepatitis C

HBV and HCV cause persistent infections of the human liver that lead to hepatocellular carcinoma. Cancer induction by HBV, a DNA virus, is associated with the HBV-X gene, whose encoded protein binds to the tumor suppressor p53, among other activities.⁵¹ Virtually all virus-induced cancers are associated with DNA viruses, like HBV, or retroviruses, whose RNA is reverse transcribed into a DNA state. The flavivirus HCV is unusual in this aspect, as it is an RNA virus that also induces hepatocellular carcinoma. The mechanism of cancer induction by HCV, while still unclear, seems to be associated with the chronic inflammation of the infected liver. For either virus, a long-term persistent infection of the liver is a prerequisite for cancer induction. A role for NK cells is suspected but not definitive. First of all, the liver is an organ rich in NK cells, and NK cell numbers increase after a virus infection.⁵² Second, studies in mice have suggested that some NK cells may express the capacity of memory and that these are particularly enriched in liver.⁵³ Third, NK cells get activated during HBV and HCV infections,⁵⁴ and experimental models with transgenic HBV mice⁵⁵ or HCV plasmid infected hepatoma cell lines⁵⁶ have indicated that NK cell-produced cytokines like IFN γ and TNF can clear hepatocytes of infection.

Undoubtedly, T cells contribute to the pathogenesis of HBV and HCV infections and to the clearance of virus. However, the interaction between NK cells and T cells can be quite complex, particularly in the environment of the liver, which is an immunosuppressive organ that can exhaust both NK cells and T cells. The induction of inhibitory molecules such as PD-1, CTLA-4, and Tim-3 and an environment rich in IL-10 and TGF β complicates this interaction.⁵⁴ Notably, HBV-specific CD8 T cells may up-regulate TRAIL receptors, rendering them susceptible to killing by IFN-induced NK cells, which up-regulate TRAIL.⁵⁷ Nevertheless, correlations have been made between the low levels of NK cells and progression of hepatocellular carcinomas.⁵⁸ Further, both HBV and HCV-persistent infections are treated with IFN, which has many properties including the ability to activate NK cells. IFN-treated HCV patients that respond with a strong virus reduction have sustained NK cell activity.⁵⁹ For IFN treatments, high pre-treatment levels of inhibitory KIR and NKG2A receptors are associated with treatment failure.⁶⁰

Long-term persistence of high levels of viral antigen is characteristic of HIV as well as HBV and HCV infections. HIV is, of course, not a tumor virus, but it can immune suppress a host and allow for recrudescence of tumor viruses. HBV, HCV, and HIV persistent infections are thought to be controlled, at least in part, by T cells,^{54,57} but why different HIV-infected individuals have different antigen load set points and why some hepatitis virus infections spontaneously resolve and others do not has remained a mystery. A series of human genetic studies has been performed by Carrington et al. in an attempt to correlate the pathogenesis of these infections with the presence of certain NKR, notably the KIR and the MHC antigens with which they engage.⁶¹ Some KIR–MHC combinations have shown strong correlations with control of infection in a rather complex pattern. There is KIR-associated selection of HIV variants that imply direct antiviral effects mediated by the NK cells⁶² and HIV-infected

T cells have clearly been shown susceptible to lysis by NK cells.⁶³ On the other hand, some KIR that correlate with better prognosis of HIV and HCV are those with negative signaling capacity.^{64–68} These findings about the negative-signaling KIR would seemingly be consistent with the concept that the suppression of NK cell activity by negative-signaling NKR would allow for greater T cell responses to control the infection. Studies with LCMV in mice have shown that the functions of NK cells activated during the first few days of infection could have long-term consequences on the levels and duration of viral persistence,^{23,24} and it remains to be determined whether these are factors in HBV and HCV infections.

C. HPV

HPV causes cervical carcinoma, the second most common cancer in women worldwide. In most individuals, HPV is cleared within 2 years after infection, but in ~10% of infected people, the virus persists long term, and can cause low-grade intraepithelial squamous lesions that may progress to dysplasia, *in situ* carcinoma, and finally invasive carcinoma.⁶⁹ HPV has developed multiple immune evasion strategies to escape CTL- and NK-cell-mediated control.

The E5 protein of HPV 16 down-regulates HLA-A and HLA-B MHC class I molecules to evade CTL responses, but the expression of HLA-E and HLA-C molecules that ligate inhibitory NK cell receptors, is unchanged.⁷⁰ The products of E6 and E7 oncogenes of the high-risk HPV16 interfere with IFN γ secretion by NK cells responding to IL-18. This is achieved by competitive binding of the E6 and E7 proteins to the IL-18 receptors on NK cells, thereby preventing IL-18 binding and signaling.⁷¹ E7 protein can also down-modulate MHC class I expression on cervical carcinoma cells. SiRNA knock-down of E7 expression can reverse this effect and restore higher class I expression.⁷² Patients with cervical cancers or high-grade intraepithelial squamous lesions have circulating NK cells with significantly lower expression of the NKG2D, NKp30, and NKp46 activating receptors than healthy subjects, suggesting that HPV-induced tumors associate with NK cell dysfunctions.⁷³

A hereditary syndrome characterized by monocytopenia and a decrease in NK and B cells was recently shown to be caused by GATA2 mutations.^{74,75} Severe HPV infections and HPV-induced tumors are the main clinical manifestations of this syndrome, in addition to a heightened susceptibility to Mycobacterium infections.^{75–77} The GATA2 defect mostly affects the CD56^{bright} NK cells, which are eliminated, and NKG2D expression is reduced on the remaining NK cells.⁷⁵ The high association of this NK deficiency with HPV pathology indicates that NK cells may have an important role in HPV control, although there are DC and B cell abnormalities also in these patients.

D. HTLV-1

HTLV-1 is a human retrovirus causing adult T-cell leukemia (ATL), a CD4 T-lymphoid malignancy in 2–4% of the infected population. Another 1–4% of people infected with HTLV-1 suffer from HTLV-1-associated myelopathy/tropical spastic paraparesis.⁷⁸ In SCID mice the frequency of tumor outgrowth from implanted HTLV-1-transformed human T cells was higher if NK cells were depleted.⁷⁹ It is unclear, however, what role NK cells play in

the pathogenesis of ATL in humans. HTLV-infected primary human CD4 T cells down-regulate MHC class I expression, but despite the low levels of MHC class I engaging negatively signaling NKR, NK cells do not kill HTLV-1-infected CD4 T cells *in vitro*. The escape of HTLV-infected cells from NK cell cytotoxicity is achieved by down-regulation of ICAM-1 and ICAM-2 by the HTLV p12 protein, which impairs the adhesion of NK cell effectors to virus-infected target cells. HTLV-1-infected cells also fail to express ligands for the activating NK cell receptors NKG2D, NKp30, NKp44 and NKp46.^{77,80} HTLV-1 infection also interferes with type 1 IFN signaling, which has antiviral activity against HTLV-1 and is also important for NK cell activation. HTLV-1 tax induces SOCS1, an inhibitor of type 1 IFN, and also increases the half-life of the synthesized SOCS1 protein.^{81,82} Tax also interferes with the induction of IFN-stimulated genes by competing with the transcriptional regulators CBP and p300, and by decreasing the phosphorylation of Tyk2 and STAT2 signaling proteins.⁸³

E. KSHV

KSHV is a gamma herpesvirus and causative agent of Kaposi sarcomas (KS), rare tumors that consist mostly of spindle cells of endothelial origin. These tumors, like many other virus-induced tumors, occur in immunocompromised people.⁸⁴ In addition to KS, KSHV can cause pleural effusion lymphomas and multicentric Castleman's disease, a lymphoproliferative disorder. The mechanisms involved in KSHV latency, reactivation and KS pathogenesis are not well understood, but it has been established that KSHV has a complex immune-evasion strategy to escape the cytotoxic effects of T and NK cells. It down-regulates MHC class I on the infected cells to evade CTL responses. This would make the cells more susceptible to NK cell cytotoxicity, but KSHV also down-regulates NK cell co-stimulatory molecules ICAM-1 and B7-2, NKG2D ligands MICA and MICB and the ligand for NKp80.^{85–87} In addition, KSHV developed multiple mechanisms to antagonize type1 IFN, including the production of viral homologues of IFN responsive factors (IRF) that interfere with the expression of IFN-1-inducible genes and IFN-1-initiated downstream signaling.⁸⁸ As type 1 IFN is an important NK cell activator, the inhibition of its effects by KSHV also favors the escape of virus-infected cells and tumors from NK-cell-mediated killing.

F. Merkel Cell Polyomavirus (MCV)

Merkel cell polyomavirus (MCV) is the only polyomavirus among the 10 human polyomaviruses discovered thus far that has been shown to cause human tumors.^{89,90} BK and JC polyomaviruses cause severe diseases in immunocompromised individuals, but their involvement in human tumors is controversial.⁹¹ The disease-causing potential of the other newly discovered human polyomaviruses is not well understood, with the exception of MCV. Merkel cell carcinomas (MCCs) are rare neuroendocrine skin tumors that occur in severely immunocompromised people, in organ transplant recipients, patients infected with HIV, in those suffering from leukemia, and in the elderly. Approximately 80% of all MCCs carry MCV integrated into the genome. The other 20% of MCC have MCV-unrelated etiologies. The role of T cells in MCC is recognized, as T-cell infiltrates of the tumors correlate with better prognosis.⁹² The role of NK cells in the resistance to MCC has not yet been investigated.

Although not verified as human tumor viruses, JC and BK polyomaviruses cause severe diseases under immunosuppressive conditions, and they apply common immuno-evasion strategies. The JC virus is associated with progressive multifocal leukoencephalopathy (PML), a fatal neurodegenerative disease in severely immune suppressed people, and BK causes nephropathy and kidney rejection in transplant recipients. JC and BK polyomaviruses encode an identical microRNA, which targets the stress ligand ULBP-3 recognized by NKG2D. The expression of this microRNA, (BKV-miR-B1-3p/JCV-miR-J1-3p) reduces ULBP-3 on the infected cells, rendering them more resistant to NK cell-mediated killing.⁹³

IV. CONCLUSION

Whether and how NK cell control virus-induced cancers in humans is still under investigation. However, the studies in mouse models and clinical observations that we have described here provide evidence consistent with a role for NK cells in the host resistance to these tumors.

Acknowledgments

This work was supported by NIH research grants AI017672, CA34461, and AI081675 to RMW and CA66644 to EST. The views expressed are those of the authors and are not necessarily the views of the NIH.

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