REVIEW ARTICLE

Enhancement of cancer immunosurveillance by infections: a particular hygiene hypothesis for tumor growth?

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Abstract

Cancer results from a multi-step biological process consecutive to uncontrolled replication of transformed cells in which interactions with the surrounding environment and the host immune system play a major role. Anti-tumoral immune responses, mediated mostly by cytotoxic T cells, natural killer cells, and NK/T cells are in charge for killing the malignant cells and eradicating the tumor. At the early stages of cancer development they usually provide the appropriate immunosurveillance that eliminates most of the transformed cells.

The connection between cancers and infections, mostly by viruses, has attracted major attention. Roughly 12% of all human cancers are caused by oncoviruses via complex mechanisms involving host genetic variability and viral oncogenesis, while, in contrast, oncolytic viruses selectively infect and kill malignant cells. In addition to these direct effects of viruses on tumor cells, infections by viruses as well as by other agents, as key activators of the immune system, may enhance the efficacy of cancer immunosurveillance through bystander modulation.

This review provides an overview of the concept of immunosurveillance with highlighting its main cellular arms. We discuss the role of infections on cancer development and especially evidences of a positive effect of infections on the inhibition of some cancer development through enhancement of innate immune responses. This effect of infection might constitute a peculiar type of hygiene hypothesis, which could lead to distinct frequency of some cancers in populations with different exposure to infectious agents.

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1. Introduction

Cancer is the product of a multi-step biological process in which a single transformed cell leads to a clonal cancerous growth through consecutive divisions. This complex process involves different stages starting from initiation, which encompasses cell damage resulting in a permanently distorted growth potential, followed by progression, representing many rounds of cell replication mediating the gradual transition towards an independent, cancerous growth. Crucial expansion of these cancerous cells to distant sites resulting in numerous tumour sites has been recognized as metastasis [1].

Malignant tumor development generally occurs through a substantial period of life. Such a lengthy period is clear when comparing for example the starting age for smoking and the usual age at which diagnosis of lung cancer frequently happen [2,3] and is supported by many human and animal studies in which a variety of premalignant lesions has been recognized.

Both genetic and environmental factors are involved in this progression towards clinical cancer. Chemical carcinogens cause DNA damage in the exposed cells [4], leading to uncontroled cell proliferation, sometimes just by producing mild toxic damage in affected tissue [5].

The immune system is a central actor in the outcome of cancer development [6–8]. Normally, a competent immune system prevents the development of emerging tumors, a concept known as cancer immunosurveillance. Indeed, cancer immunosurveillance functions as an efficient extrinsic tumor suppressor mechanism against transformed cells. This protection is mediated via diverse arms of non-specific (innate) and specific (adaptive) immune mechanisms [8].

2. Carcinogenesis and environmental factors.

In 1954, Armitage and Doll developed the concept of cancer multistage model involving several basic assumptions:

1. Malignant tumors ascend from sequential alterations of one progenitor cell.
2. The process of developing a malignancy is equally likely for all cells in the same tissue.
3. Malignancy development process in one cell is totally apart from the process in any other cell.
4. Once malignancy has developed in a cell, spread to an obvious cancer is fast and involves numerous cells in the same tissue, and possibly would include metastasis to another tissue [9].

2.1 Infections

Infections with bacterial, viral and parasitic agents might have of central role in cancer rise. Schistosomiasis is a widespread helminthic infection in Asia and Egypt. The eggs of *Schistosoma japonicum* or *S. haematobium* are deposited in the colonic and bladder mucosa, respectively, causing inflammation and subsequent colon or bladder cancer [10]. A liver fluke, *Opisthorchis viverrini*, infects millions of people in Thailand and Malaysia. The flukes settle in bile ducts and increase the risk of cholangiocarcinoma [10]. *Helicobacter pylori*, a common bacterial infection of the stomach is a major cause of gastritis, ulcers and gastric cancer [10]. Aflatoxin, a mutagenic toxin found in moldy peanut and corn products, have been shown to interact with chronic hepatitis infection resulting in liver cancer development [11- 13]. Various major viral infections have contributed to development of malignancy. These include hepatitis B virus, (HBV) hepatitis C virus (HCV), Epstein Barr Virus (EBV), high-risk Human Papillomaviruses (HPVs), Human T lymphotropic Virus-1 (HTLV-1), HIV and Kaposi's sarcoma herpesvirus (KSHV).

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Globally, oncoviruses count for about 12% of human cancers [14-16]. Even with their high incidence, significance to public health, and liability to prevention and directed therapies, understanding virus-induced cancers still has difficult challenges attributed to inadequate animal models of the disease, different nature of virally provoked cancers, and the complex nature of the virus-host cell interactions leading to cancer development [17]. However, various underlying mechanisms have been hypothesized for cellular changes leading to cancer in the course if viral infections. They include (i) Associated chronic inflammation that drives reactive oxygen species production and initiates mutations. This is evident in chronic HBV and HCV infections, where virus induced inflammatory reactions may finally lead to hepatocellular carcinoma. [18]; (ii) Recognition of viral genomes or replicative intermediates by the host leading to induction of DNA damage response needed by many oncoviruses for their replication; (iii) Signaling mimicry by viral-encoded proteins that destabilize host signaling mechanisms regulating cell growth and survival. As a result, host cells gain genetic instability, which increases their mutation rate, and speed up acquirement of oncogenic host chromosomal alterations [19]. As the host develops immune defenses against invading viral infections, viruses themselves have evolved to escape this protection. Human oncoviruses develop also strong immune evasion strategies to establish chronic infections, including anti-apoptotic and proliferative programs that in turn provoke malignant features in the infected cell [17, 20].

3. Anti-tumoral immunity and immunosurveillance

Despite being considered in the past a simple witness of the battle between pro- and antioncogenic signals, the immune system is currently being known as a central actor in the outcome of cancer development [21–23]. Immunity has apparently two contradictory effects on tumors. Normally, a competent immune system prevents the development of emerging tumors, a concept known as cancer immunosurveillance [23]. This assumption hypothesizes that the immune system can control tumour growth by identifying different antigens on cancer cell precursors and destroying them prior to becoming clinically apparent. Although only few data show immunological abolition of premalignant lesions *in vivo*, great evidence supports the cancer immune surveillance hypothesis [24]. For instance, endogenously produced interferon-γ (IFN-γ) was shown to be protective against the growth of spontaneous, transplanted or chemically induced tumors by mouse treatment with neutralizing anti-IFN-γ monoclonal antibodies [25, 26]. Alternatively, the immunological pressure induced by cancer immunosurveillance induces the intrinsic nature of developing tumors through immunoediting mechanism [27]. The 'Immunoediting' concept was established by the observation that tumors transplanted from an immune-deficient animal to a syngeneic immune-competent animal are often rejected by the recipient's immune system, while tumors rising in immune-competent animals generally grow unhindered after transplantation [28, 29]. This process includes three stages: elimination, equilibrium, and escape [30, 31]. Elimination phase corresponds to the classical assumption of cancer immunosurveillance, where transformed and early stage malignant cells are removed by immune cells. Equilibrium is the phase of immune-mediated latency following imperfect tumor destruction. Failure to eradicate all transformed cells results in the development of tumors with reduced immunogenicity that can escape immune destruction and even, control subsequent inflammatory responses to their own advantage.

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In humans, severe primary immunodeficiencies are coupled with higher incidence of various cancers as lymphomas, stomach, breast, bladder and cervical cancers [32-35]. Moreover, high incidence of tumours associated with oncogenic viruses (HHV8-related Kaposi sarcoma, EBV-related Hodgkin's and non-Hodgkin's lymphoma, HPV-associated cervical cancer and HBV/HCV-related hepatocarcinoma) has been found in HIV-infected immunodeficient patients [36]. Remarkably, a CD4 T-cell count in peripheral blood of HIV-infected individuals is inversely associated with increased cancer risk for these type of tumors [37]. Similarly, immunocompetent mice are able to reject cancer cells expressing surface ligands that can activate natural-killer (NK) cells or cytotoxic lymphocytes [38, 39], whereas $RAG2^{-/-}$ mice lacking both T and B cells are more susceptible to spontaneous and carcinogen-induced tumours [40].

Over the recent decades, the role of components of the immune system like perforin [39], interferon-γ [40] and lymphocytes [41] have been proven to limit the outgrowth of transplanted, carcinogen-induced, and spontaneous tumors. However, despite the fact that immune responses can defend against malignancy, other immune mechanisms (i.e. chronic inflammation) can support the initiation or development of cancer [42]. Both inherent and extrinsic immune-regulating mechanisms can affect and control tumor development and progression. For example, following chronic viral infections exhausted immune cells will affect anti-cancer immune responses [43].

Most solid tumors are infiltrated by a wide array of immune cells including T cells (both CD4 helper and CD8 cytotoxic T lymphocytes) and NK cells [44]. Although these infiltrating immune cells usually display inefficient anti-tumoral activity, the quality and magnitude of this infiltrate has been established as a prognostic indicator of disease progression [45]. To induce an effector and memory T cell response, specific tumor antigens are required. MAGE-1 was the primary gene known to code a human tumor antigen that is recognized by T cells [46]. Now, many tumor-associated antigens (TAAs) have been defined. TAAs can be classified in 3 main groups:1) tissue differentiation; 2) cancer-testis; and 3) naturally occurring over-expressed antigens [47]. Tissue differentiation antigens are shared antigens between tumors and the normal tissue of origin; (eg. Gp100, Melan-A/Mart-1, Tyrosinase) in melanomas [48-53] as well as prostatic specific antigen (PSA) in prostatic carcinoma [54, 55]. Many cancer-testis antigens have been identified and tested in clinical trials, including the MAGE-A1 [56, 57] NY-ESO-141 and SSX-2 [58]. Over expressed TAAs such as tumor suppressor proteins (e.g. p53), antiapoptotic proteins livin and survivin, hTERT, Mucin 1 (MUC1) have increased expression in tumor cells when compared to normal tissues [59-65]. Tumor-associated carbohydrate antigens (TACAs) are glycans uniquely expressed or over-expressed by tumors, correlating also with various stages of cancer development [66-68]. The tumor – specific nature of these neo antigens is advantageous for eliciting specific T-cell responses with no risk of autoimmune reactions. Cancer vaccines based on defined specific tumor antigens should indeed elicit a very specific effector and memory cell response [69]. In view of the large number of possible tumor antigens for each cancer, the use of whole tumor cell vaccination approach has been considered the most favorable policy to embrace all potentially relevant antigens. However, several strategies have been implemented aiming to improve immune responses to peptide-based vaccines, via provoking the innate immune response [70, 71]. Dendritic cell (DC)-based vaccines in which tumor antigens are loaded on DCs in the form of peptides, tumor lysates [72], or apoptotic debris [73], represent one of the most

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promising strategies to achieve effective anti-tumoral responses [74, 75].

3.1 Mechanisms of immunosurveillance

The early stage of anti-tumor immune response, involve the stimulation of tissue-located innate immune cells, such as macrophages and neutrophils that generate pro-inflammatory cytokines and chemokines. This pulls other innate cells, including natural killer (NK) cells, which can recognize and kill directly transformed malignant cells. Later on, dendritic cells (DCs) can process tumor antigens produced by dying tumor cells and deliver those in the lymph node to naïve T lymphocytes, leading to the activation of antigen-specific cytotoxic T lymphocytes (CTLs) and helper T cells. These cells additionally assist in tumor destruction [76]. Nevertheless, innate immune cells cannot recognize canonical neo-antigens that arise during tumorigenesis unlike T lymphocytes. They engage innate receptors to recognize ubiquitous intracellular self ligands, such as nucleic acids, that stimulate responses in certain cancer-associated contexts. In addition, other innate receptors recognize ligands that are displayed primarily by abnormal cells, so-called "induced self ligands"

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3.1.1 NK cells

NK cells are the most effector arm of innate imunosurveillance of cancer that has been studied. Initially they were characterized by their strong ability to directly kill tumor cells *in vitro* without former recognition. Different mechanisms have been postulated for the tumoricidal action of NK cells. *In vivo* and *in vitro* studies have shown that perforin play a major role in direct tumor cell lysis [77-83]. .Alternatively, the engagement of death receptor-mediated pathways like TRAIL and FasL can induce tumor cell elimination [80, 84, 85]. This capacity of NK cells to kill tumor cells may explain their protective effect against cancer development [86-88]. NK cell infiltrates in tumor biopsies have been associated with better prognoses in cancer patients [89, 90]. Recently, enhancing the tumoricidal activity of NK cells became an interesting focus for therapeutic purposes. NK cells also modulate activity of other immune cells, such as dendritic cells and T lymphocytes, through cytokine secretion or various receptor-ligand interactions [91-91]. NK-cell-derived IFN-γ has shown to polarize macrophages towards a tumoricidal "M1" phenotype that provide defense against carcinogen-induced sarcomas [26]. Cytokines secreted by innate immune cells can encompass additional direct tumoricidal activity. Stimulated NK cells are major sources for various cytokines including IFN-γ, TNF-α. IFN-γ in particular is hypothesized to be have potent antitumor effects, such as inducing MHC I expression and sensitizing tumor cells to CD8+ T cell killing. NK-cell-derived IFN-γ is related with better survival of patients in some cancers [94]. On the other hand, TNF-α via triggering caspase 8-mediated apoptosis can have direct cytolytic activity against malignant cells [95]. Together, IFN-γ and TNF-α can drive tumor cells into senescence [96].

3.1.2 NKT cells

In the context of tumor immunosurveillance, NKT cells can kill malignant cells through direct cytotoxicity or via activation of other immune cells. Type I NKT cells can directly lyse tumor cells through perforin-dependent mechanism [97], an effect that can be potentiated by granzyme B [98]. High expression levels of tumour CD1d, which restricts response of NKT cells has been associated with lower metastasis rates [101], whereas tumour cells expressing CD1d display high *in vitro* and *in vivo* susceptibility to direct NKT cell lysis [99–103].

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α-GalCer the first recognized NKT cell ligand, is a strong activator of type I NKT cells. In mice with B16 melanoma, the application of its synthetic form (KRN7000) prolonged their survival (104, 29). Upon α-GalCer stimulation of NKT cells a profuse quantity of IFN-γ is released which is crucial for tumor protection [105, 106], including anti-metastatic activity in lung and liver metastasis models [107].

Type I NKT cells can also mediate tumor immunosurveillance throuh initiatiation of Th1 cytokine cascades. A strong correlation has been shown between the Th1 cytokine profile (in terms of IFN-γ:IL-4 ratio or IFN-γ production) and the extent of protection from tumor growth in CT26 lung metastasis mice model [108]. In different tumor models, IFN-γ release by NKT cells is the best correlate for tumor protection [109-113]. Surprisingly, NKT cells can augment tumor immunity by shifting the action of immunosuppressive cells, as shown in a model of influenza A virus infection, in which the absence of type I NKT cells resulted in the expansion of myeloid-derived suppressor cells (MDSCs), which suppressed CD8+ T cell immune responses [114].

Tumor-induced inflammation is usually accompanied by production of serum amyloid A1 (SAA-1) which increases the interaction between type I NKT cells and neutrophils. Type I NKT cells not only diminish the unfavorable effect of neutrophils by suppressing production of IL-10, and enhancing IL-12, but also re-establish proliferation of antigen-specific CD8+ T cells [115].

However, Type II NKT may have an immunosuppressive role on tumor immunology through MDSC activation and production of suppressive cytokines such as IL-13 and TGF-β [102, 116-119].

3.1.3 Macrophages

Whereas much data focus on the crucial roles for T- and NK-cells in tumor immune surveillance, little evidence can show that macrophages can kill malignant cells through phagocytosis [120]. The established consensus is that macrophage activity is mostly protumorigenic through their ability to encourage angiogenesis and metastases [121]. Tumor associated macrophages (TAMs) of the M2 type can, however, be re-educated back towards a tumoricidal M1 phenotype through the production of IFN-γ, and the overexpression of miR-155 [27, 122].

3.1.4 Tumor-associated neutrophils

The presence of tumor-associated neutrophils (TANs) in human tumors correlates with advanced disease and poor outcome in several types of human cancer [123]. Although neutrophils usually play a role in tumor progression, their N2 phenotype can be reversed to an anti-tumoral N1 phenotype by TGF-β blockade [124] or by the effect of IFN-β [125].

3.1.5 Other innate cells of interest

Based on their cytokine profiles, transcriptional activity, and effector functions, innate lymphoid cells (ILCs) strongly resemble the different helper T cell subsets. Depending on the secreted cytokines and the specific tumor microenvironment, ILCs may either aid anti-tumor immune responses or promote tumor formation and growth [27, 126]. Gamma/delta (γδ) T-cells may limit cancer incidence in skin cancer mouse models and in a transgenic model of prostate adenocarcinoma through direct lysis of tumor cells [127, 128].

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4. The hygiene hypothesis

The hygiene hypothesis, first proposed by Strachan in 1989 [129], suggests that the strong increased in the frequency of allergic diseases observed in advanced industrialized countries is caused by a reduced exposure to common infections in early childhood. Initially supported by epidemiological studies, a protective effect of infections on allergic diseases has been also reported in experimental models [130, 131]. It was first postulated that a decrease of Th1-inducing bacterial and viral infections would result in a Th2 immune microenvironment prone to the development of allergies. However, Th1 autoimmune diseases increases as well as allergies, and parasite-induced Th2 microenvironments do not trigger more allergies in their host [132, 133]. Rather than a shift in Th1/Th2 balance, it has then been proposed that repeated infections inducing pro-inflammatory responses would in turn trigger Treg cell activation and secretion of immunosuppressive cytokines, like IL-10 as a counter-regulation. Therefore, the increase in both allergic and autoimmune diseases would result from a reduced immune suppression that was previously a consequence of childhood repeated infections [132-134]. A role of gut microbiota composition has also been suggested as a factor triggering such a modulation of immune response and of resulting diseases [135]. Whatever the mechanisms involved, it seems established that bacteria, viruses and parasites may sufficiently modulate the host immune microenvironment to deeply change not only the course of concomitant diseases initially unrelated to the infection, but also the probability to develop immune-regulated diseases.

4.1 Infection and cancer: a peculiar hygiene hypothesis ?

Could a decrease of infections similarly result in an increase in the development of some cancers ? As mentioned above, the relationship between infections and cancer has so far mostly be focused on the ability of several pathogens to trigger oncogenesis through cell transformation. This infectious agent-induced increased rate of cancers may sometimes result from inflammation, which would be a result radically different from what can be expected from an hygiene hypothesis.

Oncolytic viruses (OVs) can selectively infect malignant cells and kill them while sparing normal healthy cells. This selective oncolysis can be either (i) natural feature of the virus, such as parvoviruses, myxoma virus or reovirus with minimal or no pathogenicity in humans; (ii) a product of genetically-engineered virus, with mutations/deletions in genes required for replication in normal, but not cancer cells. Those OVs include adenovirus, herpes simplex virus, and vesicular stomatitis virus [136, 137]. Moreover, OVs may induce an intense host immune response, leading to the damage of remaining malignant cells and lasting antitumor immunity. Several OVs provoke immunogenic tumor cell death (ICD, such as immunogenic apoptosis, necrosis, and pyroptosis, which activates host immune responses [138, 139]. ICD is associated by cell surface exposure of calreticulin and heat shock proteins and the production of some molecules like ATP, uric acid, and high-mobility group box 1 that possess immune-stimulating characteristics. Furthermore, ICD of tumor cells also liberates tumor-associated antigens that are crucial for generating an antigen-specific antitumor immunity [140-142].

Interestingly, a few clinical studies have reported an inverse relationship between an history of febrile infections or vaccinations and the development of melanoma [143-145], a

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tumor that is known to be sensitive to destruction by NK cells [146]. In the mouse, acute infection with lactate dehydrogenase-elevating virus (LDV), a nidovirus that induces a strong modulation of the immune microenvironment of its host, including NK cell activation [147], prevents plasmacytoma growth [148]. A similar inhibition of cancer development after LDV infection has been observed with mesothelioma (Mandour, unpublished data). The protective effect of LDV infection depends on NK cell activation and on IFN-γ production by those activated cells [148]. It may thus be postulated that repeated stimulation of the innate immune system, and especially of NK and/or NKT cells by infectious agents induce levels of IFN- γ sufficient to prevent the development of cancer cells sensitive to this cytokine. Such an protective effect of infections would constitute a peculiar type of hygiene hypothesis, that would be important to confirm in order to appropriately target preventive cancer diagnosis in populations with various levels of common infections.

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References:

1.Multistage Carcinogenesis book p 85 - 88

2.Foulds L, ed. Neoplastic Development 1969; 1, London, Academic Press.

3.Weinstein IB. Carcinogenesis as multistage process-experimental evidence. In: Bartsch H, Armstong B, eds, Host Factors in Human Carcinogenesis 1982 (IARC Scientific Publications No. 39) Lyon, IARCPress, 9-25

4.Vainio H, Magee PN, McGregor DB, McMichael AJ, eds (1992) Mechanisms of Carcinogenesis in Risk Identification (IARC Scientific Publications No. 116), Lyon, IARCPress.

5.Yamasaki H, Ashby J, Bignami M, Jongen W, Linnainmaa K, Newbold RF, Nguyen-Ba G, Parodi S, Rivedal E, Schiffmann D, Simons JW, Vasseur P (1996) Nongenotoxic carcinogens: development of detection methods based on mechanisms: a European project. Mutat Res, 353: 47-63.

6.Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest 2007;117: 1137–1146.

7.Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6:715–727.

8.Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 2006; 90:1–50.

9.Gordon Rittera, Richard Wilsona, Francesco Pompeia,b and Dimitriy Burmistrova c The multistage model of cancer development: some implications.Toxicology and Industrial Health 2003; 19: 125 /145

10. International Agency for Research on Cancer, Schistosomes, Liver Flukes and Helicobacter pylori, IARC Monograph, Lyon, France: International Agency for Research on Cancer, 1994

11. Qian G-S, Ross RK, Yu MC, Yuan J-M, Gao Y-T, Henderson BE, Wogan GN, Groopman JD, A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China, Cancer Epidemiol Biomarkers Prev, 1994; 3: 3–10.

12. Groopman JD, Zhu J, Donahue PR, Pikul A, Zhang L-S, Chen JS, Wogan GN, Molecular dosimetry of urinary aflatoxin DNA adducts in people living in Guangxi Autonomous Region, People's Republic of China, Cancer Res, 1992; 52: 45–51.

13. Pons WA, High pressure liquid chromatography determinations of aflatoxins in corn, J Assoc Off Anal Chem, 1979; 62: 584–6

14. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim- Tallaa L, Guha N, Freeman C, Galichet L, et al. A review of human carcinogens--Part B: biological agents. The lancet oncology. 2009; 10:321–322. [PubMed: 19350698]

15. Boyle, P.; Levin, B. International Agency for Research on Cancer. World Health Organization. Worldcancer report 2008. Lyon Geneva: International Agency for Research on Cancer ; Distributed by WHO Press; 2008.

16. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. The lancet oncology. 2012; 13:607–615

17. zur Hausen H. The search for infectious causes of human cancers: where and why (Nobel lecture). Angew Chem Int Ed Engl. 2009; 48:5798–5808.

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18. Arzumanyan A, Reis HM, Feitelson MA. Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. Nature reviews Cancer. 2013; 13:123–135
19. McFadden K, Luftig MA. Interplay between DNA tumor viruses and the host DNA damage response. Current topics in microbiology and immunology. 2013; 371:229–257.
20. Moore PS, Chang Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nature reviews Cancer. 2010; 10:878–889.
21. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6:715–727.
22. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 2006; 90:1–50.
23. Corthay A. 2014 Does the immune system naturally protect against cancer? Front. Immunol. 5, 197.
24. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity 2004;21:137–148.
25. Dighe AS, Richards E, Old LJ, Schreiber RD. Enhanced in vivo growth and resistance to rejection of tumor cells expressing dominant negative IFN gamma receptors. Immunity. 1994; 1:447
26. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. IFN gamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature. 2001; 410:1107.
27. O'Sullivan T, Saddawi-Konefka R, Vermi W, Koebel CM, Arthur C, White JM, Uppaluri R, Andrews DM, Ngiow SF, Teng MW, Smyth MJ, Schreiber RD, Bui JD. Cancer immunoediting by the innate immune system in the absence of adaptive immunity. J. Exp. Med. 2012; 209:1869.
28. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. IFN gamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature. 2001; 410:1107.
29. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329–360.
30. Xue W, et al. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. Nature 2007; 445:656–660.
31. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011; 331:1565.
32. Mueller BU, Pizzo PA. 1995 Cancer in children with primary or secondary immunodeficiencies. J. Pediatr. 126, 1–10.
33. Salavoura K et al. 2008 Development of cancer in patients with primary immunodeficiencies. Anticancer Res. 28, 1263–1269.
34. van der Meer JW, van Munster IP, Nagengast FM, Weening RS, Schellekens PTA. 1993 Colorectal cancer in patients with X-linked agammaglobulinaemia. Lancet 341, 1439–1440.
35. Corthay A. 2014 Does the immune system naturally protect against cancer? Front. Immunol. 5, 197.

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36. Birkeland SA et al. 1995 Cancer risk after renal transplantation in the Nordic countries, 1964–1986. Int. J. Cancer 60, 183–189.
37. Cerwenka A, Baron JL, Lanier LL. 2001 Ectopic expression of retinoic acid early inducible-1 gene (RAE-1) permits natural killer cell-mediated rejection of a MHC class I-bearing tumor in vivo. Proc. Natl Acad. Sci. USA 98, 11 521–11 526.
38. Diefenbach A, Jensen ER, Jamieson AM, Raulet DH. 2001 Rae1 and H60 ligands of the NKG2D receptor stimulate tumour immunity. Nature 413, 165–171.
39. Shankaran V et al. 2001 IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature 410, 1107–1111.
40. van den Broek ME, Kagi D, Ossendorp F, Toes R, Vamvakas S, Lutz WK, Melief CJ, Zinkernagel RM, Hengartner H. Decreased tumor surveillance in perforin-deficient mice. J Exp Med. 1996; 184:1781.
41. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annual review of immunology. 2011; 29:235
42. Yu H, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol 2007;7:41–51.
43. Spits, H.; Artis, D.; Colonna, M.; Diefenbach, A.; Di Santo, J.P.; Eberl, G.; Koyasu, S.; Locksley, R.M.; McKenzie, A.N.J.; Mebius, R.E.; *et al*. Innate lymphoid cells—A proposal for uniform nomenclature. *Nat. Rev. Immunol.* **2013**, *13*, 145–149.
44. Galon J et al. 2006 Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 313, 1960–1964.
45. Galon J et al. 2014 towards the introduction of the 'Immunoscore' in the classification of malignant tumours. J. Pathol. 232, 199–209.
46. van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, Boon T. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science 1991; 254:1643-1647;
47. De Smet C, Lurquin C, Lethe B, Martelange V, Boon T. DNA methylation is the primary silencing mechanism for a set of germ line- and tumor-specific genes with a CpG-rich promoter. Mol Cell Biol 1999; 19:7327-35
48. Bakker AB, Schreurs MW, de Boer AJ, Kawakami Y, Rosenberg SA, Adema GJ, Figdor CG. Melanocyte lineage-specific antigen gp100 is recognized by melanoma-derived tumor-infiltrating lymphocytes. J Exp Med 1994; 179:1005-1009;
49. Kawakami Y, Robbins PF, Wang X, Tupesis JP, Parkhurst MR, Kang X, Sakaguchi K, Appella E, Rosenberg SA. Identification of new melanoma epitopes on melanosomal proteins recognized by tumor infiltrating T lymphocytes restricted by HLA-A1, -A2, and -A3 alleles. J Immunol 1998; 161:6985-6992
50. Kawakami Y, Eliyahu S, Jennings C, Sakaguchi K, Kang X, Southwood S, Robbins PF, Sette A, Appella E, Rosenberg SA. Recognition of multiple epitopes in the human melanoma antigen gp100 by tumor-infiltrating T lymphocytes associated with in vivo tumor regression. J Immunol 1995; 154:3961-3968;
51. Kawakami Y, Eliyahu S, Sakaguchi K, Robbins PF, Rivoltini L, Yannelli JR, Appella E, Rosenberg SA. Identification of the immunodominant peptides of the MART-1 human melanoma antigen

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recognized by the majority of HLA-A2-restricted tumor infiltrating lymphocytes. J Exp Med 1994; 180:347-352;

52. Parkhurst MR, Fitzgerald EB, Southwood S, Sette A, Rosenberg SA, Kawakami Y. Identification of a shared HLA-A*0201-restricted T-cell epitope from the melanoma antigen tyrosinase-related protein 2 (TRP2). Cancer Res 1998; 58:4895-4901;
53. Wang RF, Appella E, Kawakami Y, Kang X, Rosenberg SA. Identification of TRP-2 as a human tumor antigen recognized by cytotoxic T lymphocytes. J Exp Med 1996; 184:2207-2216;
54. Corman JM, Sercarz EE, Nanda NK. Recognition of prostate-specific antigenic peptide determinants by human CD4 and CD8 T cells. Clin Exp Immunol 1998; 114:166-172;
55. Correale P, Walmsley K, Nieroda C, Zaremba S, Zhu M, Schlom J, Tsang KY. In vitro generation of human cytotoxic T lymphocytes specific for peptides derived from prostate-specific antigen. J Natl Cancer Inst 1997; 89:293-300
56. Chaux P, Luiten R, Demotte N, Vantomme V, Stroobant V, Traversari C, Russo V, Schultz E, Cornelis GR, Boon T et al. Identification of five MAGE-A1 epitopes recognized by cytolytic T lymphocytes obtained by in vitro stimulation with dendritic cells transduced with MAGE-A1. J Immunol 1999; 163:2928-36
57. Traversari C, van der Bruggen P, Luescher IF, Lurquin C, Chomez P, Van Pel A, De Plaen E, Amar-Costesec A, Boon T. A nonapeptide encoded by human gene MAGE-1 is recognized on HLA-A1 by cytolytic T lymphocytes directed against tumor antigen MZ2-E. J Exp Med 1992; 176:1453-1457;
58. Ayyoub M, Stevanovic S, Sahin U, Guillaume P, Servis C, Rimoldi D, Valmori D, Romero P, Cerottini JC, Rammensee HG et al. Proteasome-assisted identification of a SSX-2-derived epitope recognized by tumor-reactive CTL infiltrating metastatic melanoma. J Immunol 2002; 168:1717-1722;
59. Schmollinger JC, Vonderheide RH, Hoar KM, Maecker B, Schultze JL, Hodi FS, Soiffer RJ, Jung K, Kuroda MJ, Letvin NL et al. Melanoma inhibitor of apoptosis protein (ML-IAP) is a target for immunemediated tumor destruction. Proc Natl Acad Sci U S A 2003; 100:3398-3403.
60. Schmidt SM, Schag K, Muller MR, Weck MM, Appel S, Kanz L, Grunebach F, Brossart P. Survivin is a shared tumor-associated antigen expressed in a broad variety of malignancies and recognized by specific cytotoxic T cells. Blood 2003; 102:571-6.
61. Vonderheide RH, Hahn WC, Schultze JL, Nadler LM. The telomerase catalytic subunit is a widely expressed tumor-associated antigen recognized by cytotoxic T lymphocytes. Immunity 1999; 10:673- 9.
62. Vonderheide RH, Anderson KS, Hahn WC, Butler MO, Schultze JL, Nadler LM. Characterization of HLA-A3-restricted cytotoxic T lymphocytes reactive against the widely expressed tumor antigen telomerase. Clin Cancer Res 2001; 7:3343-8.
63. Minev B, Hipp J, Firat H, Schmidt JD, LangladeDemoyen P, Zanetti M. Cytotoxic T cell immunity against telomerase reverse transcriptase in humans. Proc Natl Acad Sci U S A 2000; 97:4796-4801.
64. Umano Y, Tsunoda T, Tanaka H, Matsuda K, Yamaue H, Tanimura H. Generation of

Copyright 2017 KEI Journals. All Rights Reserved

cytotoxic T cell responses to an HLA-A24 restricted epitope peptide derived from wild-type p53. Br J Cancer 2001;84:1052-7.

65. Azuma K, Shichijo S, Maeda Y, Nakatsura T, Nonaka Y, Fujii T, Koike K, Itoh K. Mutated p53 gene encodes a nonmutated epitope recognized by HLAB*4601-restricted and tumor cell-reactive CTLs at tumor site. Cancer Res 2003; 63:854-858;
66. Ragupathi G. Carbohydrate antigens as targets for active specific immunotherapy. Cancer Immunol 3342 Human Vaccines & Immunotherapeutics Volume 10 Issue 11 Immunother 1996; 43:152-7.
67. Dennis JW, Granovsky M, Warren CE. Glycoprotein glycosylation and cancer progression. Biochim Biophys Acta 1999; 1473:21-34.
68. Hakomori S. Tumor-associated carbohydrate antigens defining tumor malignancy: basis for development of anti-cancer vaccines. Adv Exp Med Biol 2001; 491:369-40
69. Tagliamonte M, Petrizzo A,Tornesello ML, Buonaguro F, Buonaguro L. Antigen-specific vaccines for cancer treatment. Human Vaccines & Immunotherapeutics 2014;10:11, 3332—46.
70. Clive KS, Tyler JA, Clifton GT, Holmes JP, Mittendorf EA, Ponniah S, Peoples GE. Use of GMCSF as an adjuvant with cancer vaccines: beneficial or detrimental? Expert Rev Vaccines 2010; 9:519-25.
71. Parmiani G, Castelli C, Pilla L, Santinami M, Colombo MP, Rivoltini L. Opposite immune functions of GM-CSF administered as vaccine adjuvant in cancer patients. Ann Oncol 2007; 18:226-32.
72. Nestle, F. O., S. Alijagic, M. Gilliet, Y. Sun, S. Grabbe, R. Dummer, G. Burg, and D. Schadendorf. 1998. Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells. Nat. Med. 4:328–32.
73. Palucka, A. K., H. Ueno, J. Connolly, F. Kerneis-Norvell, J. P. Blanck, D. A. Johnston, J. Fay, and J. Banchereau. 2006. Dendritic cells loaded with killed allogeneic melanoma cells can induce objective clinical responses and MART-1 specific CD8 T-cell immunity. J. Immunother. 29:545–57.
74. Koido, S., E. Hara, S. Homma, Y. Namiki, T. Ohkusa, J. Gong, and H. Tajiri. 2009. Cancer vaccine by fusions of dendritic and cancer cells. Clin. Dev. Immunol. 2009:657369.
75. Osada, T., T. M. Clay, C. Y. Woo, M. A. Morse, and H. K. Lyerly. 2006. Dendritic cell-based immunotherapy. Int. Rev. Immunol. 25:377–413.
76. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002; 3:991.
77. Hayakawa Y, Kelly JM, Westwood J, Darcy PK, Diefenbach A, Raulet DH, Smyth MJ. Tumor
rejection mediated by NKG2D receptor-ligand interaction is strictly dependent on perforin. J Immunol. 2002;
78. Kagi D, Ledermann B, Burki K, Seiler P, Odermatt B, Olsen KJ, Podack ER, Zinkernagel RM, Hengartner H. Cytotoxicity mediated by T cells and natural killer cells is greatly impaired in
perforin-deficient mice. Nature. 1994; 369:31.
79. Lee RK, Spielman J, Zhao DY, Olsen KJ, Podack ER. Perforin, Fas ligand, and tumor necrosis factor are the major cytotoxic molecules used by lymphokine-activated killer cells. J Immunol. 1996; 157:1919.

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80. Smyth MJ, Thia KY, Cretney E, Kelly JM, Snook MB, Forbes CA, Scalzo AA. Perforin is a major contributor to NK cell control of tumor metastasis. Journal of Immunology. 1999; 162:6658
81. van den Broek ME, Kagi D, Ossendorp F, Toes R, Vamvakas S, Lutz WK, Melief CJ, Zinkernagel RM, Hengartner H. Decreased tumor surveillance in perforin-deficient mice. J Exp Med.1996;184:1781.
82. van den Broek MF, Kagi D, Zinkernagel RM, Hengartner H. Perforin dependence of natural killer cellmediated tumor control in vivo. European journal of immunology. 1995; 25:3514.
83. Vermijlen D, Luo D, Froelich CJ, Medema JP, Kummer JA, Willems E, Braet F, Wisse E. Hepatic natural killer cells exclusively kill splenic/blood natural killer-resistant tumor cells by the perforin/granzyme pathway. Journal of leukocyte biology. 2002; 72:668
84. Zamai L, Ahmad M, Bennett IM, Azzoni L, Alnemri ES, Perussia B. Natural killer (NK) cell-mediatedcytotoxicity: differential use of TRAIL and Fas ligand by immature and mature primary human NK cells. J Exp Med. 1998; 188:2375.
85. Deguine J, Breart B, Lemaitre F, Di Santo JP, Bousso P. Intravital Imaging Reveals Distinct Dynamics for Natural Killer and CD8(+) T Cells during Tumor Regression. Immunity. 2010; 33:632.
86. Ljunggren H-G, Karre K. Host resistance directed selectively against H-2-deficient lymphoma variants. J. Exp. Med. 1985; 162:1745.
87. Seaman W, Sleisenger M, Eriksson E, Koo G. Depletion of natural killer cells in mice by monoclonal antibody to NK-1.1. Reduction in host defense against malignancy without loss of cellular or humoral immunity. J. Immunol. 1987; 138:4539
88. Smyth MJ, Crowe NY, Godfrey DI. NK cells and NKT cells collaborate in host protection from methylcholanthrene-induced fibrosarcoma. Int Immunol. 2001; 13:459.
89. Ishigami S, Natsugoe S, Tokuda K, Nakajo A, Che X, Iwashige H, Aridome K, Hokita S, Aikou T. Prognostic value of intratumoral natural killer cells in gastric carcinoma. Cancer. 2000; 88:577
90. Martin-Fontecha A, Thomsen LL, Brett S, Gerard C, Lipp M, Lanzavecchia A, Sallusto F. Induced recruitment of NK cells to lymph nodes provides IFN-gamma for T(H)1 priming. Nat Immunol.2004; 5:1260
91. Moretta A, Marcenaro E, Sivori S, Della Chiesa M, Vitale M, Moretta L. Early liaisons between cells of the innate immune system in inflamed peripheral tissues. Trends in immunology. 2005;
92. Ames E, Murphy WJ. Advantages and clinical applications of natural killer cells in cancer immunotherapy. Cancer immunology, immunotherapy : CII. 2013
93. Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, Yokoyama WM, Ugolini S.Innate or adaptive immunity? The example of natural killer cells. Science. 2011; 331:44
94. Menard C, Blay JY, Borg C, Michiels S, Ghiringhelli F, Robert C, Nonn C, Chaput N, Taieb J, Delahaye NF, Flament C, Emile JF, Le Cesne

Copyright 2017 KEI Journals. All Rights Reserved

A, Zitvogel L. Natural killer cell IFN-gamma levels predict long-term survival with imatinib mesylate therapy in gastrointestinal stromal tumor-bearing patients. Cancer research. 2009; 69:3563

95. Peter ME, Krammer PH. The CD95(APO-1/Fas) DISC and beyond. Cell death and differentiation. 2003; 10:26
96. Braumuller H, Wieder T, Brenner E, Assmann S, Hahn M, Alkhaled M, Schilbach K, Essmann F, Kneilling M, Griessinger C, Ranta F, Ullrich S, Mocikat R, Braungart K, Mehra T, Fehrenbacher B, Berdel J, Niessner H, Meier F, van den Broek M, Haring HU, Handgretinger R, QuintanillaMartinez L, Fend F, Pesic M, Bauer J, Zender L, Schaller M, Schulze-Osthoff K, Rocken M. Thelper-1-cell cytokines drive cancer into senescence. Nature. 2013; 494:361
97. Kawano T, Nakayama T, Kamada N, Kaneko Y, Harada M, Ogura N, et al. Antitumor cytotoxicity mediated by ligand-activated human V alpha24 NKT cells. *Cancer Res* (1999) 59:5102–5.
98. Coquet JM, Kyparissoudis K, Pellicci DG, Besra G, Berzins SP, Smyth MJ, et al. IL-21 is produced by NKT cells and modulates NKT cell activation and cytokine production. *J Immunol* (2007) 178:2827–34.
99. Kawano T, Cui J, Koezuka Y, Toura I, Kaneko Y, Sato H, et al. Natural killerlike nonspecific tumor cell lysis mediated by specific ligand-activated Valpha14 NKT cells. *Proc Natl Acad Sci U S A* (1998) 95:5690–3.
100. Fallarini S, Paoletti T, Orsi Battaglini N, Lombardi G. Invariant NKT cells increase drug-induced osteosarcoma cell death. *Br J Pharmacol* (2012) 167:1533–49.
101. Hix LM, Shi YH, Brutkiewicz RR, Stein PL, Wang CR, Zhang M. CD1d expressing breast cancer cells modulate NKT cell-mediated antitumor immunity in a murine model of breast cancer metastasis. *PLoS One* (2011) 6:e20702.
102. Renukaradhya GJ, Khan MA,Vieira M, Du W, Gervay-Hague J, Brutkiewicz RR. Type I NKT cells protect (and type II NKT cells suppress) the host's innate antitumor immune response to a B-cell lymphoma. *Blood* (2008) 111:5637–45.
103. Dhodapkar MV, Geller MD, Chang DH, Shimizu K, Fujii S, Dhodapkar KM, et al. A reversible defect in natural killer T cell function characterizes the progression of premalignant to malignant multiple myeloma. *J Exp Med* (2003) 197:1667–76. 128.
104. Blount BC, Mack MM, Wehr C, MacGregor J, Hiatt R, Wang G, Wickramasinghe SN, Everson RB, Ames BN. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: Implications for cancer and neuronal damage. Proc Natl Acad Sci USA 1997; 94: 3290–3295
105. Kobayashi E, Motoki K, Uchida T, Fukushima H, Koezuka Y. KRN7000, a novel immunomodulator, and its antitumor activities. *Oncol Res* (1995) **7**(10– 11):529–34
106. Street SE, Cretney E, Smyth MJ. Perforin and interferon-gamma activities independently control tumor initiation, growth, and metastasis. *Blood* (2001) **97**(1):192–7
107. Smyth MJ, Crowe NY, Pellicci DG, Kyparissoudis K, Kelly JM, Takeda K, et al. Sequential production of interferon-gamma by NK1.1(+) T cells and natural killer cells is

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essential for the antimetastatic effect of alpha-galactosylceramide. *Blood* (2002) **99**(4):1259–66.

108. O'Konek JJ, Illarionov P, Khursigara DS, Ambrosino E, Izhak L, Castillo BF II, et al. Mouse and human iNKT cell agonist beta-mannosylceramide reveals a distinct mechanism of tumor immunity. J Clin Invest (2011) 121:683–94.
109. Sakai T, Ehara H, Koezuka Y. Synthesis of NBD-alpha-galactosylceramide and its immunologic properties. Org Lett (1999) 1 359–61.
110. Schmieg J, Yang G, Franck RW, Tsuji M. Superior protection against malaria and melanoma metastases by a C-glycoside analogue of the natural killer T cell ligand alpha-galactosylceramide. J Exp Med (2003) 198:1631–41.
111. Chang YJ, Huang JR, Tsai YC, Hung JT, Wu D, Fujio M, et al. Potent immunemodulating and anticancer effects of NKT cell stimulatory glycolipids. *Proc Natl Acad Sci U S A* (2007) 104:10299–304.
112. Wu TN, Lin KH, Chang YJ, Huang JR, Cheng JY, Yu AL, et al. Avidity of CD1d ligand-receptor ternary complex contributes to T-helper 1 (Th1) polarization and anticancer efficacy. *Proc Natl Acad Sci U S A* (2011) 108:17275–80.
113. Aspeslagh S, Li Y, Yu ED, Pauwels N, Trappeniers M, Girardi E, et al. Galactose modified iNKT cell agonists stabilized by an induced fit of CD1d prevent tumour metastasis. *EMBO J* (2011) 30:2294–305.
114. De Santo C, Salio M, Masri SH, Lee LY, Dong T, Speak AO, et al. Invariant NKT cells reduce the immunosuppressive activity of influenza A virus-induced myeloid-derived suppressor cells in mice and humans. *J Clin Invest* (2008) 118:4036–48.
115. Moses HL, Yang EY, Pietenpol JA. TGF-beta stimulation and inhibition of cell proliferation: new mechanistic insights. *Cell* (1990) 63:245–7.
116. Terabe M, Swann J, Ambrosino E, Sinha P, Takaku S, Hayakawa Y, et al. A nonclassical non-Va14Ja18 CD1d-restricted (type II) NKT cell is sufficient for down-regulation of tumor immunosurveillance. *J Exp Med* (2005) 202:1627–33.
117. Ambrosino E, Terabe M, Halder RC, Peng J, Takaku S, Miyake S, et al. Cross-regulation between type I and type II NKT cells in regulating tumor immunity: a new immunoregulatory axis. *J Immunol* (2007) 179:5126–36.
118. Terabe M, Matsui S, Park J-M, Mamura M, Noben-Trauth N, Donaldson DD, et al. Transforming growth factor-b production and myeloid cells are an effector mechanism through which CD1d-restricted T cells block cytotoxic T lymphocyte-mediated tumor immunosurveillance: abrogation prevents tumor recurrence. *J Exp Med* (2003) 198:1741–52.
119. Izhak L, Ambrosino E, Kato S, Parish ST, O'Konek JJ, Weber H, et al. Delicate balance among three types of T cells in concurrent regulation of tumor immunity. *Cancer Res* (2013) 73:1514–23
120. Klimp AH, et al. A potential role of macrophage activation in the treatment of cancer. Critical reviews in oncology/hematology. 2002; 44(2):143–161.
121. Knowles HJ, Harris AL. Macrophages and the hypoxic tumour microenvironment. Front Biosci. 2007; 12:4298–4314

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122. Cai X, et al. Re-polarization of tumor-associated macrophages to pro-inflammatory M1
macrophages by microRNA-155. J Mol Cell Biol. 2012; 4:341–343.
123. Tazzyman S, et al. Neutrophil-mediated tumour angiogenesis: subversion of immune responses to promote tumour growth. Semin Cancer Biol. 2013; 23:149–158.
124. Fridlender ZG, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer Cell. 2009; 16:183–194.
125. Jablonska J, et al. Neutrophils responsive to endogenous IFN-beta regulate tumor angiogenesis and growth in a mouse tumor model. J Clin Invest. 2010; 120:1151–1164.
126. Farrar JD et al. 1999 Cancer dormancy. VII. A regulatory role for CD8þ T cells and IFN-gamma in establishing and maintaining the tumor-dormant state. J. Immunol. 162, 2842–2849.
127. Girardi M, Oppenheim DE, Steele CR, Lewis JM, Glusac E, Filler R, Hobby P, Sutton B, Tigelaar RE, Hayday AC. Regulation of cutaneous malignancy by gammadelta T cells. Science. 2001; 294:605.
128. Liu Z, Eltoum IE, Guo B, Beck BH, Cloud GA, Lopez RD. Protective Immunosurveillance and Therapeutic Antitumor Activity of {gamma}{delta} T Cells Demonstrated in a Mouse Model of Prostate Cancer. J Immunol. 2008; 180:6044
129. Strachan DP. Hay fever, hygiene, and household size. Br. Med. J. 1989; 299:1259-60
130. Bach J-F. The effect of infections on susceptibility to autoimmune and allergic diseases. N. Engl. J. Med. 2002; 347:911-20.
131. Morimoto M, Iwata H, Hayashi T. Lactic dehydrogenase virus inhibits allergic immunoglobulin E production : *in vivo* molecular analysis of cytokines. Scand. J. Immunol. 1999; 50:211-4
132. Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic diseases: revisiting the hygiene hypothesis. Nat. Rev. Immunol. 2001; 1:69-75.
133. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis.Science 2002; 296:490-4.
134. Romagnani S. The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both ? Immunology 2004; 352-63.
135. Okada H, Kuhn C, Feillet H, Bach J-F. The “hygiene hypothesis” for autoimmune and allergic diseases: an update. Clin. Exp. Immunol. 2010; 160:1-9.
136. Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. Nat Biotechnol. 2012; 30:658–70.
137. Cattaneo R, Miest T, Shashkova EV, Barry MA. Reprogrammed viruses as cancer therapeutics:
targeted, armed and shielded. Nat Rev Microbiol. 2008; 6:529–40.
138. Boozari B, Mundt B, Woller N, Struver N, Gurlevik E, Schache P, et al. Antitumoural immunity by virus-mediated immunogenic apoptosis inhibits metastatic growth of hepatocellular carcinoma. Gut (2010) 59:1416–26.
139. Miyamoto S, Inoue H, Nakamura T, Yamada M, Sakamoto C, Urata Y, et al. Coxsackievirus B3 is an oncolytic virus with immunostimulatory properties that is active against lung adenocarcinoma. Cancer Res (2012) 72:2609–21.

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140. Bartlett DL, Liu Z, Sathaiah M, Ravindranathan R, Guo Z, He Y, et al. Oncolytic viruses as therapeutic cancer vaccines. Mol Cancer (2013) 12:103.
141. Guo ZS, Liu Z, Bartlett DL. Oncolytic immunotherapy: dying the right way is a key to eliciting potent antitumor immunity. Front Oncol (2014) 4:74.
142. Prestwich RJ, Errington F, Diaz RM, Pandha HS, Harrington KJ, Melcher AA, et al. The case of oncolytic viruses versus the immune system: waiting on the judgment of Solomon. Hum Gene Ther (2009) 20(10):1119–32.
143. Kölmel KF, Gefeller O, Haferkamp B. Febrile infections and malignant melanoma: results of a case-control study. Melanoma Res. 1992; 2:207-11.
144. Kölmel KF, Pfahlberg A, Mastrangelo G, Niin M, Botev IN, Seebacher C, et al. Infections and melanoma risk: results of a multicentre EORTC case-control study. Melanoma Res. 1999; 9:511-9
145. Krone B, Kölmel KF, Grange JM, Mastrangelo G, Henz BM, Botev IN, et al. Impact of vaccinations and infectious diseases on the risk of melanoma - evaluation of an EORTC case-control study. Eur J Cancer 2003; 39:2372-8.
146. Jackaman C, Lansley S, Allan JE, Robinson BWS, Nelson DJ. IL-2/CD40-driven NK cells install and maintain potency in the anti-mesothelioma effector/memory phase. Intern Immunol 2012; 24:357-68
147. Markine-Goriaynoff D, Hulhoven X, Cambiaso CL, Monteyne P, Briet T, Gonzalez M-D, Coulie P, Coutelier J-P. Natural killer cell activation after infection with lactate dehydrogenase-elevating virus. J Gen Virol. 2002; 83:2709-2716.
148. Thirion G, Saxena A., Hulhoven X, Markine-Goriaynoff D, Van Snick J, Coutelier J-P. Modulation of the host microenvironment by a common non-oncolytic mouse virus leads to inhibition of plasmacytoma development through NK cell activation. J Gen Virol. 2014; 95:1504-1509

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