Cancer Immunity: Lessons From Infectious Diseases

Giorgio Trinchieri

Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Innate and adaptive immunity are activated by both infections and tumors. The immune cells infiltrating infected tissues are similar to those infiltrating neoplastic tissues, but their function in the first setting is quite different from that in the latter. Infected tissues are usually characterized by an acute inflammatory environment that favors the generation of protective immunity, whereas tumors are characterized by chronic inflammation that suppresses antitumor immune responses and promotes tumor growth and escape from the immune system. During resolution of the immune response to infection or in chronic infections, immunosuppressive mechanisms that are typical of the tumor microenvironment are observed in infected tissues. Conversely, immunotherapy and chemotherapy may redirect the tumor microenvironment and allow the activation of effective anticancer immune responses. The transformation of neoplastic cells is determined by intrinsic genetic alteration but tumor progression is controlled by the tumor microenvironment and by the inflammatory and immune response to the tumors. Commensal microorganisms live in great numbers in all our barrier epithelia and control inflammation and immunity both locally and systemically. The commensal microbiota is essential for optimal immune response to pathogens and for the establishment of autoimmunity. It also modulates inflammation and immune responses that affect tumor growth and it is required for the effectiveness of anticancer immunotherapy and chemotherapy.

Keywords. immunity; infection; cancer; microbiota; cancer therapy.

When Hilary Koprowski recruited me to the Wistar Institute in 1975, he had already been working for many years at the interface of infection and cancer, studying oncogenic viruses [1] and the susceptibility of cancer cells to virus infection. Initially, I was somewhat skeptical about the idea of looking at cancers that originate from complex genetic alteration of self cells as foreign invading pathogens, but I learned from Hilary that there are many unexpected commonalities among the immune responses to transplantation antigens, infectious pathogens, and cancer, reviewed in this commentary, and that a comparative study of the mechanisms of resistance to infection and cancer, including commonalities and differences, provides a powerful tool for a better understanding of immunity and eventually for the development of preventive or curative therapies [2].

At the Wistar Institute, working together with Barbara Knowles, I followed up on the discovery by Peter Doherty that viral antigen recognition by T cells was restricted by histocompatibility antigens [3]. Unlike the prevalent opinion at that time that regulation of the cell-mediated cytotoxic response to viral antigens was different from that to tumor-associated antigens, we found not only that the recognition of tumor antigens (ie, SV40 T antigen) was, similar to recognition of antigens of infectious viruses, restricted by major histocompatibility complex (MHC) antigens, but also that self-restricted anti-SV40 T antigen T cells were induced similarly by syngeneic, allogeneic, and xenogeneic transformed cells, thus identifying the mechanism of antigen cross-presentation for tumor antigens [4]. The interpretation of those studies and the full appreciation of commonalities and differences between immunity to infections and tumors were complicated by the facts that we knew so little about the mechanisms of T-cell antigen recognition and that the structure of the T-cell

receptors was still unknown. Following many discussions with Peter Doherty, who had in the meantime joined the Wistar Institute, we published a hypothesis article [5] containing an evaluation of the possible mechanisms of dual recognition of antigens and histocompatibility antigens (Figure 1). In light of current knowledge, the apparent naivety of those models and our inability to predict the ability of peptides interacting with MHC antigens to form a unique molecular structure recognized by a single receptor show how much remained to be revealed regarding the shared mechanisms of immunity between infections and tumors before these mechanisms could be harnessed for effective cancer therapy, which has been done successfully only very recently [6].

Commonalities Between the Immune Response to Infection and Cancer

Innate resistance, tissue repair, and adaptive immunity are activated both by infection and by tumor growth. However, at first sight, acute infections always seem to be associated with evident inflammation, whereas the neoplastic lesions are initially inducing little visible inflammatory or immune reaction, and only upon extensive tumor expansion or tissue destruction do
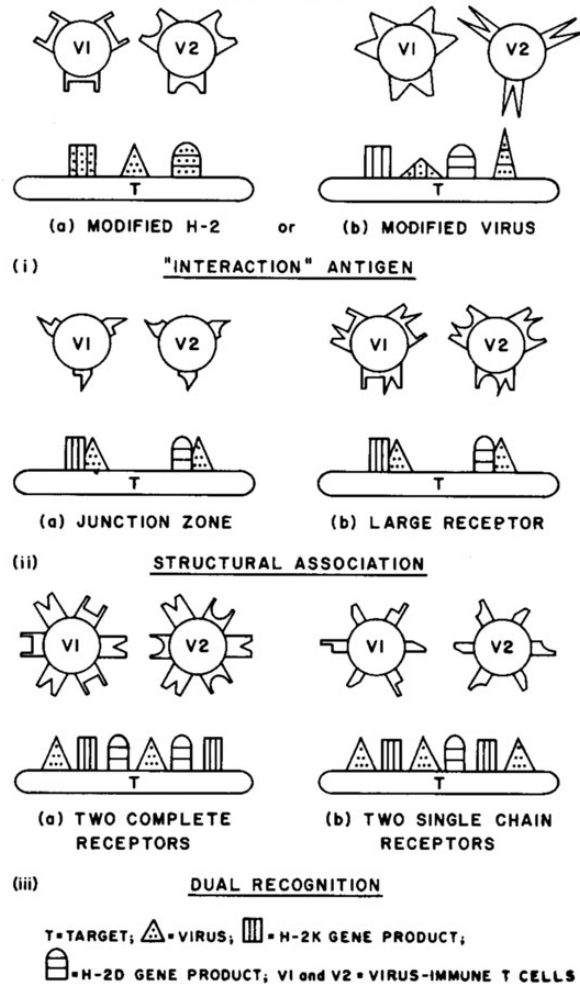

Figure 1. A 1976 vision of possible models to explain the clonality of virus-immune, cytotoxic, thymus-derived lymphocytes associated with *H-2K* or *H2-D*. The lack of knowledge at that time of the structure and specificity of the T-cell receptor and of the ability of antigenic peptides to fit in the groove of major histocompatibility complex (MHC) antigens made it very difficult to interpret the data showing a similarly restricted recognition of viral and tumor-associated antigens and those indicating the ability of tumor antigens to be cross-presented on autologous MHC antigens different from those expressed on the immunizing tumor cells [4]. Only the models depicted in (i)a and (ii)a represented a rudimental and much approximated vision of the present understanding of T-cell antigen recognition. The knowledge of the specificity and control of T-cell–mediated immunity, as well as the role of inflammation and innate resistance to both regulate adaptive immunity and tumor initiation and progression, has since allowed great advances in the understanding and translational utilization of the shared immune mechanisms between infection and cancer. Reproduced with permission from the article by Doherty et al [5].

inflammation and tissue repair become fully apparent. Yet, inflammation and immunity affect all stages of neoplastic progression, from initiation, progression, and metastasis formation to the response to cancer therapy. Although the proliferative and invasive properties of transformed neoplastic cells are determined by intrinsic genetic alterations, the ability of the transformed cells to progress and form tumors is strictly controlled by the tumor microenvironment and by the inflammatory and immune response to the tumors.

Resistance to infection by foreign pathogens is mediated by the presence of anatomical barriers and by different classes of innate and adaptive immune mechanisms. The permeability of the barrier surfaces is maintained not only by the physical obstacle of tightly joined cells but also by the humoral and cellular components of innate and immune resistance that regulate the physiology of the epithelial cells and exert antibacterial functions. This contributes to the maintenance of the equilibrium in the commensal microbial population colonizing all of the barrier surfaces and to the prevention of the invasion and growth of external pathogens, as well as of resident bacterial species (pathobionts) that may become pathogenic when escaping homeostatic control [7]. Because the exposure to commensal microbiota and pathogens, as well as the physiological cellular functions of various tissues, are different, the quality, strength, and type of immune response that is activated is differentially tailored to obtain efficient pathogen inactivation and elimination while avoiding excessive collateral tissue damage [8]. This is particularly true in tissues such as the intestinal mucosa in which, due to the presence of an abundant commensal microbiota, inflammatory and acute immune response to the commensal microorganisms should be controlled by an antiinflammatory environment that, however, should not prevent an effective immune response against infectious pathogens [9–11]. Microbes that develop evasion mechanisms and thwart the immune homeostasis at the barrier epithelia induce acute or chronic infections locally or systemically that are often associated with immunopathology and tissue damage.

Many of the mechanisms and receptors that are known to be involved in innate and immune resistance to infections are likely derived from those present in the early metazoans to communicate and maintain equilibrium with commensal microorganisms with which all animals are closely associated [12]. Thus, unlike the traditional view of immunity, it could be conceived that innate resistance that sets the stage for the strength and quality of the antigen-specific immune response is triggered not by the recognition of substances seen as foreign or dangerous but rather by those that reflect tissue damage or alteration of tissue homeostasis [13, 14]. Innate receptors respond to exposure either to microbe-associated molecular patterns present in abnormal concentrations and anatomical locations or to endogenous ligands released by damaged cells (damage-associated molecular patterns). Thus, inflammation and innate resistance

can be triggered by tissue damage and loss of homeostasis induced by either infection or a pathological tissue alteration such as tumor growth. The innate response is then amplified by the recruitment of proinflammatory cells that establish the microenvironment in which an antigen-specific immune response can be elicited but also in which antiinflammatory mechanisms are activated for resolution of inflammation, prevention of excessive tissue damage, and tissue repair [15–17].

Often tumors originate from inflamed tissues either because of infection with pathogens, some of which may directly or indirectly have oncogenic potential, or because of other aseptic causes that alter tissue integrity [18, 19]. Preexisting inflammation may be directly involved in cancer initiation by favoring genetic instability and the appearance of mutations in oncogenes or tumor suppressor genes [20]. The major effect of inflammation is, however, to establish a tumor-promoting microenvironment expressing growth factors, angiogenic factors, tissue-remodeling enzymes, and immunosuppressive cytokines, as well as receptor-ligand pairs that allow tumor progression and invasion. Expression of several oncogenes (eg, Ret, HRas, and KRas) in the transformed cells induces intrinsic inflammation characterized by the secretion of cytokines, chemokines, and metalloproteases that resembles inflammation associated with cell senescence and that contributes to the recruitment of proinflammatory hematopoietic cells mediating extrinsic inflammation [21–23]. Once the tumors are established and initiate tissue invasion, they are always associated with cancer-related inflammation that maintains the tumor-promoting and immunosuppressive microenvironment.

Although both infected tissues and neoplastic lesions are characterized by inflammation and infiltration of hematopoietic cells, the two pathological microenvironments are usually quite different, with an initial brisk immune response in acute infections that in most cases results in control or elimination of the pathogens, compared with an immunosuppressive microenvironment containing antiinflammatory cytokines such as interleukin 10 (IL-10), transforming growth factor β (TGF-β), type I interferon, and vascular endothelial growth factor, as well as immunocheckpoint receptor-ligand pairs (eg, CTLA4/CD80/CD86 and PD1/PDL1/PDL2), in tumors. Yet, an antigen-specific immune response is often activated in the tumors and modulates their progression, as shown by the powerful correlation of a brisk T-cell response with a favorable prognosis in colon and other types of cancer [24] and the recent success of cancer therapies using immune checkpoint inhibitors [25].

Interestingly, the type of inflammatory cells and their differentiation in the inflamed tissues is similar in infection and cancer and characterized by the infiltration of inflammatory monocytes that differentiate into macrophage- and dendritic-like cells, in addition to the presence of neutrophils, natural killer cells, and immune T and B lymphocytes (Figure 2) [26–28]. However, the antigen-presenting and proinflammatory functions
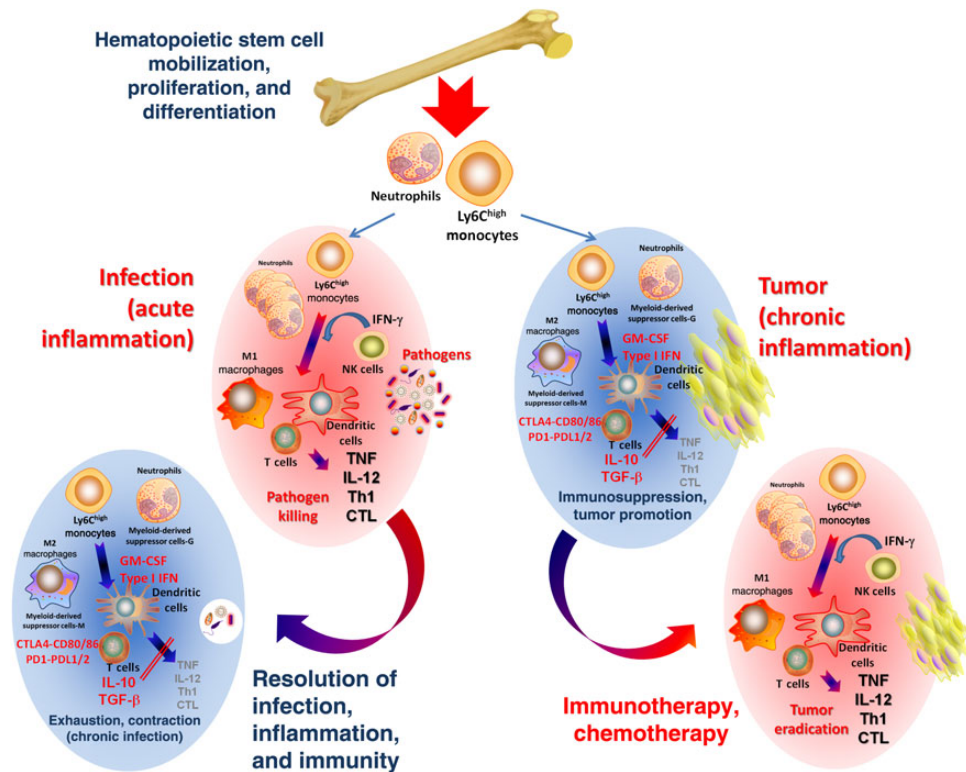
Figure 2. Commonalities in the inflammatory/immune mechanisms elicited by infection and tumors. Both infection and tumor growth produce factors that regulate hematopoietic stem cell mobilization, proliferation, and differentiation and induce reactive and extramedullary hematopoiesis. Neutrophils and Ly6C^{high} inflammatory monocytes migrate to the infected or neoplastic tissues. In both tissues, monocytes differentiate to cells with characteristics of macrophages and dendritic cells. However, the functional characteristics of the myeloid cells infiltrating infected tissues and tumors are very different. In most acute infections, the myeloid cells differentiate, in part under the influence of interferon γ (IFN-γ) produced by natural killer (NK) cells, into conventionally activated (M1) macrophages and dendritic cells producing proinflammatory and immunoregulatory cytokines such as tumor necrosis factor (TNF) and interleukin 12 (IL-12) and favoring a protective T-helper type 1 (Th1) and cytotoxic T-lymphocyte (CTL) immune response. In tumors, myeloid cells such as neutrophils and macrophages have an immunosuppressive phenotype and are often termed myeloid-derived suppressor cells–G and –M, respectively. Inflammatory monocyte-derived macrophages (often displaying an alternate M2 phenotype) and dendritic cells have an anergic phenotype—in part because of the presence in the tumor microenvironment of antiinflammatory factors such as interleukin 10 (IL-10) and transforming growth factor β (TGF-β)–and fail to produce proinflammatory and immunoregulatory cytokines. This, together with the expression on T cells and antigen-presenting cells of immune checkpoint receptor/ligand pairs such as CTLA4-CD80/86 and PD1-PDL1/2, contributes to the immunosuppressive and tumor-promoting environment. During resolution of inflammation and immunity following acute infection, many of the immunosuppressive mechanisms observed in the tumor microenvironment are activated that, in absence of complete pathogen clearance, may underlie chronic infections. Conversely, certain types of immunotherapy and immunogenic chemotherapy functionally redirect the myeloid cells in the tumor microenvironment to allow an antitumor Th1 and CTL response that may eradicate the tumors.

of the infiltrating myeloid cells are very different. In acute infection they are easily induced to produce proinflammatory factors such as interleukin 12 (IL-12) and tumor necrosis factor (TNF) and thus favor a T-helper type 1 (Th1) and T-cell cytotoxic immune response [26, 29], whereas in tumors they are refractory to production of these cytokines in response to innate receptor ligands unless antiinflammatory cytokines such as IL-10 and TGF-β are neutralized [30–32]. The antiinflammatory and immunosuppressive mechanisms, including antiinflammatory cytokines and immune checkpoints, that are observed in the tumor microenvironment largely overlap those observed during resolution of inflammation and exhaustion of the immune response after clearance of infections or during chronic infections [15, 17, 33–35]. Conversely, during immunotherapy and certain types of chemotherapy, the immunosuppressive tumor microenvironment can be reversed and the functions of myeloid cells can be redirected to production of proinflammatory and immunoregulatory cytokines and enhancement of antigen-presenting cell functions, with induction of antitumor immune responses mimicking those observed in acute inflammation [25, 30, 36]. The results of these studies and the recent success of immune checkpoint inhibitors in cancer are clearly indicating that comparative studies in infection and cancer immunity will not only improve our understanding of the basic

biology of immunity but also provide indications for effective therapy for cancer and for acute and chronic infections.

Cancer as a Disease of the Symbiont/Metaorganism

Eukaryotes evolved in symbiosis with microorganisms, such as archaea, bacteria, fungi, and viruses. Signaling between eukaryotic cells and commensal microbes initially regulated nutrition, metabolism, and morphogenesis, and some of the mechanisms and receptors involved in this interaction have been co-opted in vertebrates to mediate innate and adaptive resistance to infections [12, 37]. In humans, commensal microorganisms inhabit all of the barrier surfaces. The number of microbes is 3–10 times higher than that of our own cells, and microbial genes are at least 100 times more numerous than our human genes [38]. Thus, all animals, including humans, are symbionts or metaorganisms composed of host and microbial cells, each with their own genes (metagenome) and shared metabolic processes and products (metabolome) [39].

The interplay between the commensal microbiota and the host immune system limits the inflammatory responses to the commensals, controls indigenous pathobionts, and regulates immunity against pathogens [40, 41]. Disruption in the microbial community (dysbiosis) alters this homeostatic control and may result in inflammatory or immune pathology [42]. In addition to barrier immunity, the microbiota regulates systemic immunity, modulating both resistance to infection and autoimmunity [43–46]. While barrier immunity is regulated by the local microbiota in a compartmentalized way [47], the abundant microbiota in the gut and possibly at other anatomical sites, such as the oral cavity, appears to be mostly responsible for systemic immunity [48]. The cellular and molecular mechanisms by which the commensals regulate systemic immunity are only beginning to be understood. Germ-free or antibiotic-treated mice have defective myelopoiesis and impaired neutrophil homeostasis and are unable to resist certain bacterial [49] and virus infections [44, 45]. The inability to respond to infections appears to be largely due to altered proinflammatory and antigen-presenting functions of myeloid cells, such as dendritic cells and macrophages, that need to be epigenetically primed for optimal responsiveness by systemic signals dependent on the presence of the microbiota [50].

When cancer grows in an animal, the whole metaorganism is involved, and by regulating metabolism, inflammation, and immunity the commensal microbiota modulates the tumor microenvironment and the ability of the tumor to progress [51]. Also, through its effect on metabolic functions, the microbiota may also be responsible for cancer-predisposing conditions, such as obesity [19]. Thus, by setting the inflammatory/immune tone and by regulating the host response to oncogenic pathogens, tissue damage, and cancer-associated inflammation, the microbiota may contribute to carcinogenesis, tumor progression, cancer comorbidities, and response to therapy.

The Commensal Microbiota Is Needed for Response to Cancer Therapy

The effect of the gut commensal microbiota on cancer therapy has been analyzed by testing the response of germ-free or antibiotic-treated mice to different types of treatments. Intratumoral injection of CpG-oligodeoxynucleotide combined with antibody neutralization of IL-10 signaling induces a rapid TNF-dependent hemorrhagic necrosis followed by an effective antitumor immune response in conventionally raised mice [30] but not in germ-free or antibiotic-treated mice [52]. In microbiota-depleted mice, tumor-infiltrating myeloid-derived cells fail to produce inflammatory cytokines, including TNF and IL-12, that are required for the antitumor response activated by CpG-oligodeoxynucleotide [52]. The presence in the gut of several bacterial species was positively correlated with the TNF response, while *Lactobacillus* species decreased the response [52]. The ability of the gram-negative bacterium *Alistipes shahii* to enhance the TNF response and that of *Lactobacillus fermentum* to attenuate it was directly demonstrated by in vivo association experiments [52].

The therapeutic effect of the platinum compounds oxaliplatin and cisplatin on mouse sterile subcutaneous transplanted tumors was also almost abolished in antibiotic-treated or germ-free mice [52]. It was observed that tumor-infiltrating myeloid cells in microbiota-depleted mice failed to produce in response to the oxaliplatin reactive oxygen species that are needed for the oxaliplatin-mediated genotoxic effect on tumor cells [52].

Chemotherapy and radiation therapy are toxic for the intestinal mucosa, increasing mucosal permeability and inducing dysbiosis and transmucosal translocation of commensal bacteria. In the anticancer therapeutic protocol of adoptive transfer of tumor-specific cytotoxic CD8+ T cells, lymphoablations and myeloablations induced by total body irradiation improved T-cell survival and therapeutic efficacy [53]. Total body irradiation induces mucosal damage, infiltration of the mesenteric lymph nodes by gut bacteria, and elevated serum endotoxin levels [53]. The ability of total body irradiation to improve tumor regression by priming tumor-infiltrating myeloid cells for sustaining proliferation, survival, and activity of the transferred T cells was largely abolished in mice depleted of commensal microbiota [53].

Cyclophosphamide is among the chemotherapy agents that, similar to oxaliplatin, activate a cancer-specific immune response by inducing immunogenic cell death in conventionally raised animals but not in mice depleted of commensal microbiota [54]. In conventionally raised animals, cyclophosphamide treatment induces dysbiosis and mucositis; gram-positive bacteria that translocate into the draining mesenteric lymph nodes prime antigen-presenting myeloid cells to elicit pathogenic effector Th17 and memory Th1 cells [54]. Thus, antigen-presenting cell activation and induction of effective antitumor immune responses by chemotherapy require not only release of damage-

associated molecular patterns [36], but also the participation of commensal bacteria and/or their products in the priming and activation of myeloid cells.

Concluding Remarks

The studies in these last few years have seen a remarkable success of different protocols of cancer immunotherapy, many of which are based on the use of monoclonal antibodies to tumor antigens and to immune regulators [6]. The now known commonalities between immunity to infection and cancer, the role of the symbiont/metaorganism in modulation cancer progression and response to therapy, and the role of inflammation and several oncogenic microorganisms in cancer development show that the use of similar approaches to study infectious and neoplastic diseases and to learn from comparative studies can be very rewarding. The recent report that the protective immune response to the product of cancer-mutated genes elicited by immune checkpoint inhibition in patients with cancer was particularly effective when the mutated antigen mimicked microbial antigens opens the intriguing possibility of an even closer relationship between cancer immunity and activation of the patient immune system by antigens of pathogens and commensal microorganisms [55].

Notes

Disclaimer. The contents of this publication do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Koprowski H. A consideration of virus-host relationships in neoplasia at the level of the whole animal. Cancer Res **1960**; 20:773–83.
2. Goldszmid RS, Dzutsev A, Trinchieri G. Host immune response to infection and cancer: unexpected commonalities. Cell Host Microbe **2014**; 15:295–305.
3. Zinkernagel RM, Doherty P. Immunological surveillance against altered self components by sensitized T lymphocytes in lymphochoriomeningitis. Nature (London) **1974**; 251:547.
4. Trinchieri G, Aden DP, Knowles BB. Cell-mediated cytotoxicity to SV40-specific tumour-associated antigens. Nature **1976**; 261:312–4.
5. Doherty PC, Gotze D, Trinchieri G, Zinkernagel RM. Models for recognition of virally modified cells by immune thymus derived lymphocytes. Immunogenetics **1976**; 3:517–24.
6. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science **2013**; 342:1432–3.
7. Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. Science **2014**; 346:954–9.
8. Matzinger P, Kamala T. Tissue-based class control: the other side of tolerance. Nat Rev Immunol **2011**; 11:221–30.
9. Hand TW, Dos Santos LM, Bouladoux N, et al. Acute gastrointestinal infection induces long-lived microbiota-specific T cell responses. Science **2012**; 337:1553–6.
10. Molloy MJ, Grainger JR, Bouladoux N, et al. Intraluminal containment of commensal outgrowth in the gut during infection-induced dysbiosis. Cell Host Microbe **2013**; 14:318–28.
11. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell **2014**; 157:121–41.
12. Chu H, Mazmanian SK. Innate immune recognition of the microbiota promotes host-microbial symbiosis. Nat Immunol **2013**; 14:668–75.
13. Matzinger P. The danger model: a renewed sense of self. Science **2002**; 296:301–5.
14. Medzhitov R. Origin and physiological roles of inflammation. Nature **2008**; 454:428–35.
15. Nathan C. Points of control in inflammation. Nature **2002**; 420:846–52.
16. Nathan C, Ding A. Nonresolving inflammation. Cell **2010**; 140:871–82.
17. Wherry EJ. T cell exhaustion. Nat Immunol **2011**; 12:492–9.
18. Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell **2005**; 7:211–7.
19. Trinchieri G. Cancer and inflammation: an old intuition with rapidly evolving new concepts. Annu Rev Immunol **2012**; 30:677–706.
20. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis **2009**; 30:1073–81.
21. Borrello MG, Alberti L, Fischer A, et al. Induction of a proinflammatory program in normal human thyrocytes by the RET/PTC1 oncogene. Proc Natl Acad Sci U S A **2005**; 102:14825–30.
22. Cataisson C, Salcedo R, Hakim S, et al. IL-1R-MyD88 signaling in keratinocyte transformation and carcinogenesis. J Exp Med **2012**; 209:1689–702.
23. Ling J, Kang Y, Zhao R, et al. KrasG12D-induced IKK2/beta/NF-kappaB activation by IL-1alpha and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma. Cancer Cell **2012**; 21:105–20.
24. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science **2006**; 313:1960–4.
25. Brahmer JR, Pardoll DM. Immune checkpoint inhibitors: making immunotherapy a reality for the treatment of lung cancer. Cancer Immunol Res **2013**; 1:85–91.
26. Goldszmid Romina S, Caspar P, Rivollier A, et al. NK cell-derived interferon-γ orchestrates cellular dynamics and the differentiation of monocytes into dendritic cells at the site of infection. Immunity **2012**; 36:1047–59.
27. Shand FH, Ueha S, Otsuji M, et al. Tracking of intertissue migration reveals the origins of tumor-infiltrating monocytes. Proc Natl Acad Sci U S A **2014**; 111:7771–6.
28. Franklin RA, Liao W, Sarkar A, et al. The cellular and molecular origin of tumor-associated macrophages. Science **2014**; 344:921–5.
29. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG. TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. Immunity **2003**; 19:59–70.
30. Guiducci C, Vicari AP, Sangaletti S, Trinchieri G, Colombo MP. Redirecting in vivo elicited tumor infiltrating macrophages and dendritic cells towards tumor rejection. Cancer Res **2005**; 65:3437–46.
31. Vicari AP, Chiodoni C, Vaure C, et al. Reversal of tumor-induced dendritic cell paralysis by CpG immunostimulatory oligonucleotide and anti-interleukin 10 receptor antibody. J Exp Med **2002**; 196:541–9.
32. Stewart CA, Metheny H, Iida N, et al. Interferon-dependent IL-10 production by Tregs limits tumor Th17 inflammation. J Clin Invest **2013**; 123:4859–74.
33. Teijaro JR, Ng C, Lee AM, et al. Persistent LCMV infection is controlled by blockade of type I interferon signaling. Science **2013**; 340:207–11.
34. Ejrnaes M, Filippi CM, Martinic MM, et al. Resolution of a chronic viral infection after interleukin-10 receptor blockade. J Exp Med **2006**; 203:2461–72.
35. Anderson CF, Oukka M, Kuchroo VJ, Sacks D. CD4(+)CD25(-)Foxp3(-) Th1 cells are the source of IL-10-mediated immune suppression in chronic cutaneous leishmaniasis. J Exp Med **2007**; 204:285–97.

36. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol **2013**; 31:51–72.

37. McFall-Ngai M, Hadfield MG, Bosch TC, et al. Animals in a bacterial world, a new imperative for the life sciences. Proc Natl Acad Sci U S A **2013**; 110:3229–36.

38. Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. Nature **2012**; 489:231–41.

39. Costello EK, Stagaman K, Dethlefsen L, Bohannan BJ, Relman DA. The application of ecological theory toward an understanding of the human microbiome. Science **2012**; 336:1255–62.

40. Chow J, Mazmanian SK. A pathobiont of the microbiota balances host colonization and intestinal inflammation. Cell Host Microbe **2010**; 7:265–76.

41. Kamada N, Chen GY, Inohara N, Nunez G. Control of pathogens and pathobionts by the gut microbiota. Nat Immunol **2013**; 14:685–90.

42. Underwood MA. Intestinal dysbiosis: Novel mechanisms by which gut microbes trigger and prevent disease. Prev Med **2014**; 65:133–7.

43. Kuhn KA, Stappenbeck TS. Peripheral education of the immune system by the colonic microbiota. Semin Immunol **2013**; 25:364–9.

44. Ichinohe T, Pang IK, Kumamoto Y, et al. Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc Natl Acad Sci U S A **2011**; 108:5354–9.

45. Abt MC, Osborne LC, Monticelli LA, et al. Commensal bacteria calibrate the activation threshold of innate antiviral immunity. Immunity **2012**; 37:158–70.

46. Chervonsky AV. Microbiota and autoimmunity. Cold Spring Harb Perspect Biol **2013**; 5:a007294.

47. Naik S, Bouladoux N, Wilhelm C, et al. Compartmentalized control of skin immunity by resident commensals. Science **2012**; 337: 1115–9.

48. Brusca SB, Abramson SB, Scher JU. Microbiome and mucosal inflammation as extra-articular triggers for rheumatoid arthritis and autoimmunity. Curr Opin Rheumatol **2014**; 26:101–7.

49. Khosravi A, Yanez A, Price JG, et al. Gut microbiota promote hematopoiesis to control bacterial infection. Cell Host Microbe **2014**; 15: 374–81.

50. Ganal SC, Sanos SL, Kallfass C, et al. Priming of natural killer cells by nonmucosal mononuclear phagocytes requires instructive signals from commensal microbiota. Immunity **2012**; 37:171–86.

51. Dzutsev A, Goldszmid RS, Viaud S, Zitvogel L, Trinchieri G. The role of the microbiota in inflammation, carcinogenesis and cancer therapy. Eur J Immunol **2015**; 45:17–31.

52. Iida N, Dzutsev A, Stewart CA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science **2013**; 342:967–70.

53. Paulos CM, Wrzesinski C, Kaiser A, et al. Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8+ T cells via TLR4 signaling. J Clin Invest **2007**; 117:2197–204.

54. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science **2013**; 342:971–6.

55. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med **2014**; 371:2189–99.