The resolution of inflammation and cancer

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ABSTRACT

Inflammation has long been thought to contribute to the development of cancer; however there is also clear evidence that the immune system can recognize and eliminate cancer cells. Current research suggests that cancer-associated inflammation has a dual role in tumor progression; inflammatory mediators promote the malignant activity of cancer cells by acting as growth factors and also stimulate angiogenesis, however, cancer-associated inflammation is also linked with immune-suppression that allows cancer cells to evade detection by the immune system. In this review we will discuss the dual role of inflammation in cancer and how endogenous anti-inflammatory mechanisms may equally be important in carcinogenesis.

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1. Introduction

Inflammation is the primary response to infection or injury that functions to clear the injurious material or agent and promote tissue repair, it is characterized by the sequential release of a battery of mediators including; bioactive amines, eicosanoids, cytokines, chemokines and growth factors that regulate increased vascular permeability and recruitment of blood borne leukocytes. Increased vascular permeability also results in extravasation of plasma proteins that further amplify the inflammatory reaction. Inflammation is essentially a salutary response that normally resolves with the restoration of normal tissue structure and function, however when inflammation persists (chronic inflammation) it can cause tissue damage and loss of function. Chronic inflammation may occur due to the persistence of infection or antigen, recurring tissue injury, or a failure of endogenous anti-inflammatory mechanisms that drive the resolution of inflammation. Importantly, inflammation is a critical part of innate immunity and has a role in priming the adaptive immune system but chronic inflammation can be associated with immune-suppression.

Persistent inflammation is linked with the incidence and progression of cancer [1]; inflammation associated with chronic infection or tissue injury is linked with carcinogenesis in the affected tissue, pro-inflammatory cytokines are frequently detected in tumor tissue, although at relatively low levels, and tumors are invariably infiltrated by inflammatory cells, most notably macrophages. Studies of human cancer have correlated cancer progression with the expression of inflammatory markers and macrophage infiltration [1,2]; in addition various experimental studies in mice have shown that blocking the expression of inflammatory mediators or infiltration of inflammatory cells inhibits growth of tumors [1]. But, the immune system also has the capacity to recognize and eliminate malignant cells and act as a barrier to cancer [3]. It is clear from studies in mice that immune cells and certain cytokines inhibit cancer progression, but this activity is suppressed in the tumor microenvironment. It is also evident from clinical data that in certain contexts inflammation can inhibit cancer growth; Coley and colleagues observed in the early 20th century that cancers did not recur after post-operative infection, and indeed patients could be 'cured' of cancer by the activation of a systemic inflammatory response with killed bacteria [4]. This was the birth of immunotherapy for cancer, but to this date the only established treatment for cancer of this nature is tuberculosis vaccine; BCG; for the treatment of superficial bladder cancer [5]. Although the precise mechanism of action is not clear, recent research suggests that the tumor microenvironment is profoundly immunosuppressive and subversion of these anti-inflammatory mechanisms can prevent tumor progression and enhance the efficacy of anti-cancer therapy [6].

In this review we will discuss the 'Jekyll and Hyde' nature of inflammation in cancer and the potential role for endogenous anti-inflammatory mechanisms in carcinogenesis.

2. Cytokines

There is now convincing evidence that pro-inflammatory cytokines, particularly tumor necrosis factor (TNF) α and interleukin (IL)-6, have a role in carcinogenesis by promoting the survival and proliferation of malignant cells. The regulation of immune cells by cytokines in the tumor microenvironment is also

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critical for cancer progression [7]. The imbalance between TH1 and TH2 cytokines in tumors in particular is thought to be important in tumor progression. TH2 cytokines like IL-4, IL-10 or IL-13 are elevated in many tumors, contributing to polarization of tumor-associated macrophages (TAM) to a M2 phenotype that promotes invasion, angiogenesis and metastasis [8]. But inflammatory TH1 cytokines are almost absent in this microenvironment, particularly interferon (IFN) γ and IL-12 that can promote anti-tumor immunity. Below we will describe some of the pro- and anti-inflammatory roles for cytokines in cancer using TNFα and IL-6 as examples.

Much of the evidence for a role of inflammation in cancer is inferred from studies on TNFα, recently reviewed [9]; TNFα blockade has been successfully used for the treatment of chronic inflammatory diseases and there is significant evidence that the action of TNFα on malignant cells contributes to carcinogenesis, suggesting that targeting TNFα could be beneficial in inflammation-associated cancer [10]. But TNFα has pleiotropic roles in the immune system; for example, in certain auto-immune disease including type I diabetes and multiple sclerosis that are driven by TH1 cytokines such as IFNγ, TNFα inhibition can in fact exacerbate disease [11–13]. A recent study also showed that anti-TNFα therapy in a mouse model of arthritis is actually associated with increased activation of TH1 and TH17 cells and the therapeutic action of anti-TNFα in this model is due to the inhibition of leukocyte recruitment to the inflammatory site rather than inhibition of leukocyte activation [14]. TNFα has also been shown to drive the resolution of T cell-mediated inflammation during infection [15], these studies suggest that TNFα can suppress T cell activation and at least TH1-driven inflammatory responses. TNFα has two receptors that are differentially expressed: TNFR1 (p55) and TNFR2 (p75). While both malignant and stromal cells in tumors express TNFR1, TNFR2 is restricted to immune cells. In fact TNFR2 is highly expressed on tumor infiltrating Treg cells that block anti-tumor immune responses [16], however, it is not clear if TNFα is required for the immunosuppressive activity Treg cells in cancer. It was observed previously that TNFα can promote either TH1 or TH2 responses depending on the context; for example, in eosinophils it was necessary to combine TNFα with IFNγ to trigger TH1 cytokine secretion, but in the presence of IL-4, TNFα increased production of TH2 cytokines [17]. This suggests that in a TH2 microenvironment, that often predominates in tumors, TNFα may enhance TH2 cytokine production. These actions of TNFα could equally be relevant for the role of this cytokine in cancer.

TNFα expression and signaling is regulated by the transcription factor; nuclear factor (NF)-κB, which is thought to be a major molecular link between inflammation and cancer [18]. In various mouse models it has been shown that NF-κB activation is critical for the tumor-promoting action of inflammation. But we, and others, have also described an anti-inflammatory role for NF-κB in the resolution of inflammation [19–21]. The targeted deletion of IKKβ, an important activator of NF-κB, in myeloid cells inhibits the development of colitis associated colon cancer (CAC) and diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) in mice [22,23]. The role of NF-κB in the expression of pro-inflammatory cytokines, such as TNFα and IL-6, in tumor-associated macrophages (TAM) is thought to be the mechanism for attenuated tumor growth in these models. Our recent studies in a model of ovarian cancer also suggest that the activation of NF-κB through IKKβ maintains tumor-promoting function of TAM [24]. However, these experiments showed targeting IKKβ in TAM increased expression of IL-12, inducible nitric oxide synthase (NOS2) and MHC II, which are the hallmarks of 'classical' or M1 macrophage activation, this was associated with the inhibition of tumor growth. M1 macrophages are associated with increased production of pro-inflammatory cytokines, such as IL-12 and IFNγ,

and antigen presenting cell (APC)-activity [21], whereas 'alternatively' activated or M2 macrophages are important for the resolution of inflammation and wound healing, through the production of anti-inflammatory cytokines; such as IL-10 and TGFβ. In a parallel study we showed an important role for NF-κB in the resolution of inflammation and inhibition of M1 macrophage activation during infection through a similar mechanism, illustrating common pathways between the resolution of inflammation and cancer-associated inflammation [21]. TH2 cytokines such as IL-4 and IL-13 stimulate the development of M2 macrophages and TH1 cytokines; IL-12 and IFNγ, are associated with the M1 phenotype. TAM have a M2-like phenotype that is linked with increased tumor-angiogenesis, metastasis and immune-suppression [25]. Interestingly, the IL-4 receptor (CD124) was absent on IKKβ deficient macrophages [21], suggesting that these cells have lost the ability to respond to IL-4 and develop an anti-inflammatory and pro-tumor M2 phenotype.

IL-6 is another important pro-inflammatory cytokine, but has also been reported to have a role in the resolution of inflammation [26,27]. IL-6 binds a membrane bound receptor; IL-6Ra (gp80) that is linked to JAK-STAT signaling through interaction with the gp130 subunit, however binding to its soluble receptor (sIL6R) can trigger an alternative mode of signaling, referred to as trans-signaling, that is associated with the inhibition of inflammation [28,29]. IL-6 trans-signaling via STAT3, but not STAT1, limits the recruitment of neutrophils in acute inflammation and is essential for the termination of the innate immune response [26]. Anti-inflammatory actions of IL-6 have also been related to chronic viral infection; human herpesvirus (HHV)-8 produces an IL-6 ortholog (vIL-6) that suppresses innate immunity [30]. IL-6 has also been reported to interfere with the differentiation of dendritic cells (DC) from CD14+ human monocytes, presumably through STAT3, suggesting that the action of IL-6 could interfere with adaptive immune responses [31]. IL-10-mediated STAT3 activation has also been reported to inhibit DC activation and function [32]. Thus IL-6 appears to have important anti-inflammatory and immunosuppressive roles through the activation of STAT3.

STAT3-signaling is also a major oncogenic pathway in epithelial cells and is thought to underpin the pro-malignant activity of IL-6 [33]. However, the role of STAT3 in the regulation of immune cells, and its involvement in tumor-induced immune-suppression are important for carcinogenesis [34]. It is well established that signaling through STAT3 inhibits pro-inflammatory cytokine production and leukocyte recruitment, but this could be attributed to either IL-6 or IL-10 signaling. Blockade of STAT3 in tumors increased pro-inflammatory mediator production and leukocyte recruitment, but was associated with increased cytotoxicity and tumor regression, suggesting that STAT3 activation blocks anti-tumor immune responses [35]. In contrast, two recent studies have illustrated the important role for STAT3 in the malignant transformation of epithelial cells in CAC. Targeted deletion of STAT3 in intestinal epithelial cells (IEC) reduced tumor incidence, and similar results were obtained with IL-6 deficient mice, this was associated with increased IEC apoptosis [36]. Another study showed mice expressing a constitutively active gp130 molecule had accelerated CAC development [37]. However, in both models reduced tumor burden was associated with the increased production of pro-inflammatory cytokines. The role of this increase in inflammation in tumor regression was not assessed. These studies show that IL-6 has important effects on both malignant cells and immune cells in the tumor microenvironment that can contribute to carcinogenesis, further studies are required to evaluate the contribution of anti-inflammatory IL-6 signaling in cancer.

It is clear from the studies described above that cytokine signaling can have a dual role in cancer; cytokines can activate

oncogenic pathways in malignant cells and promote survival, proliferation and invasion. But, cytokines also regulate the phenotype of immune cells, including T cells and macrophages, that influences tumor progression by regulating the inflammatory microenvironment.

3. Lipid mediators

Ecosanoids formed from arachidonic acid (AA) metabolism, such as prostaglandins and leukotrienes, are major pro-inflammatory mediators that regulate both vascular changes and leukocyte recruitment [38]. There is extensive epidemiological and experimental evidence that cyclooxygenase (COX)-derived prostaglandin (PG) E2 can drive malignancy, particularly in colorectal cancer in which inflammation is a significant risk factor [39,40]. Most studies have focused on the ability of PGE2 to promote angiogenesis, malignant cell survival and invasion. However, PGE2 has also long been known to have immunosuppressive actions and particularly to inhibit macrophage and T cell activation [41] that may contribute to its' role in cancer. It was recently reported that PGE2 induces differentiation of myeloid-derived suppressor cells (MDSC) from bone marrow stem cells in experimental models of cancer [42]. MDSC are expanded in chronic infections and cancer and have been shown to be potent suppressors of anti-tumor immune responses. PGE2 has also been shown to be chemotactic for MDSCs and therefore regulate recruitment of these cells to tumors [42]. Recently it was also shown that degradation of PGE2 within the tumor microenvironment can redirect the profile of TAM from a pro-tumor M2 phenotype to the pro-inflammatory and anti-tumor M1 phenotype [42]. Suggesting PGE2 inhibits the anti-tumor potential of TAM and therefore contributes to tumor progression. PGE2 also inhibits expression of MHC molecules on DC [43] and macrophages [44] that may reduce priming of antigen-specific T cells in the tumor microenvironment.

There are a number of anti-inflammatory lipid mediators that have important roles in the resolution of inflammation [45], the most significant being; PGD2, lipoxins and resolvins. PGD2 is generated by the action of PGD2 synthase (PGD2S) and has been reported to be particularly important in allergic inflammation driven by TH2 cytokines such as IL-4 and IL-13 [46,47]. PGD2, and its metabolite; PGJ2, also have direct anti-inflammatory actions and inhibit TH1 immune responses [48,49]. In two different models of experimental colon cancer, PGD2 seemed to have opposite effects; in the ApcMin/+ genetic model, over-expression of PGD2S reduced the presence of intestinal adenomas up to 80%, and PGD2S−/− mice showed increased incidence of cancer [50]. However, in a model of rat CAC, treatment with a selective PGD2 receptor (DP1) antagonist significantly reduced aberrant crypt foci development, beta-catenin expression, and mucosal thickness [51]. There are 2 distinct receptors for PGD2; DP1 and DP2 [52], the positive effects of PGD2 on TH2 cytokine production are thought to be mediated through the DP2 receptor expressed on TH2 cells [47], however the anti-inflammatory effects of PGD2 are thought to be mediated by the DP1 receptor, mainly expressed on myeloid cells [51,53]. This may explain the disparity between the above studies since the later study focused on the role of DP1 receptor whereas the experiments in APCMin/+ mice did not attribute the activity of PGD2 to either receptor. The anti-inflammatory action of PGD2 may inhibit production of tumor-promoting cytokines and therefore inhibit carcinogenesis, however the role of PGD2 in TH2 cytokine production and inhibition of TH1 responses may equally promote cancer, it would be interesting to see if these different effects of PGD2 in cancer can be attributed to specific receptors.

Lipoxins are generated by the action of lipoxygenase (LOX) or the concerted action of LOX and COX enzymes [54]. The more recently described resolvins represent a series of mediators generated from the metabolism of docosahexaenoic acid (DHA), the most abundant omega 3 fatty acid in the diet [54]. There is now extensive evidence these lipid metabolites are important endogenous anti-inflammatory mediators and inhibit chronic inflammation [54]. But there is not yet any data indicating the potential role of lipoxins and resolvins in cancer. Previous studies have shown lipoxins are immunosuppressive in the context of infection, and in fact pathogens use lipoxin production to evade host immunity [55,56]. These studies would suggest a potential role for these mediators in tumor-induced immune-suppression. But equally, the anti-inflammatory properties of lipoxins and resolvins may attenuate inflammation-associated cancer, in a similar fashion as reported for PGD2.

4. Adenosine

Adenosine is also an important anti-inflammatory mediator [57]. Adenosine is constitutively present in extracellular spaces at low concentrations but is increased dramatically in tumors [58]. Adenosine interacts with at least four G protein-linked receptors; the A2A receptor (A2AR) associates with Gs and A2BR interacts with Gs and Gq to trigger adenylate cyclase (AC) and elevate cyclic adenosine monophosphate (cAMP) [57]. A2AR has been shown to inhibit activation of neutrophils, monocytes, platelets and T cells [59–61]. In contrast, activation of A1 (A1R) or A3 (A3R) receptors, through Gi/Go interactions, inhibits AC activity and decreases cAMP levels [62], A1R exerts pro-inflammatory effects by enhancing phagocytosis [63] and chemotaxis [64,65] during inflammation. A1R is highly expressed early in the inflammatory response, but is replaced by A2AR expression during the resolution of inflammation [27]. The extracellular levels of adenosine and receptor expression are critical factors in the regulation of inflammation.

Hypoxia is considered a major factor in tumor progression [66], it has been shown to increase VEGF through the activation of hypoxia inducible factor (HIF)-1α, a transcription factor that regulates the cell response to hypoxia, in a mechanism that involves interaction with STAT3 [67]. The loss of the tumor suppressor Von Hippel-Lindau (Vhl) leads to an increase in HIF-1 activation that is specifically linked with renal cancer [68,69]. Hypoxia has also been shown to inhibit T cell activation in tumors by at least of two different mechanisms; HIF-1α can inhibit antigen-induced TCR signaling, protecting tumors from cytotoxic T cells (CTL) [70]. Hypoxia also increases the levels of adenosine in the tumor microenvironment [58]. In tumors, the anti-inflammatory receptor; A2AR, is highly expressed and is linked with immune-suppression illustrating another parallel with the resolution of inflammation [58]. Adenosine mediates cAMP-elevation in CTL through A2A receptors and blocks cytotoxic activity. As described above, elevation of cAMP is an important anti-inflammatory mechanism and inhibits the activation of macrophages and DC, A2AR expression on tumor-associated myeloid cells is therefore likely to contribute to evasion of immune responses. In fact, the anti-inflammatory and immunosuppressive action of PGE2 and PGD2 can also be attributed to cAMP-elevation through EP2 [41] and DP1 receptors [53], respectively. In contrast to these potentially anti-inflammatory roles for hypoxia-induced adenosine in tumors, HIF-1α has been reported to regulate the pro-inflammatory activity of macrophages during inflammation. Targeted deletion of HIF-1α in myeloid cells was shown to reduce chronic inflammation in several models [71]. However, the specific deletion of HIF-1α in T cells showed that HIF-1α activation can inhibit auto-immune responses, therefore hypoxia-induced HIF-1α could suppress anti-tumor immunity but promote other inflammatory responses [72].
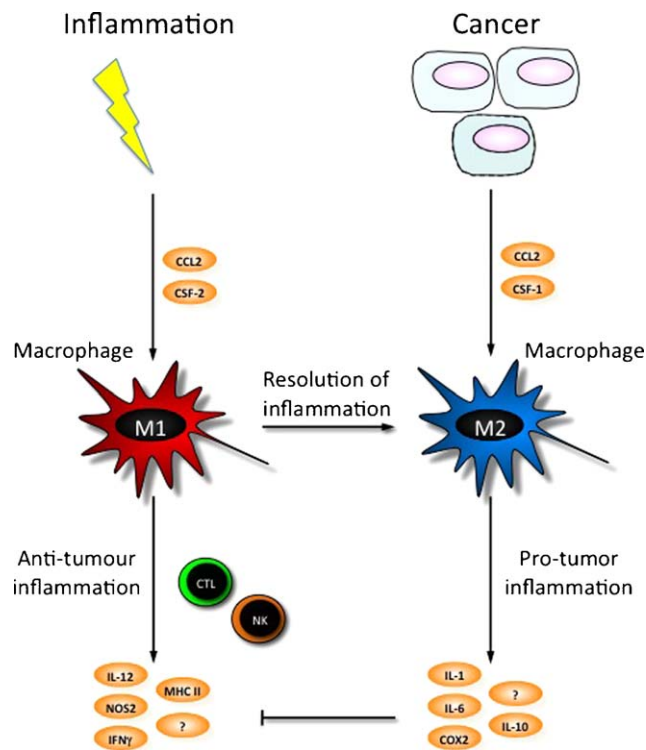
Fig. 1. Illustration of pro- and anti-tumor roles for inflammation in cancer. 'Classical' or M1 macrophage activation during inflammation is associated with increased production of pro-inflammatory cytokines, such as IL-12 and IFNγ, and antigen presenting cell (APC)-activity. However, 'alternatively' activated or M2 macrophages are also criticial for the resolution of inflammation and wound healing through the production of anti-inflammatory cytokines; such as IL-10 and TGFβ, and COX2-derived lipid mediators. Tumor-associated macrophages (TAM) have a M2-like phenotype that is associated with increased angiogenesis, metastasis and immune-suppression. Analogous to TH1/TH2 responses, M2 macrophages antagonize the M1 phenotype and vice versa.

5. Conclusions

There are multifaceted roles for inflammation in cancer that include regulation of the immune response to tumors and effects on the malignant activity of transformed cells but it is clear inflammation can either promote or inhibit carcinogenesis. There are stark parallels between the resolution of inflammation and the inflammatory microenvironment in cancer (Fig. 1); endogenous anti-inflammatory mechanisms the drive the resolution of inflammation over-expressed in cancer include; anti-inflammatory cytokines, lipid mediators and extracellular adenosine, their contribution to carcinogenesis requires further investigation. This may reflect the concept that tumors represent wounds that cannot heal as suggested by Harold Dvorak. The persistent activation of endogenous ant-inflammatory mechanisms, that may in fact be driven by pro-inflammatory pathways, could maintain; immune-suppression, angiogenesis and the synthesis of extracellular matrix that are hall marks of the tumor progression. We are beginning to understand the molecular mechanisms and mediators required for the resolution of inflammation and how these may be manipulated in the treatment of chronic inflammatory disease. Studies on the role of these mechanisms in cancer may reveal new targets for therapy that will complement the new generation of agents targeting oncogenic signaling pathways in malignant cells.

References

[1] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.

[2] Bingle L, Brown NJ, Lewis CE. The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. J Pathol 2002;196:254–65.

[3] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6:715–27.

[4] Wiemann B, Starnes CO. Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. Pharmacol Ther 1994;64:529–64.

[5] Dalbagni G. The management of superficial bladder cancer. Nat Clin Pract Urol 2007;4:254–60.

[6] Zitvogel L, Apetoh L, Ghiringhelli F, Andre F, Tesniere A, Kroemer G. The anticancer immune response: indispensable for therapeutic success? J Clin Invest 2008;118:1991–2001.

[7] Budhu A, Wang XW. The role of cytokines in hepatocellular carcinoma. J Leukoc Biol 2006;80:1197–213.

[8] Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. Front Biosci 2008;13:453–61.

[9] Balkwill F. Tumour necrosis factor and cancer. Nat Rev Cancer 2009;9:361–71.

[10] Szlosarek P, Charles KA, Balkwill FR. Tumour necrosis factor-alpha as a tumour promoter. Eur J Cancer 2006;42:745–50.

[11] Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001;44:2862–9.

[12] van Oosten BW, Barkhof F, Truyen L, Boringa JB, Bertelsmann FW, von Blomberg BM, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology 1996;47:1531–4.

[13] Yang XD, Tisch R, Singer SM, Cao ZA, Liblau RS, Schreiber RD, et al. Effect of tumor necrosis factor alpha on insulin-dependent diabetes mellitus in NOD mice. I. The early development of autoimmunity and the diabetogenic process. J Exp Med 1994;180:995–1004.

[14] Notley CA, Inglis JJ, Alzabin S, McCann FE, McNamee KE, Williams RO. Blockade of tumor necrosis factor in collagen-induced arthritis reveals a novel immunoregulatory pathway for Th1 and Th17 cells. J Exp Med 2008; 205:2491–7.

[15] Vieira LQ, Goldschmidt M, Nashleanas M, Pfeffer K, Mak T, Scott P. Mice lacking the TNF receptor p55 fail to resolve lesions caused by infection with Leishmania major, but control parasite replication. J Immunol 1996;157:827–35.

[16] Chen X, Baumel M, Mannel DN, Howard OM, Oppenheim JJ. Interaction of TNF with TNF receptor type 2 promotes expansion and function of mouse CD4+CD25+ T regulatory cells. J Immunol 2007;179:154–61.

[17] Liu LY, Bates ME, Jarjour NN, Busse WW, Bertics PJ, Kelly EA. Generation of Th1 and Th2 chemokines by human eosinophils: evidence for a critical role of TNF-alpha. J Immunol 2007;179:4840–8.

[18] Karin M. Nuclear factor-kappaB in cancer development and progression. Nature 2006;441:431–6.

[19] Greten FR, Arkan MC, Bollrath J, Hsu LC, Goode J, Miething C, et al. NF-kappaB is a negative regulator of IL-1beta secretion as revealed by genetic and pharmacological inhibition of IKKbeta. Cell 2007;130:918–31.

[20] Lawrence T, Gilroy DW, Colville-Nash PR, Willoughby DA. Possible new role for NF-kappaB in the resolution of inflammation. Nat Med 2001;7:1291–7.

[21] Fong CH, Bebien M, Didierlaurent A, Nebauer R, Hussell T, Broide D, et al. An antiinflammatory role for IKKbeta through the inhibition of "classical" macrophage activation. J Exp Med 2008;205:1269–76.

[22] Greten FR, Eckmann L, Greten TF, Park JM, Li ZW, Egan LJ, et al. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell 2004;118:285–96.

[23] Sakurai T, Maeda S, Chang L, Karin M. Loss of hepatic NF-kappa B activity enhances chemical hepatocarcinogenesis through sustained c-Jun N-terminal kinase 1 activation. Proc Natl Acad Sci USA 2006;103:10544–51.

[24] Hagemann T, Lawrence T, McNeish I, Charles KA, Kulbe H, Thompson RG, et al. Re-educating" tumor-associated macrophages by targeting NF-kappaB. J Exp Med 2008;205:1261–8.

[25] Sica A, Bronte V. Altered macrophage differentiation and immune dysfunction in tumor development. J Clin Invest 2007;117:1155–66.

[26] Fielding CA, McLoughlin RM, McLeod L, Colmont CS, Najdovska M, Grail D, et al. IL-6 regulates neutrophil trafficking during acute inflammation via STAT3. J Immunol 2008;181:2189–95.

[27] Nakav S, Chaimovitz C, Sufaro Y, Lewis EC, Shaked G, Czeiger D, et al. Anti-inflammatory preconditioning by agonists of adenosine A1 receptor. PLoS One 2008;3:e2107.

[28] Heinrich PC, Behrmann I, Haan S, Hermanns HM, Muller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J 2003;374:1–20.

[29] Ernst M, Jenkins BJ. Acquiring signalling specificity from the cytokine receptor gp130. Trends Genet 2004;20:23–32.

[30] Fielding CA, McLoughlin RM, Colmont CS, Kovaleva M, Harris DA, Rose-John S, et al. Viral IL-6 blocks neutrophil infiltration during acute inflammation. J Immunol 2005;175:4024–9.

[31] Cirone M, Lucania G, Aleandri S, Borgia G, Trivedi P, Cuomo L, et al. Suppression of dendritic cell differentiation through cytokines released by primary effusion lymphoma cells. Immunol Lett 2008;120:37–41.

[32] Wang T, Niu G, Kortylewski M, Burdelya L, Shain K, Zhang S, et al. Regulation of the innate and adaptive immune responses by Stat-3 signaling in tumor cells. Nat Med 2004;10:48–54.

[33] Aggarwal BB, Sethi G, Ahn KS, Sandur SK, Pandey MK, Kunnumakkara AB, et al. Targeting signal-transducer-and-activator-of-transcription-3 for prevention

and therapy of cancer: modern target but ancient solution. Ann NY Acad Sci 2006;1091:151–69.

[34] 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.

[35] Kortylewski M, Kujawski M, Wang T, Wei S, Zhang S, Pilon-Thomas S, et al. Inhibiting Stat3 signaling in the hematopoietic system elicits multicomponent antitumor immunity. Nat Med 2005;11:1314–21.

[36] Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, Vallabhapurapu S, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 2009;15:103–13.

[37] Bollrath J, Phesse TJ, von Burstin VA, Putoczki T, Bennecke M, Bateman T, et al. gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell 2009;15:91–102.

[38] Gilroy DW, Newson J, Sawmynaden P, Willoughby DA, Croxtall JD. A novel role for phospholipase A2 isoforms in the checkpoint control of acute inflammation. FASEB J 2004;18:489–98.

[39] Wang D, Dubois RN. Prostaglandins and cancer. Gut 2006;55:115–22.

[40] Cha YI, DuBois RN. NSAIDs and cancer prevention: targets downstream of COX-2. Annu Rev Med 2007;58:239–52.

[41] Walker W, Rotondo D. Prostaglandin E2 is a potent regulator of interleukin-12- and interleukin-18-induced natural killer cell interferon-gamma synthesis. Immunology 2004;111:298–305.

[42] Sinha P, Clements VK, Fulton AM, Ostrand-Rosenberg S. Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells. Cancer Res 2007;67:4507–13.

[43] Mittal J, Dogra N, Vohra H, Majumdar S. Effects of prostaglandin E2 and nitric oxide inhibitors on the expression of interleukin-10, interleukin-12 and MHC class-II molecules in Mycobacterium microti-infected and interferon-gamma-treated mouse peritoneal macrophages. Folia Microbiol (Praha) 2001;46:259–64.

[44] Figueiredo F, Uhing RJ, Okonogi K, Gettys TW, Johnson SP, Adams DO, et al. Activation of the cAMP cascade inhibits an early event involved in murine macrophage Ia expression. J Biol Chem 1990;265:12317–23.

[45] Lawrence T, Gilroy DW. Chronic inflammation: a failure of resolution? Int J Exp Pathol 2007;88:85–94.

[46] Honda K, Arima M, Cheng G, Taki S, Hirata H, Eda F, et al. Prostaglandin D2 reinforces Th2 type inflammatory responses of airways to low-dose antigen through bronchial expression of macrophage-derived chemokine. J Exp Med 2003;198:533–43.

[47] Xue L, Gyles SL, Wettey FR, Gazi L, Townsend E, Hunter MG, et al. Prostaglandin D2 causes preferential induction of proinflammatory Th2 cytokine production through an action on chemoattractant receptor-like molecule expressed on Th2 cells. J Immunol 2005;175:6531–6.

[48] Trivedi SG, Newson J, Rajakariar R, Jacques TS, Hannon R, Kanaoka Y, et al. Essential role for hematopoietic prostaglandin D2 synthase in the control of delayed type hypersensitivity. Proc Natl Acad Sci USA 2006;103:5179–84.

[49] Theiner G, Gessner A, Lutz MB. The mast cell mediator PGD2 suppresses IL-12 release by dendritic cells leading to Th2 polarized immune responses in vivo. Immunobiology 2006;211:463–72.

[50] Park JM, Kanaoka Y, Eguchi N, Aritake K, Grujic S, Materi AM, et al. Hematopoietic prostaglandin D synthase suppresses intestinal adenomas in ApcMin/+ mice. Cancer Res 2007;67:881–9.

[51] Zamuner SR, Bak AW, Devchand PR, Wallace JL. Predisposition to colorectal cancer in rats with resolved colitis: role of cyclooxygenase-2-derived prostaglandin d2. Am J Pathol 2005;167:1293–300.

[52] Hawcroft G, Gardner SH, Hull MA. Expression of prostaglandin D2 receptors DP1 and DP2 by human colorectal cancer cells. Cancer Lett 2004;210:81–4.

[53] Malki S, Nef S, Notarnicola C, Thevenet L, Gasca S, Mejean C, et al. Prostaglandin D2 induces nuclear import of the sex-determining factor SOX9 via its cAMP-PKA phosphorylation. EMBO J 2005;24:1798–809.

[54] Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 2008;8:349–61.

[55] Vance RE, Hong S, Gronert K, Serhan CN, Mekalanos JJ. The opportunistic pathogen Pseudomonas aeruginosa carries a secretable arachidonate 15-lipoxygenase. Proc Natl Acad Sci USA 2004;101:2135–9.

[56] Bannenberg GL, Aliberti J, Hong S, Sher A, Serhan C. Exogenous pathogen and plant 15-lipoxygenase initiate endogenous lipoxin A4 biosynthesis. J Exp Med 2004;199:515–23.

[57] Ohta A, Sitkovsky M. Role of G-protein-coupled adenosine receptors in down-regulation of inflammation and protection from tissue damage. Nature 2001; 414:916–20.

[58] Ohta A, Gorelik E, Prasad SJ, Ronchese F, Lukashev D, Wong MK, et al. A2A adenosine receptor protects tumors from antitumor T cells. Proc Natl Acad Sci USA 2006;103:13132–7.

[59] Sullivan GW, Rieger JM, Scheld WM, Macdonald TL, Linden J. Cyclic AMP-dependent inhibition of human neutrophil oxidative activity by substituted 2-propynylcyclohexyl adenosine A(2A) receptor agonists. Br J Pharmacol 2001;132:1017–26.

[60] Koshiba M, Kojima H, Huang S, Apasov S, Sitkovsky MV. Memory of extracellular adenosine A2A purinergic receptor-mediated signaling in murine T cells. J Biol Chem 1997;272:25881–9.

[61] Cooper JA, Hill SJ, Alexander SP, Rubin PC, Horn EH. Adenosine receptor-induced cyclic AMP generation and inhibition of 5-hydroxytryptamine release in human platelets. Br J Clin Pharmacol 1995;40:43–50.

[62] Olah ME, Stiles GL. The role of receptor structure in determining adenosine receptor activity. Pharmacol Ther 2000;85:55–75.

[63] Salmon JE, Brogle N, Brownlie C, Edberg JC, Kimberly RP, Chen BX, et al. Human mononuclear phagocytes express adenosine A1 receptors. A novel mechanism for differential regulation of Fc gamma receptor function. J Immunol 1993; 151:2775–85.

[64] Rose FR, Hirschhorn R, Weissmann G, Cronstein BN. Adenosine promotes neutrophil chemotaxis. J Exp Med 1988;167:1186–94.

[65] Schnurr M, Toy T, Shin A, Hartmann G, Rothenfusser S, Soellner J, et al. Role of adenosine receptors in regulating chemotaxis and cytokine production of plasmacytoid dendritic cells. Blood 2004;103:1391–7.

[66] Hockel M, Vaupel P. Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects. J Natl Cancer Inst 2001;93:266–76.

[67] Jung JE, Lee HG, Cho IH, Chung DH, Yoon SH, Yang YM, et al. STAT3 is a potential modulator of HIF-1-mediated VEGF expression in human renal carcinoma cells. FASEB J 2005;19:1296–8.

[68] van Rooijen E, Voest EE, Logister I, Korving J, Schwerte T, Schulte-Merker S, et al. Zebrafish mutants in the von Hippel-Lindau tumor suppressor display a hypoxic response and recapitulate key aspects of Chuvash polycythemia. Blood 2009;113:6449–60.

[69] Gordan JD, Lal P, Dondeti VR, Letrero R, Parekh KN, Oquendo CE, et al. HIF-alpha effects on c-Myc distinguish two subtypes of sporadic VHL-deficient clear cell renal carcinoma. Cancer Cell 2008;14:435–46.

[70] Kojima H, Gu H, Nomura S, Caldwell CC, Kobata T, Carmeliet P, et al. Abnormal B lymphocyte development and autoimmunity in hypoxia-inducible factor 1alpha-deficient chimeric mice. Proc Natl Acad Sci USA 2002;99:2170–4.

[71] Cramer T, Yamanishi Y, Clausen BE, Forster I, Pawlinski R, Mackman N, et al. HIF-1alpha is essential for myeloid cell-mediated inflammation. Cell 2003; 112:645–57.

[72] Lukashev D, Klebanov B, Kojima H, Grinberg A, Ohta A, Berenfeld L, et al. Cutting edge: hypoxia-inducible factor 1alpha and its activation-inducible short isoform I.1 negatively regulate functions of CD4+ and CD8+ T lymphocytes. J Immunol 2006;177:4962–5.

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