

Humoral immunity, inflammation and cancer

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Clinical and experimental data now clearly indicate that chronic inflammation significantly contributes to cancer development. Emerging out of these studies is an appreciation that persistent humoral immune responses exacerbate recruitment and activation of innate immune cells in neoplastic microenvironments where they regulate tissue remodeling, pro-angiogenic and pro-survival pathways that together potentiate cancer development. Population-based studies examining individuals with chronic inflammatory disorders have revealed that states of suppressed cellular immunity, in combination with enhanced humoral immunity and humoral immunity-associated cytokines, cooperate and effectively suppress anti-tumor immune responses while simultaneously enhancing angiogenesis and presumably overall cancer risk in afflicted tissue. In addition, studies in transgenic mouse models of *de novo* organ-specific cancer development have revealed that inflammation mediated by immunoglobulins and immune complexes might be functionally significant parameters of tumor promotion and progression. These recent advances support the hypothesis that enhanced states of local humoral and innate immune activation, in combination with suppressed cellular immunity and failed cytotoxic T cell anti-tumor immunity, alter cancer risk and therefore represent powerful targets for anti-cancer immunotherapeutics.

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Introduction

Early and persistent inflammatory-type responses in or around developing neoplasms are thought to regulate many aspects of tumor development [1]. The innate immune system, extensively studied in the context of autoimmune disease and wound healing following pathogen infection or

tissue damage, has only recently been revealed as an important regulator of cancer development [2,3]. By contrast, tumor immunologists have long focused on anti-tumor activities of the adaptive immune system, and as such have investigated utility of anti-tumor immunotherapeutics with which to combat neoplastic disease [1]. When considering the adaptive immune system as a therapeutic tool, however, it is important to consider both humoral immunity (HI) and cell-mediated immunity (CMI).

This review focuses on the role of persistent humoral-mediated inflammatory responses associated with tumor development and examines the molecular pathways they activate that might differentially regulate cancer promotion and/or progression.

Imbalances in humoral and cell-mediated immunity are associated with cancer development

Pre-malignant and malignant tissues are known to be associated with alterations in immune cell functions (Table 1). Such alterations include suppressed CMI, associated with failure to reject tumors, in combination with enhanced HI that can potentiate tumor promotion and progression [4]. Distinctive CD4⁺ T-cell subsets (e.g. Th1 or Th2 T helper cells) secrete unique repertoires of cytokines that mediate their responses. Th1 cells produce interleukin (IL)-2 and interferon (IFN)- γ for example, and therefore direct CMI responses, whereas Th2 cells produce IL-4 and IL-10, for example, and facilitate local HI responses. In peripheral blood of patients with bladder and colorectal cancer, proportions of Th1 cells, identified by intracellular production of IFN γ or IL-2, is markedly reduced, whereas proportions of Th2 cells producing IL-4, IL-6 and/or IL-10 is significantly elevated, as compared with proportions of Th1 and Th2 in otherwise healthy patient populations [5,6]. A recent study investigating characteristics of leukocytic infiltrations within colorectal cancers found that CD3⁺ T lymphocyte densities within tumor biopsies, as opposed to peripheral blood, represented a better predictor of patient survival than current histopathological staging methods [7^{**}]. Moreover, in human cervical carcinomas, CD3⁺ tumor infiltrating T cells display enhanced Th2 cytokine profiles, specifically increased IL-4 and reduced IFN- γ production [8].

In keeping with these findings, alterations in immune cell status (suppressed CMI and enhanced HI) have also been reported in chronic inflammatory diseases associated with increased cancer risk (Table 1) [4,9,10,11^{*},12,13]. For

Table 1

Enhanced humoral immunity in pre-malignant and malignant diseases.

Disease state	Reported alteration in immune status/function	References
Malignant tissue		
Bladder cancer	Decreased number of Th1 cells and increased number of Th2 cells in peripheral blood	[5]
Colorectal cancer	Decreased number of Th1 cells and increased number of Th2 cells in peripheral blood and increased Th2 cytokines in serum	[6]
Cervical cancer	Lymphocytes derived from human cervical cancer tissue consisted mainly of Th2/Tc2 phenotypes	[8]
Gastric cancer	Decreased ratio of Th1 cell to Th2 cell in peripheral blood and increased IL-10 in serum	[6,22*]
Head and neck cancer	High level of immune complexes correlates with increased tumor burden and poor prognosis	[34–36]
Breast cancer		
Genitourinary		
Pre-malignant tissue		
Ulcerative colitis	B cell activation and markedly skewed local IgG ₁ response in intestines	[4,9]
Asbestosis	Increased immunoglobulin and immune-complex, and higher levels of IL-6 and IL-8 in the peripheral blood of patients with asbestosis	[4,10]
Barrett's esophagus	Replacement of Th1 effector cells with Th2 effector cells in inflamed tissue	[11*]
HCV-related cirrhosis	Decreased number of Th1 cells and increased number of Th2 cells in peripheral blood	[4,12]
Chronic obstructive airway disease (COPD)	T lymphocytes in bronchoalveolar lavage from patients with COPD displayed increased intracellular expression of Th2 cytokines	[4,13]

example, intestinal B cell responses have been observed in ulcerative colitis, a benign condition with a high risk for colorectal cancer development [4,9]. Decreased Th1/Th2 ratios in peripheral blood have been reported in Hepatitis C virus-related liver cirrhosis, a liver disease closely associated with hepatocellular carcinoma [12]. In Barrett's esophagus, an intermediate step in the progression from reflux esophagitis to esophageal adenocarcinoma, infiltration of Th1 effector cells (macrophages and CD8⁺ T cells) is largely replaced by Th2 effector cells (IgG producing plasma cells and mast cells) when reflux esophagitis progresses to Barrett's esophagus [11*]. Taken together, these compelling clinical findings indicate that pronounced HI may underlie increased risk for neoplastic progression in tissues afflicted with chronic inflammatory disease pathologies.

Autoimmune disorders caused by B cell hyperactivity are also associated with cancer [14]. B cells are known to initiate autoimmunity through several mechanistic pathways including enhanced production of autoantibodies, immune complexes, dendritic and T cell activation and cytokine production [15]. The pathogenic role for B cells in autoimmune disease is supported by clinical success of B cell depletion therapy using a chimeric monoclonal antibody (MoAb) specific for human CD20 (e.g. Rituximab) in patients with rheumatoid arthritis, systemic lupus erythematosus (SLE) and others [16,17]. Rituximab has also found clinical efficacy in adult acute lymphoblastic leukaemia (ALL) — monotherapy in patients with relapsed ALL has achieved modest success, but greater effects have been found in combination with chemotherapy and in treatment for minimal residual disease [18]. Although Rituximab effectively deletes the vast majority of circulating B cells, no increased susceptibility to

infection has been observed in patients treated with Rituximab for rheumatoid arthritis or non-Hodgkin's lymphoma [17], thus engendering support for systemically manipulating humoral immune responses as a therapeutic approach.

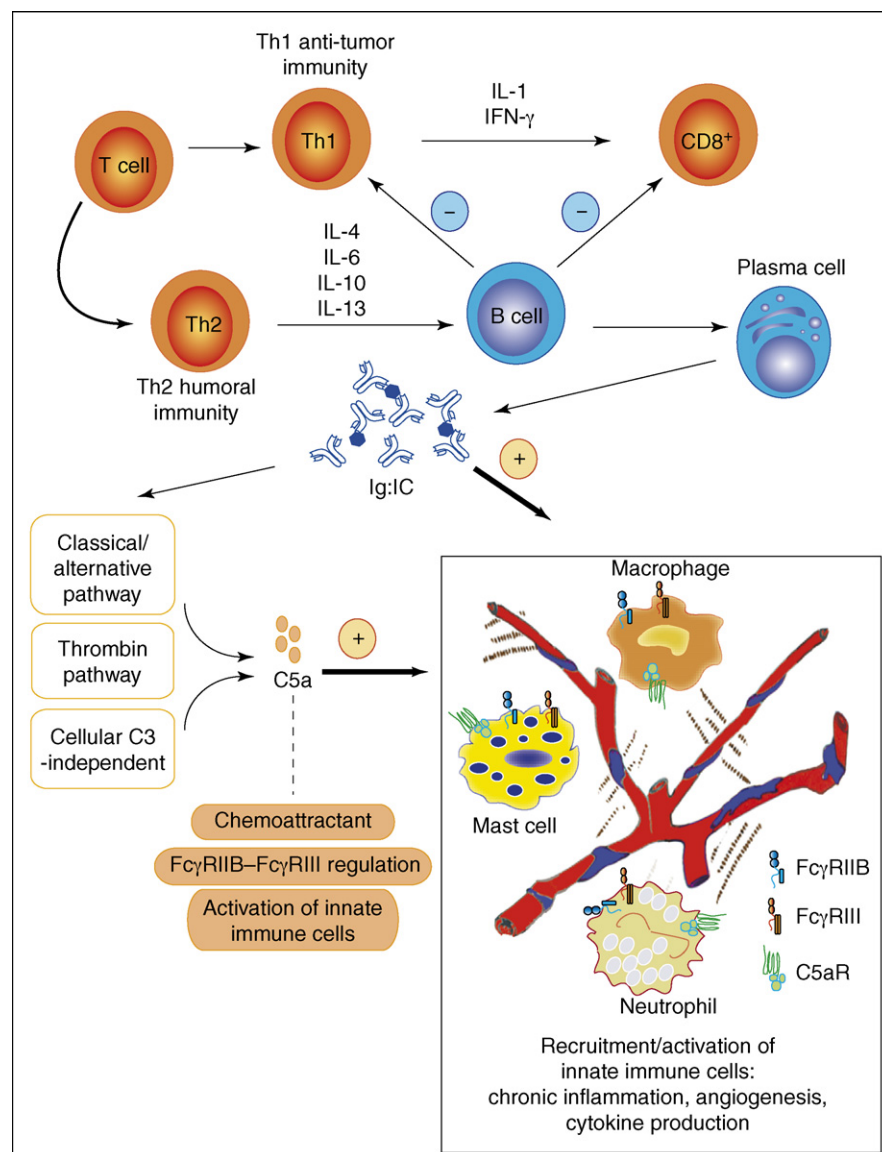
The mechanistic links between autoimmune diseases, such as rheumatoid arthritis, Sjogren's syndrome and SLE, with non-Hodgkin's lymphoma are undisputed; however, the association of solid tumors with autoimmunity has not been well described [14]. Cohort studies have found increased risk for lung cancer in rheumatoid arthritis patients [14], and a modestly increased risk for all cancers, particularly lung cancer and hepatobiliary cancers, in SLE patients [14]. Clinical studies of patients with systemic sclerosis have also revealed increased risk for lung cancer, non-melanoma skin cancers and breast cancer [19]. Mechanisms contributing to these enhanced cancer risks are largely elusive; however, given pronounced humoral immune responses in afflicted tissues, it is intriguing to speculate that autoantibody–antigen complex formation and deposition in neoplastic microenvironments might contribute. Support for this hypothesis comes from a limited clinical study where advanced colon cancer patients were treated with Rituximab. In these individuals, numbers of CD21-hyperpositive lymphocytes were reduced in parallel with a 50% reduction in tumor burden with no ill-effects as a result of the therapy [20]. Taken together, the clinical data indicate a role for enhanced HI and inflammation, in combination with suppressed CMI, in the pathogenesis of several human cancer types — mechanistic investigation of the molecular and cellular pathways mediating enhanced cancer risk will surely identify new therapeutic targets with which to combat neoplastic disease.

HI-associated cytokines as mediators of tumor development

Molecular mechanisms by which HI impacts cancer initiation, promotion and progression are almost certainly multifaceted (Figure 1). Cytokines derived from evolving neoplastic cells, activated resident stromal cells or infiltrating immune cells can regulate tumor growth by affecting angiogenesis, cell survival, death or differentiation. CMI and Th1-associated cytokines, such as IFN- γ , tend to exhibit anti-angiogenic bioactivities [21], whereas

several HI and Th2-associated cytokines, such as IL-10, stimulate angiogenesis, and are therefore pro-tumorigenic [22^{*}]. Increased IL-10 expression in patients with gastric cancer correlates with tumor angiogenesis, attenuated CD8⁺ T cell infiltration, and poor prognosis [22^{*}]. Although, the literature has implicated IL-6 in both Th1- and Th2-type responses, in several chronic inflammatory diseases and various types of cancers, IL-6 is better known to direct Th2-type responses and play a central role as a differentiation and growth factor of

Figure 1



Model for role of humoral immunity during inflammation-associated cancer development. Pre-malignant and malignant tissues are associated with suppressed Th1 responses (i.e. IL-1 and IFN γ) in combination with enhanced Th2 responses (i.e. IL-4, -6, -10 and -13). The latter leads to activation of B cells that can inhibit Th1 anti-tumor immunity. Conversely, B cell activation also leads to immune complex (Ig:IC) accumulation in serum and tissue interstitia that subsequently initiates pro-inflammatory activities and recruitment of innate immune cells (e.g. macrophages, neutrophils and mast cells), possibly via C5aR and Fc γ Rs, leading to chronic tumor-promoting inflammatory responses. C5a, generated through classical/alternative, thrombin and/or cellular C3-independent pathways, induces chemotaxis of innate immune cells and modulates their function via regulation of activating versus inhibitory Fc γ Rs.

neoplastic epithelial cells [23,24]. IL-13 promotes survival and/or growth of selective tumor types through direct action on neoplastic cells, in addition to suppressing CMI [25]. IL-23, a cytokine produced by dendritic cells and macrophages following bacterial exposure and Toll-like receptor engagement, is also found highly expressed in various types of human carcinomas compared with adjacent normal tissue, indicating a potential important role in tumor development [26]. In a mouse model of chemical carcinogenesis, absence of IL-23 resulted in a significant reduction in local inflammatory responses in the tumor microenvironment that paralleled an increase in cytotoxic T-cell infiltration, together resulting in resistance to carcinogenesis [26]. Thus, whereas IL-23 is not generally considered as a Th2 cytokine, in this context, it is exerting Th2-like cytokine bioactivities by promoting inflammatory responses and inhibiting cytotoxic T cell responses. The degree to which effectiveness of IL-23 neutralization will translate to other mouse models of *de novo* carcinogenesis and/or human cancer development is yet to be defined.

Thus, Th1- and Th2-associated cytokines act antagonistically in different tumor microenvironments, while in general a cytokine profile skewed toward Th2 responses correlates with enhanced tumor promotion and progression. It is unclear at present, however, if pro-tumor bioactivities of Th2-associated cytokines are limited solely to their direct abilities to enhance pro-tumor pathways (inflammation or angiogenesis), or more in their ability to suppress CMI responses, or a combination of both.

B-lymphocytes inhibit Th1 anti-tumor immunity

As the central component of HI, B-lymphocytes function in antibody production, antigen presentation and secretion of pro-inflammatory cytokines. In the context of cancer development, in addition to altering local and circulating profiles of cytokines, B cells also inhibit Th1-mediated anti-tumor immune responses.

In a syngeneic mouse mammary xenograft model, partial B cell depletion resulted in significantly reduced tumor burden [20]. In experimental mouse models of lung adenocarcinoma, B cell deficiency significantly enhanced therapeutic efficacy of combinatorial chemotherapy and IL-15, a Th-1 cytokine with IL-2-like anti-tumor bioactivities [27]. In a mouse model of melanoma, B cell deficiency provided a therapeutic advantage to a melanoma vaccine where enhanced tumor protection in the absence of B cells was associated with an increased magnitude and longevity of specific cellular immune response provoked by vaccination [28]. Moreover, Shah and colleagues [29•] have reported that B-cell-deficient mice exhibit resistance to several histologically diverse primary syngeneic tumors. Increased tumor resistance in B-cell-deficient mice was found to be associated with enhanced anti-tumor Th1 cytokines and cytolytic T

lymphocyte (CTL) responses [29•]. Adoptive transfer of B lymphocytes, but not serum, from wild-type mice to B cell-deficient mice restored tumor growth accompanied by reduced Th1 cytokines and CTL response, suggesting antibody-independent mechanisms [29•]. Together, these experimental findings support the concept that B cells limit anti-tumor immunity by inhibiting Th1 and CTL responses while simultaneously bolstering Th2-effector cell pro-tumor functions.

Do immunoglobulins play a functional role in solid tumor development?

Cancer patients often develop antibodies to tumor-associated antigens — evidence exists to support this for c-myc, HER-2/neu and p53 [30]. However, production of these antibodies does not confer protection, but, paradoxically, correlates with poor prognosis and decreased survival for several human cancer types [31]. Anti-tumor antibodies are thought to enhance tumor growth by promoting pro-tumor immune responses and in general protecting tumor cells from CTL-mediated killing [32]. Increased levels of immunoglobulins (Ig) in neoplastic microenvironments also result in accumulation of immune complexes (ICs) that engender tumor-promoting inflammatory responses [1,33]. Ig-IC formation is a significant feature of cancer development: high circulating levels of ICs are associated with increased tumor burden and poor prognosis in patients with breast, genitourinary, and head and neck malignancies [34–36], and Ig deposition in neoplastic stroma has been reported in pre-malignant and malignant human breast and prostate tissues [1]. McDonald and colleagues [37] recently reported that deposition of extravasated Ig in tumor stroma is due to enhanced leakiness of tumor blood vessels. Using a mouse model of islet cell carcinogenesis, non-specific and epitope-specific antibodies (directed against extracellular matrix antigens) were infused into tumor-bearing animals and both were found to preferentially localize adjacent to leaky tumor blood vessels in tumor stroma [37], thus implying that Ig-IC depositions in neoplastic tissues is a general phenomenon associated with cancer development and not necessarily a directed process towards specific antigens, even when specific antigens are present.

In addition to forming immune complexes, IgG has also been identified in complex with latent transforming growth factor (TGF)- β [38]. Such complexes were proposed to diminish directed primary CTL responses but underlying mechanisms were not fully resolved. TGF β is a potent regulator of CTL function where it inhibits secretion of cytolytic factors [39]. Kim and colleagues [40••] recently reported that genetic deficiency of key components of the TGF- β intracellular signaling cascade (e.g. *Smad4*) in CD4⁺ T cells significantly influenced initiation, promotion and progression of epithelial cancer. Mice harboring homozygous null deletions in the *Smad4* gene preferentially in CD4⁺ T cells spontaneously

develop epithelial cancers in the gastrointestinal tract where prominent plasma cell hyperplasia was evident adjacent to developing duodenal polyps. Mice harboring germline mutations in *Smad4* did not exhibit any of these same characteristics [40^{••}]. *Smad4*-deficient T cells become skewed in their cytokine profile and prominently express several Th2-type cytokines including IL-4, -5, -6 and -13. These pro-tumor mediators also enhance plasma cell differentiation, thus demonstrating that altering local balances of important cytokine pathways, by differential regulation of either HI or CMI, profoundly influences malignant risk and argues that perturbing these balances to favor anti-tumor immunity represents a powerful anti-cancer approach.

ICs have long been suspected as initiators of inflammatory cascades associated with tissue destruction in autoimmune diseases but underlying molecular mechanisms have been elusive [41]. Recent investigations of these mechanisms using an experimental mouse model of airway remodeling following *Mycoplasma pulmonis* infection have demonstrated that peripheral B cell responses and local Ig-IC deposition are the critical triggers for recruiting innate leucocytes into infected airways, that then activate pro-angiogenic and tissue remodeling pathways necessary for resolving infection [42]. We have reported complimentary findings using a transgenic mouse model of squamous carcinogenesis [43,44[•]]. Here, oncogenes from human papillomavirus type 16 (HPV16) are expressed in skin keratinocytes under direction of a human keratin 14 (K14) promoter/enhancer and initiate multi-stage development of squamous cell carcinomas (SCCs) in skin and cervix [43,44[•],45]. In HPV16 transgenic mice, combined B- and T-lymphocyte-deficiency eliminated IC deposition in premalignant skin and attenuated innate immune cell infiltrations, resulting in diminished tissue remodeling activity, failure to activate angiogenic vasculature, retention of terminal differentiation programs in skin keratinocytes and a 43% reduction in overall SCC incidence [44[•]]. Adoptive transfer of B-lymphocytes or serum isolated from HPV16 mice (but not from wild-type naïve mice) into B- and T-lymphocyte-deficient/HPV16 mice restored IC deposition, chronic innate immune cell infiltration in pre-malignant skin and reinstated parameters for full malignancy [44[•]]. These data indicate that B-lymphocyte-derived factors, possibly Ig, are essential for establishing chronic inflammatory pathways that potentiate cancer development. In support of this concept, anti-tumor antibodies are known to enhance outgrowth and invasion of murine and human tumor-cell xenografts through recruitment and activation of granulocytes and macrophages [33], which are important sources of vascular endothelial growth factor (VEGF) [46] that possesses pro-angiogenic bioactivities. Thus, serum proteins (presumably antibodies) produced by B-lymphocytes locally or peripherally, at least in some scenarios, are crucial factors that initiate chronic inflammatory programs,

that are not only essential for resolving acute tissue damage but also essential for promoting tumor development in initiated tissues.

FcγR and C5a are key regulators of IC-mediated inflammation

Inflammatory responses to ICs have been extensively studied in transgenic mouse models of various autoimmune diseases [47]. Mechanisms by which ICs initiate inflammation are still not fully understood; however, receptors for the Fc portion of IgG (FcγRs, especially FcγRIII) and complement factors (particularly C5a anaphylatoxin) are recognized as co-dominant effectors in the process [47]. Considering the fact that tissues damaged by autoimmune dysfunction and by cancer have similar characteristics (e.g. chronic innate immune cell infiltration, tissue remodeling, angiogenesis, altered cell survival pathways) [48], it seems probable that similar IC effector pathways are involved in pathogenesis of both diseases.

Expressed on most leucocytes, FcγRs are classified into four groups (FcγRI/CD64, FcγRII/CD32, FcγRIII/CD16 and recently identified FcγRIV) according to their distinct affinities for IgG, cell distributions and functions. FcγRI and FcγRIII, predominantly FcγRIII, mediate immune cell activation via their FcR γ chain that contains an intracellular tyrosine-based activating motif (ITAM). Activating signals mediated by ITAM trigger oxidative bursts, cytokine release and phagocytosis by macrophages, antibody-dependent cell-mediated cytotoxicity (ADCC) by natural killer (NK) cells, and degranulation of mast cells [41]. In contrast, engagement of FcγRIIB that instead contains immune tyrosine-based inhibitory motifs (ITIM) inhibits these same inflammatory responses [41]. These two opposing regulatory pathways coexist on innate immune cells and thus, in part, determine the magnitude of IC-mediated inflammatory responses. Indeed, the ratio of activating to inhibitory FcγR is low in 'normal' homeostatic tissues, and by contrast is highly increased in inflamed microenvironments [47].

Receptors for the Fc portion of IgG, FcγRs play a central role in regulating immune responses following interaction with ICs [41]. It was recently demonstrated that presence or absence of sialic acid at the terminus of the core glycan in the Fc region of IgG regulates immune response [49^{••}]. Sialylation of the Fc region of IgG reduces binding affinities towards FcγRs thereby inhibiting pro-inflammatory activities of IgG, whereas reduction of sialylation, upon antigen challenge, switches the immune response pathway from anti-inflammatory to pro-inflammatory via differential engagement with FcγRs on effector cells [49^{••}]. Regulatory functions of FcγRs have been studied using genetically engineered animal models. Mice deficient in the FcR γ chain or activating type FcγRs are resistant to a wide range of IC-mediated hypersensitive reactions, such as vasculitis, glomerulonephritis and skin Arthus reaction

[41]. Conversely, mice deficient in FcγRIIB exhibit enhanced IC-mediated inflammatory responses [41]. Although these elegant genetic studies demonstrate functional importance of FcγRs in IC-mediated inflammation and autoimmune diseases, little is known about their role in tumor development.

Complement activation is a central event during innate immune defence following pathogenic tissue assault. Three different pathways of complement activation have been identified, namely classical, alternative and lectin pathways. Foreign antigens and ICs activate complement cascades resulting in formation of lytic membrane attack complexes and formation and liberation of anaphylatoxins; for example, C3a and C5a, potent pro-inflammatory factors that induce recruitment and activation of leukocytes. Deposition of complement proteins is a common occurrence at sites of inflammation. Studies utilizing complement depleted mice and C3- or C5-deficient mice have identified their crucial roles in regulating disease pathogenesis [50,51]. We previously reported abundant deposition of C3 in neoplastic skin of HPV16 mice; but found that C3-deficiency was without functional consequence, indicating that if Ig-ICs enhance premalignant progression, they most likely contribute via regulation of either FcγR or through C5a [52].

C5a is a proteolytic fragment of C5 generated by the high-affinity C5 convertase, C3b complexed with C4b and C2a. Of note, complement-independent enzymes, such as thrombin, neutrophil elastase and a macrophage serine protease, have C5 convertase activity and therefore generate C5a in a C3-independent manner [53•] (Figure 1). C5a induces chemotaxis of macrophages, granulocytes, mast cells, dendritic cells and B-lymphocytes, and modulates their function through differential regulation of activating FcγRs versus inhibitory FcγRs [54•]. The initial contact between ICs and pulmonary alveolar macrophages results in complement-independent C5a production that causes decreased levels of inhibitory FcγRIIB, increased levels of activating FcγRIII, and highly induced FcγR-mediated cytokine production [54•] (Figure 1). Whether C5a-dependent modulation of FcγRs is a common mechanism operative in IC inflammation has yet to be determined. Nevertheless, a cellular pathway of C5a production is evident in cultured macrophages induced by antibody complex ligation to activating FcγR, indicating a complex regulatory network of multiple interactions between FcγR and C5a/C5aR [47]. Considering that autoimmune diseases and cancer have common characteristics such as pronounced HI and IC deposition, FcγR and C5a/C5aR are likely to play a role in cancer-associated inflammation.

Conclusions

Both clinical data and experimental animal studies indicate that sustained humoral immune responses

initiate significant pro-tumor effects on developing neoplasms. We propose that bolstering anti-tumor cell-mediated immune responses, in combination with neutralizing potent pro-tumor humoral immune responses with efficacious immuno-therapeutics, would effectively direct tumor suppression while establishing an immune environment favoring therapeutic responses to conventional anti-tumor modalities. Certainly, further studies are needed to determine the universality of this approach and specifically which types of human cancers would be amenable to such therapy. Nonetheless, a dedicated attempt to reveal the molecular and cellular mechanisms linking HI, inflammation and cancer will also provide important insights into viable therapeutic targets for anti-cancer therapy.

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