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Review article

Distinct T helper cell-mediated antitumor immunity: T helper 2 cells in focus

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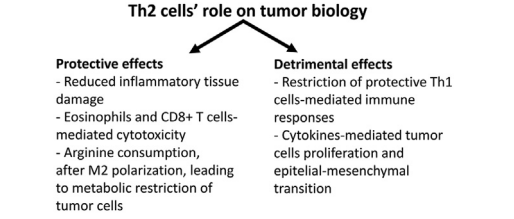
HIGHLIGHTS

- Different T helper cells subsets affect antitumor immunity against distinct tumors
- Th2 cells can promote antitumor immunity or tumorigenesis and metastasis
- Th2 cells effects depend on tumor metabolism
- Th2 cells can promote antitumor immunity in low tolerance organs
- Tumor cells' cytokine receptor expression differently affects Th2 cell-mediated immunity

GRAPHICAL ABSTRACT



Th2 cells-mediated immunity can be both detrimental or host protective, dependindg on the circumstances: Depending on tumor metabolism, site of tumor development and tumor cells cytokine's receptor expression, Th2 cells can have a dichotomic role on tumor biology, promoting or restraining antitumor immunity.

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ABSTRACT

The adaptive arm of the immune system is crucial for appropriate antitumor immune responses. It is generally accepted that clusters of differentiation 4^+ ($CD4^+$) T cells, which mediate T helper (Th) 1 immunity (type 1 immunity), are the primary Th cell subtype associated with tumor elimination. In this review, we discuss evidence showing that antitumor immunity and better prognosis can be associated with distinct Th cell subtypes in experimental mouse models and humans, with a focus on Th2 cells. The aim of this review is to provide an overview and understanding of the mechanisms associated with different tumor outcomes in the face of immune responses by focusing on the (1) site of tumor development, (2) tumor properties (i. e., tumor metabolism and cytokine receptor expression), and (3) type of immune response that the tumor initially escaped. Therefore, we discuss how low-tolerance organs, such as lungs and brains, might benefit from a less tissue-destructive immune response mediated by Th2 cells. In addition, Th2 cells antitumor effects can be independent of CD8+ T cells, which would circumvent some of the immune escape mechanisms that tumor cells possess, like low expression of major histocompatibility-I (MHC-I). Finally, this review aims to stimulate further studies on the role of Th2 cells in antitumor immunity and briefly discusses emerging treatment options.

Introduction

Innate immunity, which is evolutionarily conserved, is responsible for tumor detection and elimination as well as allogeneic tissue rejection in invertebrates through different mechanisms, such as phagocytosis and the release of antimicrobial peptides (AMPs).[1] In jawed vertebrates, adaptive immunity prepares the organisms to face and adapt to repetitive challenges. Recently, the concept of trained immunity has been used to explain the adaptive properties of innate immunity, defying the "adaptive immunity" nomenclature.[2] The presence of an adaptive immune

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system is crucial for mammalian organism homeostasis and protection against pathogens, cancer, and allogeneic tissue rejection.[3] Adaptive immunity is orchestrated by activated cluster of differentiation 4^+ ($CD4^+$) T helper (Th) lymphocytes. There are at least six major subsets of $CD4^+$ Th cells: Th1, Th2, Th9, Th17, regulatory T cells (Tregs), and follicular helper T cells (Tfh).[4–8] Each subtype emerges after antigen presentation by professional antigen-presenting cells (APCs), mainly activated dendritic cells (DCs), but also activated macrophages, basophils, and B cells.[9,13] Antigen presentation occurs when the T cell receptor (TCR) interacts with a complex formed by the antigen peptide and major histocompatibility complex I or II (MHC-I or MHC-II) and requires the presence of costimulatory molecules and cytokines released by APCs or nearby cells. Cytokines released during antigen presentation in the context of MHC-II coordinate naïve $CD4^+$ T cell polarization toward each effector Th subset, influencing the course of adaptive immune responses.[10] Th2 cell polarization occurs after antigen presentation in the presence of interleukin (IL)-4. The cellular source of IL-4 in this context is still under debate because DCs do not secrete IL-4, despite being critical for Th2 cell polarization. Thus, it seems that accessory IL4-producing-cells, such as basophils, natural killer T (NKT) cells, and type 2 innate lymphoid cells (ILC2s), are crucial for the expression of GATA binding protein 3 (GATA-3) in naïve $CD4^+$ T cells followed by Th2 cell differentiation and function.[11–13] APCs' cytokine expression is governed by activated transcription factors after pattern recognition receptors (PRRs) engagement by either pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs).[14] The number, type, and subcellular localization of distinct PRRs and the consequent activation of specific signaling pathways will depend on the type of pathogen or hazardous stimulus.[14] Thus, the pattern of cytokines correlates with the types of PRRs activated, leading to the onset of the appropriate adaptive immune response to each specific pathological condition. Therefore, certain types of effector Th cells are associated with a protective immune response, whereas others correlate with susceptibility to specific pathogens.[15] In general, Th1 cells confer protection against viruses and intracellular pathogens, Th17 fight fungal and extracellular bacterial pathogens, Th2 provide immunity to helminths, and Tfh is crucial to the humoral arm of the adaptive immunity by supporting antibody class-switch and somatic hypermutation. In contrast, Tregs are essential mediators of organism homeostasis, fine-tuning immune responses and hampering autoimmunity.[15] Many studies describe a protective role for Th1 cells against tumors,[16] and recent studies have also described other types of $CD4^+$ T cell subsets mediating antitumor immunity.

Here we do not intend to dissect the effector mechanisms of different Th subsets concerning cancer, as previously reviewed.[16–22] Instead, we aim to discuss the distinct aspects associated with the opposing outcomes of Th subsets in antitumor immunity. We hypothesize that different types of tumors will be eradicated by specific types of adaptive immune responses, including Th2 cells. Th1 cells are associated with the elimination of the majority of tumors, whereas Th2 cells can have protective action in the case of some cancer types, such as small-cell lung cancer and glioblastoma. The circumstances that lead to these distinct outcomes in tumor biology are: (1) the site of tumor development (especially, but not restricted to low-tolerance organs, such as the brain and lungs), (2) the tumor properties, i.e., tumor metabolism and expression of cytokine receptors, and (3) the type of immune response that the tumor initially escaped.

Adaptive immunity in cancer

The increased incidence of cancers in animals and humans with defective adaptive immune responses highlights the importance of antitumor adaptive immunity.[23] In addition, certain class I and class II MHC molecules can be considered risk factors for cancer development,[24–26] similar to their role in conferring susceptibility to infectious diseases,[27] and tumors that express low neoantigen levels are usually resistant to immunotherapy. Defective antigen presentation may occur when specific MHC alleles fail to present tumor- or pathogen-derived antigens owing to the reduced affinity between MHC and antigenic peptides.[28] Despite the fundamental role of adaptive immunity, it must be tightly regulated to exert its protective effects that lead to tumor elimination. The type and intensity of the adaptive immune response, as observed for many different processes in mammalian physiology, such as hypersensitivity,[29] will greatly affect the outcome and even the development of tumors. In this sense, different Th cells lead to protective or detrimental effects in tumor biology, depending on many factors, such as the specific types of tumors in question, as is extensively discussed in the literature.[16–22] Even Th1 cells, which are associated with increased antitumor immunity and a better prognosis in the majority of tumors, have already been reported to be correlated with poor prognosis in non-small cell lung cancer (NSCLC).[30] In contrast, Tregs, which are associated with poor prognosis and inhibition of antitumor immunity, can be related to better prognosis in colorectal, head and neck, esophageal, and ovarian cancers.[31,32] Further complicating matters, recent studies reported the presence of mixed phenotypes of Th cells (Th1/Th2) infiltrating tumors after immunotherapy,[33,34] and, for some cancers, an equilibrium between different infiltrating Th cells dictated the outcome.[35] Thus, the identification of the many variables that affect immune responses and tumor outcomes is of great value for improving therapies.

T cell-produced cytokines greatly affect the tumor microenvironment, and tumor cells can respond to these cytokines. For example, gamma-interferon (IFN-γ) can be associated with resistance to checkpoint inhibitor immunotherapy in a mechanism dependent on tumor expression of the receptor-interacting serine/threonine protein kinase 1 (RIPK1) and secretion of suppressive cytokines.[36] Likewise, IL-4 can increase cancer cell survival after the upregulation of anti-apoptotic genes.[37,38] In contrast, IFN-γ can promote MHC-I expression in tumor cells, leading to increased T cell activation and tumor elimination.[39] Thus, the expression of cytokine receptors by tumor cells is another factor that affects the type of protective adaptive immunity and is an additional variable to be considered.

Differences and similarities between effector mechanisms of the adaptive immunity against tumors and infectious diseases

Tumor cells possess specific properties and nutritional requirements depending on their genotype and tissue of origin.[40,41] In this regard, Yuneva et al.[28] elegantly demonstrated that the metabolism of glutamine and glucose varied in tumor cells generated by transgenic overexpression of different protooncogenes (*MYC* or *MET*), also depending on the site of tumor development (lung or kidney). As a central hub to both immune cell activity and tumor survival, metabolites affect the interplay between these cells. For example, L-arginine depletion by alternatively activated macrophages (also known as M2 macrophages) can lead to myeloma elimination.[42] However, L-arginine depletion also contributes to immune silencing in other conditions, for instance, in a melanoma model in which L-arginine supplementation promoted M1 macrophages and $CD8^+$T cell-mediated antitumor immunity[43] [Figure 1]. As such, tumorigenesis can be more complex than the pathogenesis of most infectious diseases, and the type of protective adaptive immune responses might differ depending on the tissue and immune context from which the tumors originated. In some situations, both Th2 and Th17 immune responses can lead to tumor elimination, and the dichotomy between Th1 and Th2 responses will not always reflect the outcome in tumor biology, different from immunity to some pathogens, such as mycobacterial and *Leishmania* sp. infections.[44]

Th1 cells secrete various cytokines, such as tumor necrosis factor (TNF), IL-2, and IFN-γ, which support the cytotoxicity of $CD8^+$ T cells and natural killer (NK) cells;[45,46] stimulate MHC-I expression by infected or transformed cells;[47] drive immunoglobulin (Ig)G class-switch by plasma cells (activated antibody-producing B cells);[48] and enhance the expression of antimicrobial and tissue-destructive mediators produced by

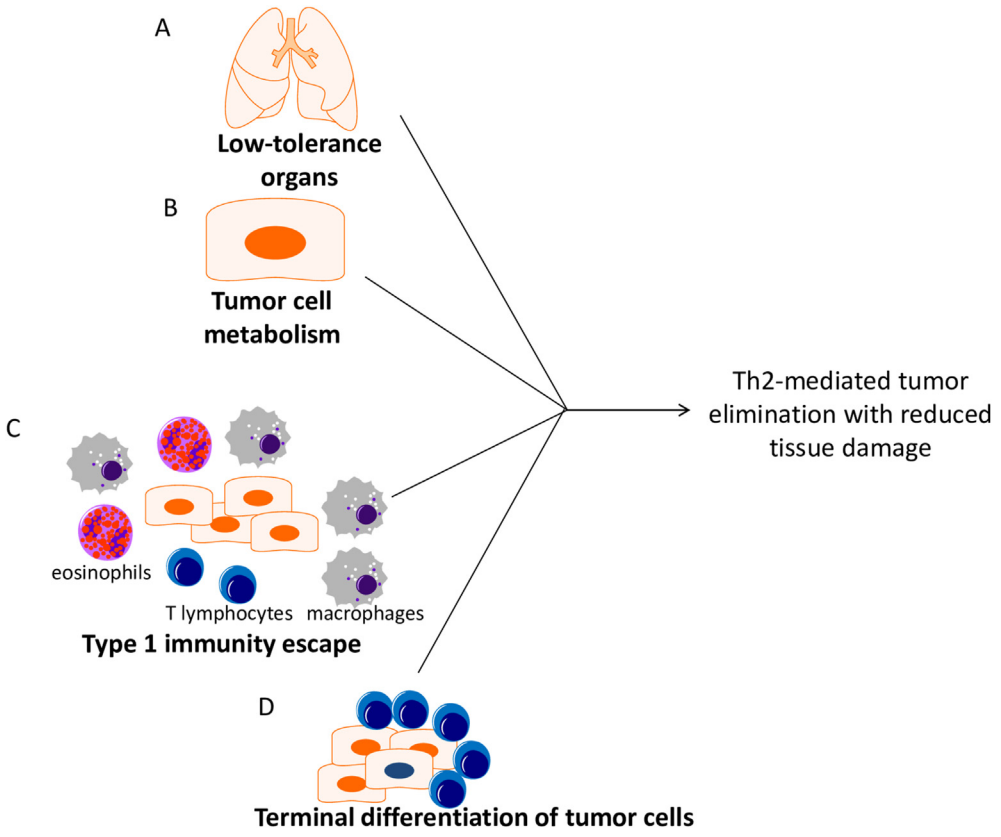

Figure 1. Major factors driving T helper 2 (Th2) cell-mediated antitumor immune responses. (A) Low-tolerance organs, such as the lungs and brain, are highly susceptible to secondary tissue damage induced by immune responses, especially Th1-mediated cytotoxicity. In this sense, it is hypothesized that some tissues are intrinsically prone to Th2-mediated responses to control excessive tissue damage,[146] a feature that can also be important to antitumor immunity in these sites. (B) Different metabolic requirements from tumor cells, even those that arose in the same site, can also explain a successful Th2-mediated immune response. For example, arginine depletion by M2 macrophages, differentiated in a Th2-dependent manner, led to tumor elimination in a mouse model of myeloma.[42] (C) Immune escape mechanisms from Th1-mediated antitumor immune responses, such as low expression of major histocompatibility complex class I (MHC-I) molecules by tumor cells, can be circumvented by a change in the subset of T lymphocytes to Th2 cells. In these settings, cluster of differentiation (CD)8$^+$ T cells can drive tumor elimination indirectly, after eosinophil infiltration.[126] (D) At last, Th2 cells inhibit tumorigenesis and restrict tumor development after impairment of epithelial-mesenchymal transition and induction of terminal differentiation of breast cancer cells.[131].

innate immune cells, such as neutrophils, monocytes, and macrophages.[49–51] All these features are key drivers of intracellular pathogen and tumor elimination (generally stated as type 1 immunity) but not of some multicellular infections by helminths.[52] Different from most pathogens, tumors usually develop after a long period in which immune responses destroy some tumor cells, while the resistant ones proliferate after immune evasion.[53] Several factors can contribute to immune evasion, including Tregs and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment. These cells, in contact-dependent and -independent manners, through anti-inflammatory cytokine secretion, restrain adaptive immunity to tumor neoantigens and mediate a reduced expression of MHC-I by tumor cells.[54]

Th17 cells induce AMP secretion and neutrophil recruitment, which is a crucial effector mechanism leading to allogeneic tissue and cancer elimination.[55] However, the role of neutrophils in tumor immunity might depend on different factors, including the microenvironment,[56] and diverse outcomes are expected for Th17-mediated responses. Furthermore, due to their plasticity, Th17 cells can acquire and accumulate the characteristic phenotypes of Th1 cells or Tregs, making their role in antitumor immunity even more diversified, as reviewed elsewhere.[57]

Th9 cells have been recently characterized by Veldhoen and Dardalhon.[58] These cells secrete a unique set of cytokines, primarily IL-21, IL-10, and IL-9, after being activated in the presence of transforming growth factor beta (TGF-β) or IL-1β and IL-4.[59,60] Although some researchers report that Th9 cells might be a terminal differentiation state of Th2 cells,[61] the requirement of a different transcription factor for their differentiation, compared to Th2 cells (PU.1 for Th9 cells and GATA-3 for Th2), does not corroborate this.[62] The function of Th9 cells also has some degrees of redundancy with that of Th2 cells, and Th9 cells play a dual role in cancer biology, as do many other immune cells.[63] Th9 cells, through recruitment of mast cells, led to skin melanoma elimination in mice,[64] and were also associated with protective effects in a mouse model of lung melanomas, but through DC recruitment and consequent CD8$^+$ T cell activation.[65] On the other hand, Th9 cells can be associated with pro-tumor effects through mast cell and Treg recruitment in patients with B cell Hodgkin lymphoma, inhibiting antitumor immunity. Once more, the dual role of immune cells might lead to opposing outcomes, depending on the circumstances. Furthermore, Th9 cells-mediated increase in chemokine (C–C motif) ligand (CCL20) expression can be associated with epithelial-mesenchymal transformation in hepatocellular carcinoma, promoting tumor pathogenesis. Interestingly, IL-10, secreted by Tregs and Th9 cells, also plays a dual role in tumor biology, decreasing MHC-I expression by APCs[66] but also controlling the optimal activation of CD8$^+$ T cells.[67]

Th2 cells secrete several cytokines, such as IL-4, IL-5, IL-33, and IL-13, which support the activation of tissue-resident mast cells and differentiation of alternatively activated macrophages (M2 subset).[68,69] IL-5 is also involved in the development of eosinophils and basophils from myeloid hematopoietic progenitors.[70] Th2 cells are crucial to several adaptive immune responses (type 2 immunity), including those that govern allergies and helminth elimination. Th2 cells that are activated after excretory/secretory helminth antigen presentation by APCs[71] can promote helminth elimination through multiple mechanisms, including the release of proteases and inflammatory mediators by myeloid-derived cells. Proteases, such as chitinases, metalloproteinases, and chymases, as well as AMPs, promote helminth tissue damage and possibly also tumor damage.[72–74] Inflammatory mediators, such as histamine and IL-4, secreted by eosinophils, mast cells, and basophils, induce increased peristalsis[75–77] and promote the enhancement of physical barriers after stimulation of mucus secretion by modified epithelial cells in the mucosa,[52,57] a feature that has not been directly associated with tumor elimination yet. In addition, Th2 cells are known for their ability to control tissue damage under some circumstances through IL-4- and IL-13-mediated epithelial cell proliferation,[78] while promoting immunopathology in others, such as in allergies, influencing immunoglobulin E (IgE) production by B cells and recruitment/activation of eosinophils and basophils.[79] The interplay between Th2 and CD8$^+$ T cells is complex. The role of CD8$^+$ T cells in helminth elimination has not been deeply

investigated. The majority of the studies aim to understand how helminth-induced type 2 immunity regulates $CD8^+$ T cell development and activity against other pathogens, such as viruses.[80,81] In the context of allergen-driven type 2 immunity, $CD8^+$ T cells can prevent or contribute to the allergic immune response depending on the model.[82,83] The mechanisms involved in $CD8^+$ T cell-mediated prevention of allergic responses are not fully determined, but IFNγ secretion by $CD8^+$ T cells can influence the polarization of $CD4^+$ T cells to Th1 as opposed to Th2 cells.[82] Furthermore, $CD8^+$ T cells are involved in the elimination of APCs that present antigens in the context of MHC-I, a feature associated with restricted immune responses.[82,84] The role of dependent and independent effects of $CD8^+$ T cells on the antitumor activity of Th2 cells will be discussed later.

Human studies indicate a protective role for T helper 2 cells against certain tumors

Atopic individuals, who possess excessive Th2 responses, seem to be less likely to develop certain types of solid tumors while being more susceptible to others.[85–89] Numerous diseases are associated with atopy, and the affected organs will influence the incidence of tumors in these sites. For example, people with asthma have an increased risk of developing lung cancer,[90] while people with atopic dermatitis possess a decreased risk for lung cancer but an increased risk for keratinocyte carcinoma.[85] Importantly, the increased incidence of tumors in the affected sites of type I hypersensitivity in atopic individuals is probably due to the effect of chronic inflammation in tumorigenesis,[91] and not associated with the type of adaptive immune response *per se*. Atopy is a multifactorial disease in which immune and non-immune gene polymorphisms can be associated with the disease risk. Interestingly, further analysis of some of these polymorphisms may help to understand the impact on the incidence of cancers. In this sense, polymorphisms in genes that code for crucial proteins and/or cytokines for Th2 cells polarization, such as the cytokine IL-4, are important candidates for observational studies. According to these polymorphisms, tracking for cancer susceptibility might indicate that Th2 responses can correlate with resistance to some cancers. Indeed, individuals with the single nucleotide polymorphism (SNP) rs2243250 TT in the *IL-4* gene, which is associated with atopy,[92,93] had a lower risk of developing different cancers, like prostate, breast and oral carcinomas, while possessing no correlation or an increased risk for others, such as hepatocellular carcinoma and leukemia.[94,95] Interestingly, for infectious diseases in which Th2 cells have been associated with susceptibility, like tuberculosis and leprosy, SNP rs2243250 TT correlates with increased risk of infection/severity,[96,97] as expected. Thus, though this correlation can be a sophism, especially in multifactorial diseases like cancer and atopy, it is tempting to hypothesize that Th2 responses can drive tumor elimination in humans, as demonstrated in different mouse studies, which will be discussed next.[42,98] In contrast, in some tumors, for example, in gastric cancer, blood circulating IL-4-producing $CD4^+$ T cells (Th2 cells) were associated with poor prognosis.[99] Importantly, another possible explanation for the reduced incidence of some cancers in atopic individuals is avoidance behavior, which is crucial to preventing episodes of hypersensitivity and certainly reduces the exposure of atopic individuals to allergens and irritants, some of which are considered mutagens.[100]

Other studies also evaluated the role of Th2 cells in different cancers through the use of different Th2 cell markers and transcriptomic analysis. For example, GATA-3 (the major transcription factor driving Th2 cell differentiation) and cellular muscular aponeurotic fibrosarcoma (c-Maf) (another transcription factor crucial for Th2 cell development) expression in breast cancer and classical Hodgkin lymphoma, respectively, have been associated with good prognosis.[101,102] Nonetheless, Th2 cell tumor infiltration can also be associated with poor outcomes, as discussed next.

Although transcriptomic studies in humans provide very important insights and conclusions for different diseases, some confounding features must be considered. For example, ILC2s express several cytokines (IL-4, IL-13, and IL-33) and transcription factors (GATA-3) in common with Th2 cells.[103] In addition, Th9 cells can also express GATA-3, though at decreased concentrations compared to Th2 cells.[104] ILCs are derived from lymphocyte progenitors and do not express clonally selected receptors, in contrast to B and T cells. These cells are activated by stress signals and cytokines and support specific immune responses after secreting distinct cytokines according to their subtype, similar to $CD4^+$ T cells. As rapid responders to stress signals, ILC2s can influence both tumor development and antitumor immunity in a dichotomic way similar to Th2 cells.[105,106] Thus, transcriptomic studies based only on GATA-3, IL-4, IL-13, and IL-33 expression by tumor-infiltrated cells cannot discriminate between ILC2s and Th2 cells. In this regard, CD3, a lineage marker, differentially expressed by Th2 cells in comparison to ILC2s, and PU.1 expression can be used to better discriminate between Th2 cells or ILC2s or Th9 cells, and their supposed influence on tumor outcomes.[104]

Human studies that indicate a detrimental role for T helper 2 cells in different cancers

Several studies reported a detrimental role associated with Th2 cell infiltration in different cancers. The presence of Th2 cells in tumors or in draining lymph nodes was associated with poor prognosis, recurrence, and metastasis.[107,108] Although the specific mechanisms that govern this detrimental role of Th2 cells were not systematically evaluated, it is possible that the cytokines secreted by Th2 cells contribute to the immune escape or proliferation of cancer cells.[109] Th2 cell infiltration evaluated by GATA-3 expression was associated with poor prognosis in patients with pancreatic cancer,[110] while IL-4 and IL-13 expression supported cutaneous T-cell lymphoma proliferation.[109] Using a global gene expression profile, which allows a more robust analysis, other studies also found a poorer prognosis associated with Th2 cell infiltration in neuroblastoma[111] and many other cancer types, such as lung adenocarcinoma, adrenocortical carcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, and oropharyngeal squamous cell carcinoma.[110,112–114] Interestingly, Zuo et al.[112] and others did not find a prognostic value associated with Th2 cells in many different cancers, like glioblastoma, NSCLC, melanoma, breast cancer, and colorectal cancers.[112,115,116] Compellingly, Le et al.[115] found that Th2 cell infiltration in breast cancer tissue positively correlated with advanced cancer stage but not with reduced infiltration of other immune cells, such as M1 macrophages and $CD8^+$ T cells, known for their antitumor properties. However, it is important to note that Th2 cells might exert a greater impact on the function of other infiltrating immune cells, but not on their infiltration ability *per se*. Therefore, Th2 cells effects on the differentiation of $CD8^+$ T cells, leading to cytotoxic T cell type 2 (Tc2) generation, can be detrimental to antitumor immune response. Tc2 cells possess reduced antitumor activity compared to Tc1 cells, differentiated under the influence of Th1 cells.[117] In contrast to the findings of Le et al.,[116] in lung tumors, a higher ratio of Th1/Th2 cells was associated with increased infiltration of $CD8^+$ T cells.[118] It is important to highlight that the majority of these studies specifically evaluated Th2 cell markers, which are different from the confounding factors associated with Th9 cells. Therefore, we believe that the above-mentioned studies appropriately differed regarding Th2 and Th9 cell infiltration. Finally, the specific properties of cancer cells might influence the type of protective immunity in a reciprocal way. In this sense, stratification of tumor cells based on their metabolism and cytokine receptor expression profile can provide a clearer prognostic value related to Th cell infiltration rather than simply classifying the tumors based on their cell type and site of development. All these findings confirm that the role of Th2 cells in antitumor immunity depends on the type of tumors, as will be later discussed,[119] while for some, like pancreatic cancers, Th2 cell infiltration clearly predicts a worse prognosis [Table 1].

Table 1
Prognostic value of Th2 cell infiltration in tumors from human studies.

Tumor	Methodology	Prognostic value of Th2 cells infiltration
Breast cancer[101]	GATA binding protein 3 (GATA-3) expression	Good
Classical Hodgkin lymphoma[102]	c-Maf expression	Good
Gastric cancer[120]	Global gene expression profile/Multiple gene transcriptomic analysis	Good
Prostate cancer[107]	Global gene expression profile/Multiple gene transcriptomic analysis	Poor/recurrence
Gastric cancer[108]	Intracellular interleukin (IL)-4 expression	Poor/metastasis
Pancreatic cancer[110]	GATA-3$^+$ T cells	Poor
Cutaneous T-cell lymphoma[109]	IL-4 and IL-13 expression	Poor
Neuroblastoma[111]	Global gene expression profile/Multiple gene transcriptomic analysis	Poor
Lung adenocarcinoma; adrenocortical carcinoma; kidney chromophobe; kidney renal papillary cell carcinoma; pancreatic adenocarcinoma[112]	Global gene expression profile/Multiple gene transcriptomic analysis	Poor
Pancreatic adenocarcinoma[114]	T helper 2 (Th2) cell markers gene expression: *C–C chemokine receptor type 3* (CCR3), CCR4, CCR8, C-X-C chemokine receptor type 4 (CXCR4), ST2/IL-1 R4, Signal transducers and activators of transcription 5 (STAT5), STAT6, and GATA-3, IL-4, IL-5, IL-9, IL-13	Poor
Oropharyngeal squamous cell cancer[113]	Global gene expression profile/Multiple gene transcriptomic analysis	Poor
Glioblastoma, non-small-cell lung cancer, melanoma, and breast cancer[112,115]	Global gene expression profile/Multiple gene transcriptomic analysis	None
Colorectal cancer[116]	IL-4, IL-5, and IL-13 gene expression	None

c-Maf:Cellular muscular aponeurotic fibrosarcoma.

T helper 2 cells in mouse models of cancer

Pre-clinical animal studies are crucial for the development of new treatment modalities, providing mechanistic insights for the amelioration of different diseases. Similar to what is observed in human correlational studies, there is a great variance among the outcomes associated with Th2 cells in mouse models of cancer. IL-4 effects on antitumor CD8$^+$ T cells can also be variable, promoting, repressing, or not affecting their activity in a context-dependent way, adding more complexity to the role of Th2 responses in cancer.[42] IL-4 also impacts variably and paradoxically the CD8$^+$ T cell cytotoxicity. In a protective way, Th2 cells mediate antitumor immunity after the impairment of Treg homeostasis.[121] Ras homolog A (RhoA), a guanosine triphosphatase (GTPase) crucial for Th2 cell differentiation, heterozygosis was responsible for the Treg functional impairment and consequent antitumor effects of Th2 cells.[121] Although IL-4 secretion by tumor cells can promote tumor development[122] in distinct models, it can also lead to antitumor effects. These antitumor effects associated with IL-4 expression by tumor cells correlated with increased infiltration of eosinophils, macrophages, and CD8$^+$ T cells.[123–125] Furthermore, IL-4 affects the interaction between CD8$^+$ T cells and infiltrating eosinophils, leading to spontaneous adenocarcinoma elimination.[126] In agreement with this study, CD8$^+$ T cells were crucial for the antitumor effects of both Th1 and Th2 cells on two distinct tumor mouse models: ovalbumin (OVA)-expressing lymphoma cells[127] and brain tumors.[128] In addition, CD8$^+$ T cell recruitment by eosinophils also mediated an improved response to immunotherapy against melanoma cells injected in mice.[129] In contrast, neutrophils, but not eosinophils, mediated the antitumor effects of IL-4-expressing melanoma cells.[130] Thus, further studies are necessary to better understand the role of eosinophils, neutrophils, CD8$^+$ T cells, and Th2 cells in the antitumor activity of IL-4-expressing tumors, which seems to be context-dependent. Interestingly, other studies did not support an essential role of CD8$^+$ T cells in the antitumor effects of Th2 cells.[131] In a breast cancer mouse model, the protective effects of Th2 cells were associated with the conversion of tumors into low-grade fibrocystic structures in an antigen-dependent way but independent of CD8$^+$ T cells. This was mediated by Th2 secretion of IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) that provided the differentiation signaling in tumor cells expressing the appropriate receptors for these cytokines. Furthermore, Th2 cells blocked breast carcinogenesis, inhibiting epithelial-mesenchymal transition and cell proliferation, promoting epigenetic changes associated with normal mammary gland development. Thymic stromal lymphopoietin (TSLP), expressed by epithelial cells, and IL-4 were crucial components for the activation and polarization of Th2 cells and protective immunity in these settings.[131] All these studies highlight that Th2 cells can exert antitumor effects in well-controlled mouse models [Table 2].

Th2 cells and related cytokines have also been reported to exert protumor effects in distinct mouse models. Th2 cells and IL-4 promoted anti-apoptotic protein expression in different tumor cells (breast, prostate, and bladder tumor cell lines) that express the IL-4 receptor. Not surprisingly, these tumor cells were resistant to chemotherapy *in vivo*.[38] IL-4

Table 2
The effects of Th2 cells on different tumor mice models.

Tumor-derived cell lines used	T helper 2 (Th2) cells' role in tumor biology	Mechanistic effects of Th2 cells
Colon adenocarcinoma[121]	Protective	Interleukin (IL)-4 expression
Plasmacytoma, melanoma, adenocarcinoma, renal cancer, lymphoma, fibrosarcoma, and mammary carcinoma[123–126,128,129]	Protective	Cytotoxicity through IL-4-mediated recruitment of eosinophils, macrophages, and cluster of differentiation (CD)8$^+$ T cells
Melanoma[130]	Protective	Neutrophils recruitment
Breast cancer[131]	Protective	IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM–CFS)–mediated inhibition of carcinogenesis
Breast, prostate, and bladder tumor cell cancers[38]	Detrimental	Anti-apoptotic proteins expression in an IL-4 receptor-dependent way
Colorectal tumor cells[132]	Detrimental	IL-4-dependent epithelial-mesenchymal transition
Multiple myeloma[135]	Detrimental	Not determined
Chemically-induced mammary carcinomas[143]	Detrimental	IL-4 promoted M2 macrophages differentiation and metastasis
Mammary tumors[144]	Detrimental	Macrophages-dependent tumor regrowth after radiotherapy
Melanoma[145]	Detrimental	IL-4 dependent metastasis

also promoted epithelial-mesenchymal transition in colorectal cancer cells, leading to a more aggressive disease *in vivo*.[132] Interestingly, Th2 cell polarization can be induced by specific tumor antigens, such as epithelial cell adhesion molecule (EpCAM). The induction of Th2 cells by EpCAM led to IL-4 secretion and tumor growth after colorectal cancer cell injection in mice.[133] In addition, signal transducers and activators of transcription 6 (STAT6) and GATA-3 expression by tumor cells were important for tumor establishment in mice, highlighting that tumor cells can play an active role in shaping the tumor microenvironment, secreting Th2 cell-related cytokines (IL-4 and IL-13) and expressing their own pro-metastatic and anti-apoptotic proteins.[132,134] Tumor cells, in particular multiple myeloma cells, can also actively induce Th2 cell differentiation through microbial antigen presentation, which seems to be an important mechanism for tumor development.[135] All these studies highlight that Th2 cells and their cytokines promote tumor pathogenesis through multiple mechanisms, including impairment of Th1 cell differentiation and antitumor activity, promotion of anti-apoptotic protein expression by tumor cells, and tumor metastatic phenotype development [Table 2].

The role of myeloid cells in T helper 1 and T helper 2 antitumor immunity

During hematopoiesis, myeloid progenitors will lead to several distinct types of immune cells: macrophages, monocytes, neutrophils, eosinophils, and basophils.[136] Macrophages are resident phagocytic myeloid cells that acquire specific characteristics according to the tissues where they reside in. Upon cytokine stimulation, macrophages can differentiate into a diverse spectrum of subtypes with two functional opposite subsets: classically activated pro-inflammatory macrophages (M1 subset) and anti-inflammatory alternatively activated macrophages (M2 subset). M1 macrophages, activated by IFNγ-secretory Th1 cells, can be associated with antitumor immunity through distinct mechanisms. They can induce cytotoxicity after (1) the production of reactive oxygen and nitrogen species (ROS and RNS, respectively) and (2) enhanced phagocytosis of infected/transformed cells. Furthermore, M1 macrophages secrete several pro-inflammatory cytokines, such as TNF-α and IL-12, that support antigen presentation by APCs (including activated macrophages themselves), leading to Th1 cell polarization, infiltration of inflammatory monocytes and neutrophils and induction of tumor cell death.[137] The role of macrophages in tumor biology can be diverse, similar to other immune cells, as discussed earlier. M2 macrophages, activated by Th2 cells, can lead to myeloma and B cell lymphoma elimination through depletion of L-arginine, due to arginase expression, in $CD8^+$ T cell-, NKT- and B cell-independent ways.[42] The authors believe that these effects were associated with the tumor cells' impaired protein metabolism in the absence of L-arginine, implying tumor metabolism in the center of the M2-mediated antitumor immunity. Furthermore, eosinophils, recruited by Th2 cells, also mediated tumor elimination in a mouse melanoma B16-OVA model of tumor-lung dissemination.[98] In contrast, in other circumstances, M2 macrophages, through secretion of anti-inflammatory cytokines, such as IL-10, low antigen presentation ability, and lymphocyte proliferation impairment due to L-arginine depletion,[138] can lead to antitumor immune response suppression, tumorigenesis, and even metastasis.[139,140] The role of other myeloid cells in antitumor immunity has also been evaluated. Surprisingly, eosinophils, usually associated with type 2 immunity, led to M1 macrophage recruitment after cryo-thermal treatment and antitumor immune responses against melanoma.[141] Consistent with this, the presence of Th1 cells and M1 macrophages in lymph nodes and the spleen was correlated with the regression of melanoma and lung adenocarcinoma cells after injection in mice. In contrast, infiltration of Th2 cells was associated with tumor relapse after immunotherapy with checkpoint inhibitors.[142] Moreover, a shift in Th cell infiltration, from Th2 to Th1, was associated with the regression of both melanoma and ovarian cancer cells.[142] Th2 cells, through secretion of IL-4, also promoted M2 macrophage differentiation and metastasis of chemically-induced mammary carcinomas. Secretion of epidermal growth factor (EGF) by M2 macrophages promoted pulmonary metastasis in this model.[143] Furthermore, Th2 cells, IL-4, and IL-13 were associated with mammary tumor regrowth after radiotherapy, a feature that also depended on macrophage (probably M2 macrophages) infiltration in tumor sites.[144] Thus, the circumstances, metabolism of the tumor cells, and tumor microenvironment will affect the protective or detrimental role of M2 macrophages, eosinophils, and Th2 cells in tumor mouse models. Metabolism is in the center of this dichotomy, as arginine depletion by M2 macrophages can, on the one hand, restrict tumor protein metabolism, while, on the other hand, impair infiltrating Th1 cell function and proliferation and, thereby, impair antitumor immunity.[30,83]

The intrinsic resistance to tissue damage and renewal ability of the organs in which the tumor developed

The site of tumor development might also be crucial to the type of protective or detrimental adaptive immune response. For example, tissues with low tolerance to damage, such as the lungs and brain,[146] might not benefit from a strong Th1-mediated adaptive immune response[147] and the consequent secondary tissue damage that happens as a collateral effect. In this case, Th2 responses might be more appropriate,[147] leading to M2 macrophage polarization and a less inflammatory and tissue-destructive microenvironment. Accordingly, as already discussed, different studies showed that atopic individuals possess a lower risk of developing lung and brain tumors, two low-tolerance tissues.[88] Furthermore, eosinophil infiltration correlates with a better prognosis in glioblastoma, the most common primary brain cancer, and in some cases, of NSCLC.[148] The variance of outcomes associated with eosinophil (and related Th2 responses) infiltration in brain and lung cancers might also depend on intrinsic tumor cell metabolism and cytokine receptor expression, as discussed earlier. In this sense, amphiregulin and TGF-α secretion by eosinophils can activate the EGF receptor, which promotes tumorigenesis in different tumor models, including glioblastoma.[148] In addition, the dual role of inflammatory mediators secreted by eosinophils in tumorigenesis, tissue damage, and antitumor immunity might impact the outcome. Thus, different tumors in these sites can be associated with opposing outcomes in relation to Th2-related immune responses. For example, individuals with squamous cell lung cancers that present eosinophil infiltration usually are at higher risk of death.[149] Besides their cytotoxic effects, under some circumstances, eosinophils can promote tissue protection and probably protect tumor tissue as well.[150] In addition, chronic inflammation during tumorigenesis in organs that are prone to type 2 immunity might lead to immune evasion of the Th2 cell antitumor immune responses. Interestingly, it seems that the low prevalence of molecular markers of $CD4^+$ Th responses (both Th1 and Th2) was associated with a better prognosis in glioblastoma compared to any of the Th responses with a high prevalence of Th cell markers.[151] Thus, we speculate that controlled activation of adaptive immunity effector responses might be the ideal scenario for tumors that develop in low-tolerance tissues. Nevertheless, this does not mean that immune silencing is associated with a better prognosis in the brain because Treg levels are considered a bad prognostic predictor.[152] In contrast, tissues, such as the intestines and skin, which possess a high tolerance to damage and increased renewal ability, benefit from Th1-mediated immunity in comparison to Th2 immune responses to drive tumor elimination[153] [Figure 1]. Thus, mouse models based on subcutaneous injection of tumor cells might not reflect the interplay between Th cells and tumors in their organs/tissues of origin.

T helper 2 responses as an alternative to tumor escape mechanisms

The well-known and diverse cytotoxic mechanisms associated with Th1 responses are important players in antitumor immunity.[154] Despite this, several viruses, which can be associated with tumor development, possess immune-escape mechanisms, such as anti-inflammatory

virokines and silencing of the antigen presentation machinery of the host cells.[155,156] During the progression phase of cancer (after immune evasion), similar mechanisms can lead to resistance against immunotherapies, especially those that depend on $CD8^+$ T cells and MHC-I expression by tumor cells.[157] In this sense, Th2-mediated antitumor immune responses can be an interesting alternative to drive tumor rejection because the majority of the effects associated with Th2-protective immunity did not involve $CD8^+$ T cell cytotoxicity, which depends on MHC-I expression, at least for some cancers [Figure 1].[98] Therefore, Th2 responses associated with multicellular helminth resistance can be helpful against certain solid tumors in a situation that parallels a "multicellular pathogenic organism" and thus, would be the ideal adaptive immune response in these cases.

Discussion

The majority of immunotherapies currently available focus on reactivating T cells through the use of immune checkpoint inhibitors, and although some exciting outcomes were obtained, the therapy's success remains unsatisfactory.[158] This means that improvements are necessary and are currently the focus of several research groups. In this regard, combined therapies aiming to act both in T cells and innate immune cells in the tumor microenvironment have been shown to enhance the beneficial effects of checkpoint inhibitors.[159] As discussed above, exploiting eosinophils' antitumor effects after being recruited to sites enriched in Th2 cells can be an interesting strategy to improve immunotherapy. In this regard, Th2 cell or eosinophil adoptive cell transfer, after *in vitro* differentiation and activation, is an emerging treatment modality in combination or not with other treatments, such as cryo-thermal therapy.[160] Furthermore, we believe that focusing on the infusion of activated T cells from subtypes other than Th1 cells can be a promising strategy to be pursued, to circumvent the escape mechanisms of some already developed tumors, at least in some tumor types. Complementarily, understanding the mechanisms associated with the pro-tumor effects of Th2 cells might enable the conversion of these cells into antitumor ones, especially in tumors in which Th2 cell infiltration correlates with worse outcomes. Thus, target inhibition of the molecules associated with these detrimental Th2 effects, for example, inhibition of the IL-4 receptor in tumor cells and TGF-β receptor in Th2 cells are interesting strategies for breast, prostate, and bladder cancer immunotherapies.[37,38,161] Another compelling strategy to pursue is the reactivation of infiltrated T cells in tumors, as the tumor microenvironment might be the major player in immune escape. In this sense, low availability of nutrients, such as glucose and lipids, due to cancer cell consumption, can restrain Th2 cell functions and, consequently, the antitumor effects.[162] Nutrient replenishment using nanoparticle injection might recapitulate the Th2 cell effector functions. Furthermore, as discussed throughout this text, Th2 cells and IL-4 secretion can lead to resistance of tumor cells to both radiotherapy[144] and chemotherapy.[38] As such, combining radio and chemotherapies with IL-4 receptor inhibition or tumor-infiltrated Th2 cell depletion might be a compelling strategy to improve cancer treatment.

Immunotherapy might also benefit from other strategies. Specific autoimmunity associated with programmed death 1 (PD-1) or cytotoxic T lymphocyte antigen 4 (CTLA-4) deficiency might give essential clues to the most appropriate therapy for specific tissue-derived tumors. Immune checkpoint therapies using anti-PD-1- or anti-CTLA-4-blocking antibodies can be selected according to the organs in which each of these molecules plays a more relevant role. For example, CTLA-4 deficiency in humans can be associated with pathologies in several organs, such as the lungs, gastrointestinal tract, brain, bone marrow, kidney, and retroperitoneal tissue.[163]

As already cited, the ability to mount a specific immune response against neoantigens is probably the most important part of the antitumor immune response. Thus, trogocytosis of foreign MHC–II–peptides from tumor antigens might overcome the inability of the host MHCs to be loaded with specific peptides from the tumors and is a new immunotherapeutic strategy to complement T cell (re)activation. Interestingly, the high mutation burden of tumor cells correlates with immunotherapy success, probably due to the increased presence of neoantigens.[164] In contrast, a low mutation burden might be a more suitable target for new chemotherapy drugs, such as kinase inhibitors, due to a more restricted amount of oncoproteins to be targeted.[165] Therefore, individualized therapies can be crucial to circumvent tumor mechanisms to escape immune responses.

Conclusion

Specific Th subtypes can fight tumors in tumor-type- and tissue-site-depending ways. The cytotoxic role of Th2 immune responses, mediated by M2 macrophages and eosinophils, is an aspect that is underexplored in the literature. If, on the one hand, the antitumor immune responses overlap many different mechanisms and effectors to anti-viral immunity, on the other hand, the multicellularity and diversity of metabolic requirements within solid tumors might resemble those of multicellular pathogens, such as helminths. In this case, Th2 responses might be the ideal subtype to drive tumor elimination, especially after $CD8^+$ T cell cytotoxicity failure owing to the absence of MHC-I-loaded tumor peptide. Thus, we propose that the individualized immunotherapy against tumors should focus on six main features: (1) neoantigen presentation after trogocytosis or "cross-dressing" of MHC-tumor-peptides from the microvesicles of non-self DCs (with an MHC that binds to neoantigens)[166]; (2) the site of tumor development to understand the importance of possible collateral inflammatory damage associated with the immunotherapy; (3) the metabolic signature of the tumor cell, to understand the role of different Th-mediated immune responses; (4) the cytokine types within the tumor microenvironment and the cytokine receptor expression by tumor cells that can promote resistance or cell death, depending on the context[37,38,167]; (5) different molecular targets for immunotherapies will have major effects in distinct organs, for example, PD-1 deficiency or blockade can be associated with auto-immune pneumonitis and, therefore, can be especially active (in a good or bad way) against lung cancers; and (6) reactivation of infiltrated T cells, especially Th2 cells that are associated with poor prognosis in some cancers. All these features add more complexity to the interplay between tumors and immune responses, and we are beginning to understand how important these many factors can be and how to manipulate them to improve immunotherapies against tumors. In this sense, vaccine adjuvants can be associated with Th1 or Th2 immune responses in mice,[168–170] and it might be interesting to test different adjuvants in cancer vaccine studies, comparing the outcomes associated with distinct tumor models related to distinct vaccine-activated Th cell mechanisms of tumor rejection.

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Author contributions

Rafael Cardoso Maciel Costa Silva: Writing - original draft preparation; Marcela Freitas Lopes and Leonardo Holanda Travassos: Writing -reviewing and editing, text and topic addition (discussion and conclusion).

Ethics statement

Not applicable.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflicts of interest

None.

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