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EDITORIAL

ALLERGOONCOLOGY: AN EXPANDING RESEARCH AREA

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The relationship between allergic diseases and cancer is a very controversial topic, widely discussed in the last decades. Many studies have demonstrated inverse association between allergy and cancer, but others have reached neutral conclusions or have indicated a positive role of allergy in the development of cancer. However, either inhibiting or favoring, many cells and molecules relevant in the allergic process play a role in tumorigenesis. On the one hand, activated immune cells, like classically activated macrophages "M1", activated dendritic cells, IL-33 and amphiregulin stimulated Innate Lymphoid Cells (ILC2), Th1, IFN-γ producing T CD8+ and B lymphocytes have inhibitory effects on tumorigenesis and tumor progression. On the other hand, tolerogenic immune cells, like alternatively activated macrophages "M2" (M2a, M2b and M2c), tolerogenic dendritic cells, ILC3, T regulatory and B regulatory lymphocytes, while inhibiting allergic sensitization and response, appear to favour carcinogenesis. Furthermore, M2 subtypes macrophages (M2a, M2b), IL-25 stimulated ILC2 and Th2 lymphocytes have a role both in inducing allergic reactions and in favouring cancer progression. In addition, mast cells, pivotal cells in allergy, have a different effect of tumorigenesis based on their location - they can promote cancer progression or inhibit it. Finally, eosinophils have shown a prevalent tumoricidal function mediated by α-defensins, TNF-α, granzymes A and IL-18. Better understanding the role of various cells on carcinogenesis can help in developing new strategies (diagnostic, therapeutic and of follow up) against tumor.

The relationship between allergic diseases and cancer is a very controversial topic, widely discussed in the last decades. Allergy published two well-documented studies on this topic in 2005. The first, carried out at the Stockholm Karolinska Institute, analyzed the possible presence of neoplasia in various organs and the allergic condition of 70,000 patients, reaching a neutral conclusion that allergy does not protect or promote the onset of tumors. The second, performed at the University of Heidelberg in Germany, was a review based on 80 previous epidemiological studies. In total, the clinical condition of 52,000 patients was analyzed, reaching a conclusion that allergy has a certain protective activity (currently, with some discrepancies) for tumors of colorectal cancer, breast, pancreas, brain (glioma, but not for meningioma) and leukemia. On the contrary, allergy could be a risk factor for lung

Key words: allergy; cancer; eosinophils; macrophages; mast cells; lymphocytes; innate lymphoid cells; dendritic cells

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cancer. The authors concluded that "Further research should focus on a more carefully defined 'atopy' status and manifestation of different atopic diseases, to advance our understanding of the role that allergies might play in the risk of developing cancer" (1).

Other epidemiologic studies have explored the potential association between allergy history and cancer (first of all brain, lymphatic and hematopoietic cancers). However, the majority of studies has relied on self-reported allergic history, being typically limited, retrospective and associated with potential biases. Successive observations have reported an inverse association between allergy and colorectal carcinoma, but not with hematopoietic or prostate cancer. Other studies evaluated also biological indicators of allergy history and immune function. In particular, recent evidence suggests a role for IgE

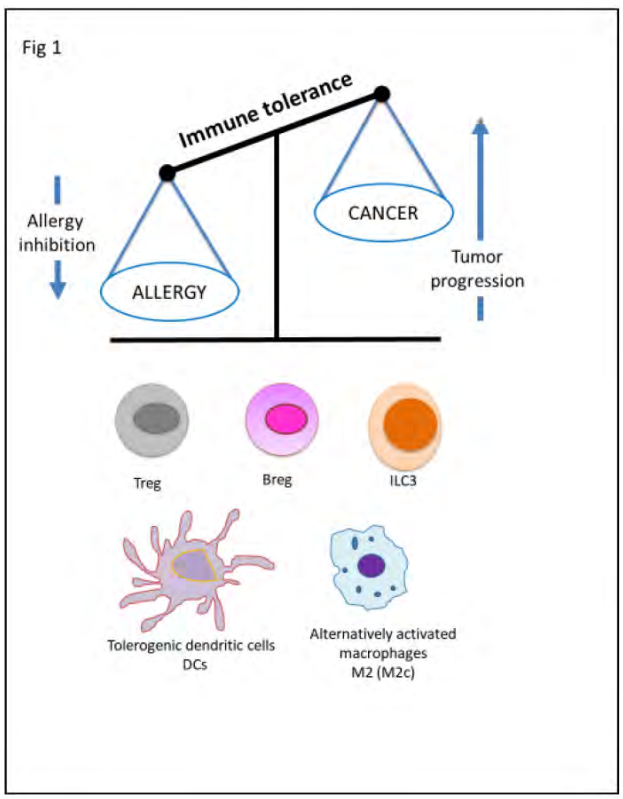

Fig. 1. *When the "immunebalance" hangs towards immune tolerance, the allergy response is inhibited and tumor progression is favored. Alternatively activated macrophages M2 (M2c), tolerogenic dendritic cells (DCs), Treg, Breg and ILC3s (Innate Lymphoid Cells type 3) appear to promote tumor progression, while inhibiting allergy sensitization and response.*

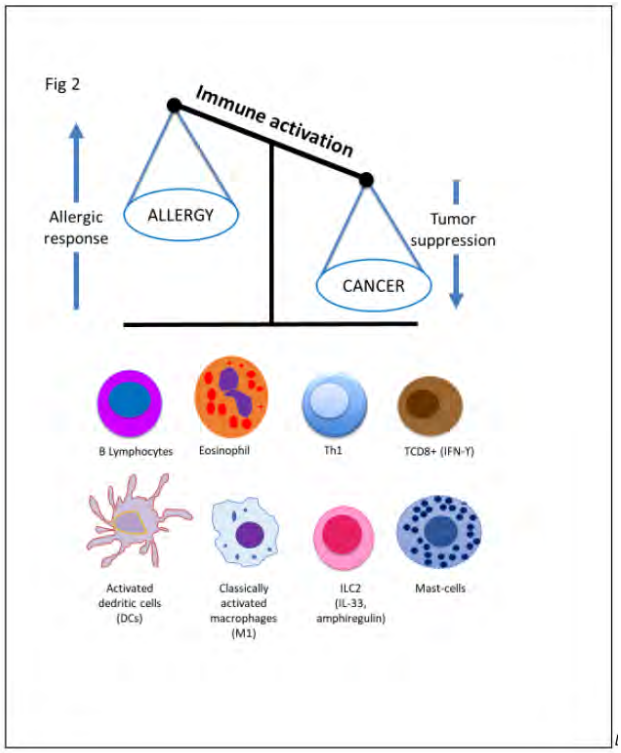

Fig. 2. *When the "immunebalance" hangs towards immune activation, the allergic response is favored and tumor progression is inhibited. Classically activated macrophages M1, activated dendritic cells (DCs), Il-33 and amphiregulin stimulated ILC2 (Innate Lymphoid Cells type2), eosinophils, mast-cells, Th2, Th1, TCD8+ (IFN-γ delivery) and B lymphocytes seem to have inhibitory effects on tumorigenesis and tumor progression. Activated dendritic cells, Th2 and eosinophils are also involved in the enhancement of allergic response.*

antibodies in natural tumor surveillance as well as in active and passive cancer immunotherapy (1). The level of total and specific IgE seems to have an inverse relationship with the development of neoplasia such as melanoma, glioma, gynecological tumors and female breast cancer (2). Further research in large-scale prospective studies using validated measures of self-reported allergy history and/or biomarkers of allergy is needed.

At present, no conclusive results have been achieved and the literature data are inconsistent and contradictory, suggesting the importance of immuno-epidemiology studies on cancer (1) that take into account other interfering factors, such as environment, lifestyle, age, sex, job, alcohol, smoking

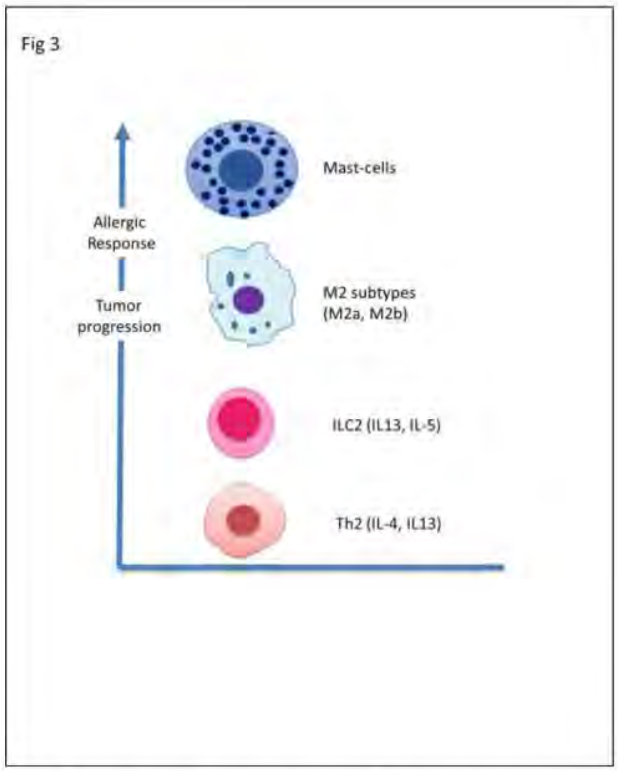

Fig. 3. *M2 subtypes (M2a, M2b), mast-cells, IL-25 stimulated ILC2 (Innate Lymphoid Cells type2) (IL-13, IL- 5,TSLP), Th2 (IL-4, IL-13) promote sensitization and allergic reactions and are associated with tumor progression.*

use, type and duration of allergic disease, other than the simple allergic status. The European Academy of Allergy and Clinical Immunology established a Task Force on AllergoOncology to evaluate the relationships between cancer and allergy with the goal of studying both allergic problems in clinical oncology and the immunomodulatory mechanisms eventually protecting cancer in order to develop new oncological immunotherapy (cellular vaccines expressing IgE-binding tumor antigens; recombinant antitumor IgE) (1).

Some speculative observations support the hypothesis of an inverse relationship between tumor growth and allergy. For example, the fact that in allergic patients the immunotolerance is desirable and is the goal of specific immunotherapy, while it is a negative mechanism in tumor microenvironment, inducing an evasion from the immune-surveillance with a promotion of tumor progression. Effectors of immunotolerance are regulatory cells and therapies blocking these cells, such as monoclonal antibodies (mAbs) against immune checkpoints, have a profound role in inhibiting tumor growth (e.g., mAbs anti-CTLA-4 and PD-1/PD-L1) (3).

Immune cells of relevance in allergy development include dendritic cells (DC), macrophages, innate lymphoid cells (ILC), lymphocytes, mast cells and eosinophils (Figs. 1, 2, 3); the comprehension of their activity on carcinogenesis and tumor restriction can explain the different results observed in epidemiological studies. Hereafter, the present knowledge on the matter is discussed (Table I).

Role of immune cells in allergy and cancer

Macrophages - Macrophages are involved in innate as well as in acquired immunity. They play an important role in the defense against pathogens through phagocytosis and the ability to generate reactive oxygen species (ROS), nitrogen intermediates and other cytotoxic factors. ROS and nitrogen intermediates are also responsible for the exacerbation of allergy and asthma severity (4). They are professional antigen-presenting cells (APC) involved in various mechanisms of allergic and autoimmune response, especially in delayed-type hypersensitivity.

Due to their microenvironmental condition, macrophages could be polarized into two phenotypes: classically activated or "M1", induced by IFN-γ and lipopolysaccharide (LPS), predominant in the first phase of inflammatory response, and alternatively activated or "M2", induced by IL-4 and IL-13, predominant in the delayed-response (wound healing, tissue repairing, carcinogenesis).

M1 were observed in exacerbation of lung injury and airway remodeling in allergic asthma via nitric oxide production. The presence of M1 macrophages in tumor microenvironment has been associated with extended survival of certain cancers (5) also through the production of several angiogenic and lymphangiogenic factors (6).

M2-polarized macrophages can be further divided into three subpopulations: M2a, M2b and M2c, according to specific stimulators (cytokines, chemokines). M2a are triggered by IL4 and IL-13

and positively correlate with the severity of airway inflammation in allergic asthma (7). In cancer, a low M1/M2a ratio was associated with poor prognosis in a variety of murine and human malignancies. M2b and M2c are involved in immune regulation, tissue remodeling, angiogenesis and tumor progression. M2b are induced by IgG immunoglobulin complex and lipopolysaccharide (LPS) and are reported in the context of allergy as well as cancer (8). M2c induced by glucocorticoids, TGF-β and IL-10 and support induction of Tregs, correlate with tumor progression and poor prognosis (1, 9).

Tumor-associated macrophages (TAMs) differentiate from circulating monocytes, recruited to tumor sites by pro-inflammatory chemokines (CCL2, CCL3, CCL5, VEGF, colony-stimulating factors GM-CSF and M-CSF). The prevalence of macrophage phenotype in tumor environment depends on the type, the stage and the place of the tumor. M1/M2 ratio determines the negative prognosis in glioma and breast cancer and the best prognosis in carcinoma of the stomach, colon, prostate and non-small cell lung (10).

The M2 phenotype predominates in hypoxic areas and seems to have unfavorable effects in tumor growth. New therapeutic strategies will be available in order to re-educate these macrophages promoting the positive effect of M1 phenotype (11).

Dendritic cells – DCs are "skilled" cells responsible for uptake, proteolytic processing and presentation of antigens to T cells. In an allergic condition, they activate naïve CD4+ T cells to differentiate into Type 2 helper T cell through the production of specific cytokines. Th2 cells and their cytokine production driven by IL-4 and IL-13 promote/facilitate the production of allergen-specific immunoglobulin E (IgE) antibodies from B cells**.** Therefore, IgE-mediated antigen presentation supports DC-based immunity rather than leading to DC-mediated tolerance. On the contrary, activated DCs are converted into tolerogenic phenotypes in the tumor microenvironment, where they promote Tregs (and not T-effector cells), with the production of TGFβ and IL-10 as an escape mechanism from immune clearance (5). Therefore, allergy and cancer have different dendritic cell phenotypes, prevailing the activated DC in atopic subjects, while the antigen presentation by tolerizing DCs is induced in cancer

Table I. *Different roles of immune cells in tumor environment*

CELLS	Tumor-promoting effect	Tumor-inhibiting effect
Macrophages	M2 phenotype (M2a, M2b, M2c)	M1 phenotype
Dendritic cells (DC)	DCs tolerogenic phenotype	DCs activated phenotype
Innate Lymphoid Cells	IL-25 stimulated (IL-13, IL-5) ILC2 ILC3	IL-33 and amphiregulin stimulated ILC2
Lymphocytes	Th2 (IL-4, IL-13, TSLP) Treg lymphocytes Breg lymphocytes	Th2 (Hodgkin's lymphoma, colon cancer cells) Th1 TCD8+ (IFN-Y) B lymphocytes
Mast cells	Mast cells	Mast cells
Eosinophils		Eosinophils

environment, preventing anti-tumor T cell responses. The possibility to drive the activation of effector DCs can be a key to stimulate anti-tumor immunity by the activation of cytotoxic CD8+ lymphocytes against tumor antigens (12).

Innate lymphoid cells– Innate lymphoid cells (ILCs) broadly reflect helper T-cell subsets. Based on their cytokine production, they are classified into 3 groups (13). ILC1s phenotypically like Th1, respond to IL-12, IL-15 and IL-18 and are defined by the production of IFN-γ. ILC2s, similar to Th2 cells, respond to epithelium-derived cytokines, such as IL-33, IL-25, TSLP, eicosanoids and IL1-β. The cells are defined by production of IL-4, IL-5, IL-9 and IL-13. Activated ILC2s participate in both initiation and enhancement of allergy, interacting with other immune cells, such as macrophages and DCs. In cancer, the stimulation of ILC2s activated by macrophages through IL-33 induces the secretion of IL-13 and IL-5, which favor tumor progression. On the other hand, amphiregulin-stimulated ILC2s can establish an immunosuppressive tumor microenvironment (13). ILC3s resemble Th17 and Th22 cells. They respond to IL-1β and IL-23 and are defined by the production of IL-17 A ed IL-22. Cells of the ILC3 subtype secrete IL-22 upon IL-23-stimulation by macrophages and have tumorigenic effects. Furthermore, ILC3 could induce tolerance by increasing IL-10 and retinoic acid secretion by DCs upon stimulation by microbiota and macrophages or by enabling T-cell tolerance through the expression of MHC Class II in the absence of costimulatory molecules. Among the ILC type, ILC3s seem to favor tumor growth and tolerance.

T and B Lymphocytes - Th2 cells play an important role in the induction and maintenance of the allergic inflammatory modulation by the production of IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. They induce differentiation, activation and in situ survival of eosinophils (through IL-5), stimulate B-lymphocytes to produce IgE (through IL-4 or IL-13), and favor mast cell and basophil growth (through IL-4, IL-9, and IL-10). Their role in cancer is controversial. It has been observed that the shift in immune response from Th1 to Th2 is characteristic of patients with more aggressive tumors (14). In some cancers, including breast, gastric and pancreas, Th2 cells and associated cytokines (IL-4 and IL-13 and TSLP) contribute to tumor progression (1). Thus, IL-4 and IL-13 receptors are promising anticancer targets. However, in some types of cancer, the Th2 have a protective role (Hodgkin's lymphoma, and colon cancer cells). Th1 and T CD8+ lymphocytes play a central role in the suppression of cancer cells both directly and through the production of IFN-γ, which mediates the activation of macrophages, as well as the presentation and processing of antigens (15).

B lymphocytes, stimulated by Th2 cytokines, produce IgE which are essential in the development of allergy. On the contrary, B regulatory cells, parallel to Treg cells, inhibit allergic sensitization.

B cells are present in many solid tumors (melanoma, colorectal, non-small cell lung) and are associated with an improved prognosis. In particular, B cells associated with T CD8+ cells suggest a cooperation between T and B lymphocytes in inducing an effective immune reaction (5). Breg cells, parallel to Treg cells, favor tumor progression, by promoting immune tolerance.

Mast cells – Mast cells are the main effector cells of allergy. They produce a large number of cytokines, chemokines, growth factors (IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, TNF-α, MCP-1, VEGF, NGF) and eicosanoids (prostaglandin D_2 and cysteinyl leukotrienes). These cells also release preformed mediators, such as histamine, heparin and neutral proteases (chymase and tryptase) when activated by both FcεRI-dependent and FcεRI-independent stimuli. Mast cells can also be activated by other stimuli (CD30 ligand, IL1, TLR-2), to release selected cytokines and chemokines without degranulation. They have a central role not only as effector cells of an IgE-dependent reaction, but through released proteins, participate in the initiation of the allergic immune response, providing signals inducing IgE synthesis by B-lymphocytes and Th2 lymphocyte differentiation. Beyond allergy, mast cells have critical proinflammatory activity, as well as potential immunoregulatory roles, in various immune and inflammatory disorders. They are also involved in host defense mechanisms against parasitic infestations, tissue repair and angiogenesis. Human mast cells produce VEGFs and have VEGF receptors

on their surface. They are both a source and a target of VEGF. Targeting mast cells and their angiogenic factors could be a strategy with which to block inflammatory and neoplastic angiogenesis (16).

In the context of the tumor microenvironment, multiple stimuli may serve to activate mast cells including anti-tumor antibodies, hypoxia, alarmins, cytokines and chemokines. Therefore, mast cells can have both profound tumor-promoting and tumor-inhibiting immunoregulatory effects. It seems that their role depends on microlocalization, stage of tumor and on mast cells density in intratumoral and/or peritumoral localization. In certain neoplasias (e.g, thyroid, gastric, bladder, pancreas, Hodgkin's and non-Hodgkin's lymphoma mast cells play a pro-tumorigenic role, in others (e.g., breast cancer) a protective role, whereas in yet others they are apparently innocent bystanders (17). In stage I non-small-cell lung cancer (NSCLC), but not in stage II, peritumoral but not intratumoral mast cell density was an independent favourable prognostic factor; mast cells were pro-tumorigenic in the initial stages of prostate cancer but not in the later ones; mast cells in perilesional stroma of melanoma play a protective role. In pancreatic ductal adenocarcinoma, mast cell density in the intratumoral border zone, but not the peritumoral or the intratumoral center zone, was associated with a worse prognosis. In prostate cancer, high intratumoral mast cell density was initially associated with good prognosis. Subsequently, it was reported that intratumoral mast cells inhibited tumor growth, whereas peritumoral mast cells stimulated human prostate cancer (17). These findings suggest that the microlocalization of mast cells should be investigated in different stages of clinical and experimental tumors.

Stem cell factor (SCF) seems to be one of the most important substances attracting mast cells into the tumor microenvironment where they secrete pro-angiogenic factors, which promote tumor vascularization and invasiveness. The list of tumor products attracting mast cells in TME includes angiopoietins and several chemokines (CXCL8, CXCL2, CXCL1, and CXCL10, PGE_2, TSLP, and osteopontin). Furthermore, SCF stimulates mast cells to produce matrix metalloprotease-9 (MMP-9) that facilitates the recruitment of other mast cells to the tumor and increases tumor-derived SCF production in an amplification feedback loop. Mast cells may also suppress the development of protective antitumor immune responses by promoting regulatory T cell (Treg) mediated suppression in the tumor microenvironment.

Last but not least, the protumorigenic activities of mast cells can be subverted by targeting cells to promote tumor destruction. In a murine allograft model, the activation of mast cell degranulation by IgE antibodies blocked Treg and allowed tumor destruction through a CD4 + CD8 + mediated response. Furthermore, mast cells cause tumor cell death, in an *in vitro* lymphoma model, when incubated with an anti-CD20 IgE antibody (18). These findings represent the potential to deviate the response of these cells against cancer through immunotherapies.

Eosinophils - Eosinophils are multifunctional cells with pleiotropic functions. They are not only implicated in protection against parasitic infections but play a major role in allergic reactions and chronic inflammatory diseases. Activated eosinophils release cytotoxic proteins (e.g., ECP, MBP, EPX, EDN), growth factors, cytokines, chemokines and lipid mediators contributing to inflammation. Eosinophils have also been reported to participate in the control of tumor growth and the formation of metastasis. Increasing evidence indicates that IL-33, released in the extracellular space, where it functions as an alarmin for the immune system, may have opposing functions, promoting, or dampening tumour immunity, depending on the tumor type, site of expression, and local concentration (19).

In most epidemiological and clinical studies, eosinophils demonstrate "tumoricidal" action mediated by α-defensins, TNF-α, granzymes A and IL-18 (19). Moreover, eosinophils might support antitumor immune responses indirectly (for example, by facilitating T cell migration into tumors). Tumor cells themselves can attract eosinophils by producing CCL1 and stimulating eosinophils to secrete IL-8 that facilitates eosinophil-cancer cell interaction leading to tumor cell death. In allergic patients, they show a greater cytotoxic action, and this suggests that the "allergy state" promotes anticancer processes. In

future, eosinophils can be activated by immunotherapy such as checkpoint inhibitors or GM-CSF-based vaccines, or by adoptive transfer of these cells in an appropriate setting.

In several neoplasias (e.g., melanoma, gastric, colorectal, oral and prostate cancer) eosinophils play an anti-tumorigenic role, in others (e.g., Hodgkin's lymphoma, cervical carcinoma) have been linked to poor prognosis, whereas in yet others they are apparently innocent bystanders. The role of eosinophils and their mediators appears to be cancer-dependent. The microlocalization (e.g., peritumoral *vs* intratumoral) of eosinophils could be another important aspect in the initiation/progression of solid and hematological tumors (20).

Recently, Holland et al. demonstrated that the increased expression of dipeptidyl peptidase 4 (also known as CD26) has been observed in mouse and human tumors and is associated with worse survival. On the contrary, the inhibition of CD26 can improve antitumor immune response by enhancing the effect of eosinophils through IL-33-dependent eosinophil-mediated control of tumor growth. IL-33, a tumor-derived alarmin, in solid tumor induces eosinophil migration and promotes CCL11–mediated eosinophil infiltration and degranulation, which in turn leads to tumor cell cytotoxicity and reduced tumor growth. In addition, it has been demonstrated that combined immunotherapy using checkpoint blockade in the presence of CD26i inhibits tumor growth (21).

In summary, it can be hypothesized that type 1 and type 2 immune responses are not entirely antagonistic pathways, and, in some instances, they may collaborate to control tumor growth.

CONCLUSION

There are unclear answers whether allergies in general can protect against cancer. Current evidence does not provide definitive results. Generally, the mechanisms of immunotolerance are known to be low in allergy and enhanced in cancer but recent evidence highlights more complex mechanisms. Much seems to depend on the type of cancer and the microenvironment, and every immune cell may have different actions based on this. However, there are no data associating cancer development in subjects treated by allergen immunotherapy, the efficacy of which is at least partially due to potentiated immune tolerance. Cells involved in allergy are associated with a variable cancer prognosis, depending on the phenotype, tolerogenic cells (such as M2 macrophages and tolerogenic DC) induce tumor growth and progression, whereas activated cells (such as M1 macrophages and effector DCs) have an unfavorable effect on tumor cell growth. Mast cells have been correlated with tumor progression, while mast cell degranulation, normally associated with IgE–immune complex formation, have been correlated with a more favorable prognosis. The stimulation of ILC2s activated by macrophages through IL-33 favor tumor progression while amphiregulin-stimulated ILC2s inhibit tumor progression. ILC3 have a preponderant role in promoting cancer. Eosinophils appear to have a prevalent tumoricidal effect.

Therapeutic strategies for anticancer treatment are directed to modify the tolerogenic environment protecting carcinogenesis into effector cells/proteins able to activate an effective antitumor immunity. A clinical trial evaluating an antitumor IgE antibody in patients with cancer is ongoing, based on the presupposition that IgE directed against tumor antigens engenders antibody-dependent cell-mediated cytotoxicity by human monocytes. IgE are cross-linked by densely packed tumor antigens forming tumor-associated molecular patterns on a cancer cell surface and therefore triggering effector cell activation at sites where antitumor immunity is needed. Although further research is needed, treatments based on the knowledge gained studying the relationships between allergy and oncology might provide strategies that complement existing and emerging immuno-oncology therapies.

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