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Review Article

Effect of Allergic Immune Response in the Modulation of Cancer Progression: Pivotal Role of the HIF1α/Th17

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Summary

There is an important interest in finding whether people with allergic disorders, such as hay fever, asthma, and eczema, haver an increased or decreased risk of developing cancer(1). Although an association between allergic disorders and cancer risk is supported by epidemiologic studies, the exact nature of the association remains controversial. A promising discipline is the emerging field of AllergoOncology, which focuses on Th2 and IgE-mediated immune responses in the cancer context, but this field has shown opposite results supported by two different theories and contradictory. In the correlation between allergy and cancer, exist different components, cellular and immunological, that could be involved on important way resulting in a pro-tumor or anti-tumor effect depending the cancer type and the immunological context. One molecule that may be involved is the hypoxia-inducible factor 1 (HIF-1), a key oxygen sensor that is implicate in the tumor growth and play an important role in the differentiation T cell, in part, by the cytokine environment in the tumor microenvironment (EMT), one of these effects is to regulate the balance between regulatory T cell (Tregs) and T cells 17 (Th17) differentiation. In addition, is describing that Th17 cells are implicate directly in the severity of allergic diseases like allergic asthma.

In the present review we going to highlight the evidence to suggest that the IL-17 overexpressed as well of the HIF1 high activation during allergic disease, induces the promotion of Th17 / IL17/Tregs balance and that results in a pro-tumor or anti-tumor response, depending of the cytokine environment.

Keywords: AllergoOncology; Allergic Asthma; HIF1; Th17/IL17.

INTRODUCTION

Immune Response in Asthma

The World Health Organization estimates that 300 million people worldwide suffer from asthma, this the most important allergic diseases by high prevalence, its chronic character, it ranks second place in frequency of after allergic rhinitis, and up to 80% of cases it is established or diagnosed as allergic asthma(2,3). The disease affects people of all ethnic groups, from infancy to old age(4,5). The prevalence of asthma, or more generally wheezing, differs remarkably between geographical regions and over time being more common in western developed countries (e.g. 4% in India and Algeria and 29% in Australia and Wales), it poses substantial burden to individuals and families and is often a lifetime concern (5,6).

Allergic asthma usually is induced by sensitization to environmental allergens, as house dust mites (HDM), grass, weed and tree pollens, fungal spores, animal dander, etc. After sensitization, symptoms of allergic asthma usually occur due to the subsequent exposures to the allergens(7) A recent study indicated that different types of aeroallergens and specific sensitization profiles are related to different clinical manifestations of allergic respiratory diseases (rhinitis with/without asthma), different clinical symptoms, and different levels of severity(8,9). Allergic asthma is characterized by variable airflow limitation secondary to airway narrowing, airway wall thickening and increased mucus(10). Airway narrowing results from chronic airway inflammation secondary to plasma extravasation and influx of the inflammatory cells such as eosinophils, neutrophils, lymphocytes, macrophages and mast cells. Airway hyperresponsiveness (AHR) is an important physiologic feature of asthma. Although asthma is often defined as a reversible airway obstruction, it can evolve into irreversible lung function impairment(11), increasing mucus production in the

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airway lumen is one of the possible causes of the persistent airflow obstruction. Another mechanism of persistent airflow obstruction is airway remodeling including pathologies such as goblet cell hyperplasia, excessive subepithelial collagen deposition, decreased epithelial and cartilage integrity, airway smooth muscle hyperplasia and increased vascularity(12).

Initiation of immune response often begins with the activation and differentiation of allergen specific Th2 cells and triggered by allergens. Later, immunoglobulin E (IgE) is produced against allergens, dependent mast cells are activate and eosinophils recruit into the lungs, and eventually persistent airway inflammation and asthma symptoms occur(13). Th2 cells mediate these functions by producing various cytokines such as IL-4, IL-5, and IL-13, they are considered as important molecules for management of allergic asthma. IL-4 is a cytokine that induces differentiation of naïve T cells to Th2 cells (14). IL-5 is responsible for the maturation and release of eosinophils in the bone marrow(15). IL- 13 induces proliferation of IgE-producing B cells and endothelial cells(16). Recent developments revealed that the induction of allergen reactive Th2 cells requires a two-step procedure including initial exposure or "sensitization" and reactivation with second exposure. T cell induction with an allergen is a complicated process that requires numerous interactions between several cell types in the lungs and lymph nodes(17). Another Th2 cytokine, IL-31 and IL-31R concentrations are also increased in the serum of allergic asthma patients together with stem cell factor(18), indeed, IL-33 is demonstrated to induce the expression of Th2 cytokine and activation of basophils and eosinophils(9). Chemokine receptors such as CCR4, CCR8, CXCR4 and CCR3 are expressed on Th2 cells. CCR4 regulates chemotaxis of Th2 cells and its ligands CCL17 and CCL22, are increased in the patients with allergic asthma. CCR8 can induce eosinophilia and AHR and may be elevate in Th2 cells in the lungs and airways of allergic asthmatics(13,19) CXCR4 which is participated in Th2 cell migration into the lungs and treatment of allergic mice with selective CXCR4 inhibitors, significantly reduces AHR and inflammatory responses(13).

Role of TH17 in Allergic Asthma

The Th1/Th2 imbalance is the main mechanism of allergic asthma, and cytokines such as IL-4, IL-5, IL-13 secreted by Th2 cells can promote the synthesis of IgE, the recruitment of eosinophil cells, and the secretion of mucus(20). However, this cannot fully explain the cause of asthma pathology, recently; numerous studies have shown that Th17 cells and their cytokines are largely associated with the development of asthma. Th17 cells are novel effector T cells unlike Th1 and Th2 cells, which secrete cytokines such as IL-17A/F, IL-21, IL-22, TNF-α(21), and participate in various immune diseases, including asthma(22-25).

The role of IL-17 has been shown to both positively as well as negatively regulate immune responses in experimental models of allergic airway disease its pro-inflammatory signaling has been widely studied in allergic asthmatic mouse models where blockade of its signaling has demonstrated a reduction in airway inflammation and airway hyperresponsiveness (AHR)(26). Besides, the presence or absence of Th2-mediated inflammation remarkably influences IL-17 response, are known to induce a predominantly neutrophilic airway inflammation and adoptively transferred antigen specific Th17 cells alone induce only neutrophil infiltration and not eosinophils into the airways(27). However, adoptive transfer of both antigen-specific Th17 cells and Th2 cells was found to promote antigen-induced Th2-mediated eosinophilic inflammation in addition to AHR(27). In another study, asthmatic mice deficient in IL-17R gene (IL-17R KO) demonstrated a decrease in airway eosinophil recruitment and eosinophil peroxidase activity due to impaired priming of Th2 cells leading to attenuated Th2 responses in the absence of IL-17R signaling(28). This weakening in Th2 response may be governed by the role of IL-17 in spontaneous germinal center (GC) development by promoting the interactions between CD4+ T cells and B cells that are essential in GC formation(29). On the other hand, in the absence of IL-4 and IL-13, an exaggerated IL-17A response was elicited systemically and locally in the lungs upon epicutaneuous sensitization resulting in inflammation and hyperresponsiveness of the airways(30) indicating asthmatics with elevated IL-17 levels present a distinct phenotype by itself with IL-17 exhibiting both Th2-dependent and Th2-independent functions.

IL-13 is known to positively regulate airway inflammation and airway hyperresponsiveness. IL-17A enhances IL-13-driven responses, including AHR, airway inflammation, mucus hypersecretion and IL-13-induced gene expression (31) IL-17 from γδ T cells were found to have a dose-dependent effect on IL-13-induced allergic airway inflammatory response(32). In addition, in BALB/c mice, they were administered intranasally with IL-13 or IL-17 alone or in combination and their asthma phenotype assessed after 8 days, IL-13 alone promoted the airway inflammatory response and infiltration of CD4+ and γδ T cells capable of producing IL-17, although combination treatment reduced the number of IL-17 producing γδ T cells, it led to increased eosinophilia, interestingly, combination treatment but with a higher dose of IL-17 was found to attenuate the IL-13-induced inflammatory response. IL-33 belonging to the IL-1 cytokine family polarizes naïve CD4+ T cell differentiation into Th2 cells(33,34) suggesting their involvement in the development and maintenance of Th2 allergic response (35). IL-17A enhanced IL-33-induced neutrophilic inflammation and AHR through increased infiltration of CXCR2-expressing alveolar macrophages (AMs)(36) that promote the development of airway inflammatory responses. AMs are another important cellular source of IL-17. Mast cell-released soluble mediators activate AMs leading to increased expression of IL-17 by these macrophages. Macrophage-derived IL-17 is essential for the establishment of acute allergic inflammation in asthma mouse models and IL-10 is capable of downregulating IL-17 expression in human AMs(37). In addition, the complement regulation of the IL-17 signaling axis was found to be an important determinant of severity in experimental allergic asthma(38) Furthermore, IL-17A mediated neutrophilic inflammation also impairs the oxidant-antioxidant balance in airway epithelial cells through upregulation of oxidative stress markers and downregulation of antioxidants(39)At the same time, there have also been reports on IL-17 as a negative regulator of allergic asthma. In a study, IL-17 was shown to be essential during antigen sensitization in the induction of allergic asthma and then function in the effector phase to attenuate allergic responses by inhibiting dendritic cells and chemokine synthesis (28). Here, neutralization of IL-17 amplified the allergic inflammatory response and this dual role of IL-17 was regulated in an IL-4-dependent manner. In another study, administration of anti-IL-17 monoclonal antibody (mAb) before allergen inhalation showed potent reduction of bronchial neutrophil induction that is comparable to dexamethasone treatment but surprisingly enhanced bronchial IL-5 production aggravating allergen-induced bronchial eosinophilic inflammation(40). Although prolonged

neutralization of IL-17 using IL-17 mAb reduced bronchial neutrophilia, a proportional increase in eosinophilia was observed.

All these findings demonstrated that TH17 are playing a very important role in an allergic disease. One of the transcription factors that is reported that is crucial for the TH17 development is HIF-1, which our group demonstrated it is importance in the pathogenesis of asthma.

Hypoxia Inducible factor-1 alpha

A key regulator of the cellular response to hypoxia is transcription factor, hypoxia-inducible factor 1 (HIF-1)(41). The predominant form of HIF-1 is a heterodimer consisting of HIF-1alpha (HIF-1α) and HIF-1 beta (HIF-1β) subunits, both of which are members of the basic helix–loop–helix family of transcription factors. Although HIF-1β is constitutively expressed, the expression of the HIF-1α subunit is regulated by O2 concentrations. The HIF-1α protein is degraded in normoxic conditions but stabilized under hypoxic conditions is regulated by a family of oxygen- and iron-dependent prolyl hydroxylases, whose activities direct the rapid degradation of HIF-1α by the ubiquitin-proteasome pathway, depends on the Von Hippel–Lindau tumor suppressor protein (vHL). Under hypoxia, prolyl hydroxylase activity is inhibited, resulting in the stabilization of HIF-1α, that is translocate to the nucleus, where it binds the constitutively expressed HIF-1β. the resulting HIF-1 complex regulates the expression of genes involved in angiogenesis, oxygen transport, glucose metabolism and vascular tone as well as the function of cytotoxic T-lymphocytes (CTL)(42,43).

Further, hypoxia is a common feature of numerous malignancies, despite the cancer dependency on hypoxia, the mechanisms of regulation are not identical. Overexpression of HIF-1α is associated with aggressive cancer cell behavior and is correlated with poor overall patient survival. Tumor cells react to low oxygen levels by inducing HIF-1α expression, which results in an activation of many crucial cancer hallmarks, such as angiogenesis, glucose metabolism, cell proliferation/viability, invasion and metastasis. Even though hypoxia was initially identified as a driver of HIF-1α expression, it has become clear in recent years that its overexpression in cancer can be also driven by genetic alterations, such as gain-of-function mutations in oncogenes or loss-of-function mutations in tumor-suppressor genes(44).

Tumor cells develop hypoxia as a result of an inadequate supply of oxygen (chronic hypoxia) or transient fluctuation in blood flow (acute hypoxia)(45). The impairment in diffusion, the abnormalities in the tumor microvessels and the disturbed microcirculation, all lead to deficiency or even abolishment in oxygen supply in the tumor microenvironment(46), eventually, tumor cells become necrotic due to lack of oxygen. Hypoxia negatively influences the results of radiotherapy and chemotherapy and potentiates tumor metastasis. HIF is intrinsic markers of tumor hypoxia in which their expression is increased in hypoxic cells as a means of an adaptive response to the hypoxic environment and tumor progression and metastasis(47).

On the other hands, our research group showed for the first time that HIF-1α increases after challenge in patients with asthma and its overexpression positively correlates with the expression of VEGF and CCL2 190,191. There is upregulation of HIF-1α in the smooth muscle, submucosa and bronchoalveolar lavage (BAL) cells and lung tissue of asthmatic patients(15-18), while conditional genetic knockout (KO) of HIF-1 results in reduction in eosinophilia, lung inflammation and specific IgE(48). HIF-1α regulates inflammatory responses of another myeloid cell, the eosinophil, which is a major effector cell in allergic inflammatory airways disease (AIAD). HIF-1α accumulation is critical for sustaining human allergic effector cell survival and function (49). In addition, our group confirmed the importance of HIF-1α that allergen exposure leads to upregulation this protein and VEGF in endobronchial biopsies and BAL cells of asthmatic and patients and in nasal lavage of rhinitis patients. Our clinical observations therefore support a role for HIF in the development of allergic airway diseases(17). Further, we demonstrated that HIF levels may serve as a useful biomarker for poor asthma control and a clinical therapeutic target. With regard to the latter notion, a number of compounds have been identified that downregulate the HIF pathway(50), and there is a major effort underway in both academia and the pharmaceutical industry to develop specific small molecule inhibitors of HIF1(51). Those studies, shown that such molecules will represent potential novel treatments for asthmaAbout 90% of severe asthma attacks feature hypoxia that increase HIF-1, which exacerbates the condition(52). Studies have shown that HIF-1α deficiency diminishes Th17 cell development but enhances Treg cell differentiation and protects mice from autoimmune neuro-inflammation(53). In an allergic airway inflammation model, hypoxia was found to increase airway inflammation, but HIF-1α knockout mice were resistant to airway inflammation(54). In Addition, sputum analysis confirmed that patients with a simultaneous increase in IL-5 and IL-17A had significantly worse lung function parameters and that uncontrolled asthmatics tended to have higher IL-5 and IL-17A mRNA levels than controlled asthmatics(55). Importantly, is has been shown that HIF-1 can regulates the balance between TH17(56). We next, going to focus in this mechanism.

HIF-1α activation and balance of Th17

It has been demonstrated that hypoxia-inducible factor 1 plays an important role in modulating the balance between Tregs and Th17 differentiation, HIF-1 induced imbalance may result in some chronic inflammatory and autoimmune diseases(49,57–59). Th17 cells are important against extracellular bacterial infections in the intestine and airways and play a very important role in the pathogenesis of several autoimmune diseases(49) are induced by IL-6 and TGF-β from naïve T cells and are propagated by IL-23 and IL-21, Th17 cells are characterized by high expression of the transcriptional factor RORγt. Tregs cells can be induced upon exposure to TGF-β and are propagated by IL-2, Tregs express Foxp3 as a core subset-specific transcription factor. Th17 and Tregs cells share a common requirement of TGF-β in their differentiation requirements and demonstrate opposing functions (inflammatory versus anti-inflammatory). Depending on environmental signals, such as the relative amounts of IL-6 and TGF-β, one or the other subset emerges as the dominant phenotype. In addition, Tregs mediated suppression of Th17 responses often play a protective role against pathology associated with the disease(49,56,60). Significant evidences shown that HIF-1α regulates the Th17/Tregs balance. This regulation is thought to occur by these mechanisms: 1) HIF-1α attenuates Tregs development by binding Foxp3 and targeting it for proteasomal degradation, this regulation occurs under both normoxic and hypoxic conditions. 2) HIF-1α enhances Th17 development through direct transcriptional activation of RORγt. 3) A complex HIF-1α with RORγt and p300 bind to the IL-17 promoter that result enhances Th17 differentiation(49,56).

Role of the balance of Th17/Tregs in cancer

CD4+CD25+regulatory T cells (Treg) are another important tumor-infiltrating population controlling growth and metastasis in vivo, in part at least through downregulation of the protective functions

of CD4+, CD8+, NK, and NKT cells(61–63). Importantly, despite the disparate functions of Treg and Th17 subsets, the two subsets show strong interrelation(64). It has been reported that TGFβ in the absence of inflammatory cytokines induces Foxp3+ Treg cell differentiation, while inflammatory cytokines which promote Th17 responses counteract activation and function of Tregs(5,65,66). More recently, it was reported that Th17 cells themselves can be a source of tumor-induced Foxp3+ cells(67). IL-17 may also impact on other regulatory cells within the tumor microenvironment, as suggested by a recent report indicating that suppression of IL-17A at tumor sites eliminated myeloid-derived suppressor cells and regulatory T cells at tumor sites and indirectly augmented cytotoxic activity at tumor sites(68). Recently, in a pancreatic tumor model, a unique subset of tumor-infiltrating dendritic cells (CD11b+CD103− DCs), expressing high IL-23 and TGF-β, was shown to promote tumor growth by inducing FoxP3neg tumor-promoting IL-10+IL-17+IFNγ+ regulatory CD4+ T cells. This differentiation was further modulated by DC expression of retinoic acid, and the Th signature seen mimicked closely that seen in human pancreatic carcinomas again associated with immune depression and poor survival(69).

Participation of tumor microenvironment in the Th17/ Tregs regulation

Tumor cells have enhanced capacities of proliferation, neo-angiogenesis development, and metastasis (70,71). The tumor microenvironment, which comprises malignant and nonmalignant cells distinguished by specific markers and interacting in a dynamic fashion, is an important aspect of cancer biology that contributes to tumor initiation, tumor progression, and responses to therapy(72). Cells and molecules of the immune system are a fundamental component of the TME (Tumor microenvironment). While important for antitumor responses, cells of the immune system including macrophages, neutrophils, mast cells, dendritic cells (DCs), and lymphocytes can also promote the development and progression of almost every solid tumor (73–75), often producing cytokines and mediators which modify the TME such that it becomes more favorable to tumor development and progression (76,77), It was not altogether surprising to discover an important role for Th17 and other cytokines in cancer development and progression(21,78–80).

Intratumorally Th17 cell infiltration has been described like dual role, that means could be pro-tumor or anti-tumor in other words the result of these behavior impact in a good or bad prognosis, and this infiltrate can be detected in the microenvironment of tumors of multiple histological types, with their numbers often correlated with disease stage(72). Th17 cells are now well characterized in terms of their cytokine secretion profile, transcription regulation, and immune functions(75). Their development is regulated by RORγt, STAT3, and IFN regulatory factor-4 transcription factors, along with several cytokines(81). In mouse, these include TGF-β and IL-6/IL-21(82) and IL-23(83), while in humans it seems that IL-1 is a major controlling cytokine, with an important role for IL-23, IL-6, and TGF-β also now well documented(84). Phenotypically, tumor-infiltrating Th17 cells express CD45RA−CD45RO+ CD49+ but not Foxp3 and PD-1 (unlike Tregs(85)), and they express other surface receptors controlling their trafficking to peripheral tissues including CXCR4, CCR6, and C-type lectin CD161(86). Lacking CCR2, CCR5, and CCR7, Th17 cells have limited traffic to lymph nodes(87). Within the TME are high levels of CCL20 (which Th17 also produce) and CXCL12, likely responsible for maintenance of Th17 within in the TME(57).

Indeed, tumor infiltrating Th17 cells were reported for many cancers in mice and humans, including melanoma, breast, colon, hepatocellular, ovarian, pancreatic, prostate, and renal tumors(70). Moreover, Th17 cells accumulate specifically in many different tumors (esophageal carcinomas, breast, colon cancers, and melanoma) compared to healthy tissues(57,58,79,88), demonstrating a specific recruitment of Th17 cells by the tumor microenvironment itself. However, it is still unknown whether Th17 cells are induced, recruited, expanded, or converted from Tregs in tumors. It is likely that all these processes coexist. Intratumorally recruitment of Th17 cells was proposed to rely on various chemokines depending on the tumor context, such as CCL20(89), CCL17, CCL22, MIF, RANTES, MCP1(58,88,90), or CCL4 produced by immature myeloid cells(91). Moreover, cancer cells, tumor-derived fibroblasts, and antigen-presenting cells secrete several key cytokines for Th17 differentiation such as IL-1β, IL-6, IL- 23, and TGF-β. In the tumor, IL-1β, probably produced by tumor-associated macrophages, was shown to be critical for the expansion of memory Th17 cells(79).

Th1 and Th2 cells that are considered as stable lineages. In contrast, Th17 cells exhibit high degree of plasticity and present a different behavior depending of the cellular and immune context, this quality gives them the power to act as master regulators of various cellular processes and to modify the regulation and behavior of cells and the immune response in normal and disease state such as cancer.

Tumor-promoting functions of IL-17

Several reports demonstrated that IL-17 may involve in many cellular process and determine how induce or favor the tumor growth, one of the most important mechanisms of cancer is the angiogenesis, the vascularity play an important role in the tumor growth, because IL-17 can induce CXC chemokines with a characteristic ELR (glutamic acid-leucine-arginine) motif, which are potent angiogenesis promoters(92). These chemokines, including CXCL1, CXCL5, CXCL6, and CXCL8, act via the receptor CXCR2 on endothelial cells stimulating their migration and proliferation. The angiogenic activity of ELRC-CXC chemokines has been documented in several animal models of disease, including cancer, corneal neovascularization, and fibrosis (92,93). The potential role of IL-17 in angiogenesis was further inferred from the observations that microvessel density in tumors correlated with the number of infiltrating IL- 17-producing cells (94–98). Moreover, it has been found that IL- 17-transfected cancer cells formed larger and more vascularized tumors when transplanted in mice, and these effects could be significantly abrogated by the blockade of the CXCR2 receptor (97). It has been reported that serum concentrations of IL-17 and VEGF correlate both with each other and with adverse prognosis in patients with colorectal(99) and non-small cell lung cancer(100). In this respect, IL-17 has been shown to directly induce VEGF in several malignant cell lines, including gastric(96), breast(101), and lung cancer(97,102), as well as in tumor-associated neutrophils(103). IL-17 can also stimulate VEGF release by normal fibroblasts from the lung, skin, and cornea(104,105), by synoviocytes(106,107), and chondrocyte-like cells from the nucleus pulposus(108). Such an effect, however, does not seem to be a general phenomenon, as VEGF secretion was not detected in IL-17-stimulated dermal microvascular endothelial cells(109) and in a number of cancer cell lines(110). In the latter, the absence of VEGF induction was attributed to the lack or weak expression of

functional IL-17 receptor(110). The relationship between IL-17 and VEGF in tumor microenvironment may become even more complex during anti- VEGF therapy. It has been demonstrated that treatment with anti-VEGF drugs leads to an increase in IL-17 in the tumor micro-environment, which initiates a paracrine network that elicits an angiogenic response independently of VEGF and thus contributes to drug resistance(111).

On the other hand, IL-17 has tumor-promoting effects by directly stimulating cancer cells as well as by indirectly inducing an immunosuppressive tumor environment. IL-17 binds IL-17R on tumor cells, signaling the downstream activation of transcription factors (NF-κB, STAT, and AP-1), kinases (MAPK and HER1), tissue remodeling matrix metalloproteinases (MMPs), and anti-apoptotic proteins (Akt, Erk, mTOR, Bcl-2, and Bax) in a myriad of cancers. For example, IL-17 ligation stimulates the proliferation and self-renewal of ovarian cancer stem cells in a dose-dependent fashion via the NF-κB and MAPK pathways(112). Similarly, IL-17 ligation up-regulates NF-κB signaling in a dose dependent fashion in glioblastoma cell lines(113); mediates intracellular NF-B, MAPK, and AP-1 activity in gastric cancer(82); and promotes hepatocellular carcinoma invasion and prostate cancer epithelial to mesenchymal transition in vivo via MMP-2,MMP-7,MMP-9, and NF-B signal transduction(114). Finally, IL-17 directly contributes to the proliferation of keratinocytes via the IL-17R-Act1-TRAF4-MEKK3-ERK5 circuit in skin cancer, and promotes MMP-dependent cell invasion, supports angiogenesis, inhibits TGF-β–dependent cellular apoptosis, and enhances MEK-, ERK-, JNK-, and STAT3-mediated cell proliferation in breast cancer (115,116). Thus, IL-17 has been implicated in the oncogenesis of many tumor types. IL-17–mediated ERK activation and HER1 phosphorylation also promote resistance to docetaxel-based chemotherapy and tyrosine e kinase inhibition, highlighting the role of IL-17 not only in cancer cell growth but also as a mechanism of treatment resistance(117,118). IL-17 ligation on pancreatic cancer cells directly up-regulates ERK signaling, which increases cancer cell invasion and endothelial cell migration and supports the survival of cancer cells at distant organs(115). Notably, treatment with an antagonistic IL-17 antibody blocks the development of pancreatic cancer metastasis in a murine xenograft model. In colorectal cancer, both secretory and membrane-bound forms of IL-17 can contribute to cell cycle progression and oncogenesis(119–121). The amount of IL-17 also correlates directly with the severity of dysplasia in the colonic adenoma-to-carcinoma sequence, making IL-17 an attractive cytokine for colon cancer diagnosis and severity(122). Together, these results suggest that IL-17 supports tumor growth, tumor progression, treatment resistance, and metastasis.

Regardless of the mechanism by which IL-17 promotes tumor growth, compiled data support the hypothesis that the protumoral properties of IL-17 affect the early stages of carcinogenesis and oncogenesis rather than the later stages in an established tumor. IL-17 signaling has been shown to drive the early stages of pancreatic and colorectal cancer formation(123,124), and inhibition of IL-17 signaling prevented neoplastic initiation. Yet, the role of IL-17 blockade in established cancer models has been consistently less clear(125). This may be because the established tumor is a complex microenvironment, rich in immune cells, stromal components, and redundant signaling pathways that make the effect of any individual cytokine less predictable(126,127). This is an important distinction, that requires further investigation, suggesting that cytokine-based IL-17 inhibition may be more useful during early tumor growth.

Antitumoral function by IL-17 expression

In contrast, It has been suggested that Th17 cells may contribute to protective immunity through recruitment of other cells to the tumor microenvironment(128) or may even themselves evolve into such effector, inflammation-inducing cells (IFNγ-producing cells), which could be beneficial in tumor resistance(129,130). As but one example, in a neuroblastoma mouse model, investigating the delivery of IFNγ as an antitumor therapeutic agent using mesenchymal stromal cell (MSC) therapy, it was observed that the MSCs polarized murine macrophages to an M1 phenotype. In vivo delivery of the MSCs in nude mice did indeed lead to a reduced tumor growth rate and increased survival(131). It has been reported that other tumor-associated inflammatory cytokines including IL-6 and TNFα regulate levels and activity of Th17 cells in the tumor microenvironment in a murine ovarian cancer model(132).

In a mouse colon cancer model, an antitumor effect of IL-17 gene transfection was thought associated with a change in the distribution of different subsets of spleen lymphocytes in mice, altered lymphocyte infiltration into tumor tissues, and increased expression of IFNγ in tumor tissue, with reduction in expression of IL-10 and IL-13, all combining to produce an antitumor effect(133). In addition, in a recent study mouse melanoma model in which, the authors investigated the therapeutic potential of blocking the IL-17/IL-17RA pathway, on melanoma tumor growth(134), while recombinant IL-17 was seen to increase proliferation of mouse B16F10 cells and human melanoma cells (A375 and A2058), when they were silenced IL-17RA by small hairpin RNA (shRNA) in B16F10 cells reduced proliferation, migration, and invasion, along with reducing vascular endothelial growth factor and matrix metalloproteinase production(134). Indeed, Th17 cell infiltration in human tumors was correlated with better survival in ovarian cancer patients(57), prostate cancer patients, lung carcinoma, and squamous cell carcinoma patients(135) or with bad prognosis in hepatocellular(94), colorectal(136), pancreatic(98), and hormone resistant prostate carcinoma patients(137). Other group reported that IL-17 deficiency led to decreased tumor growth in B16 melanoma and MB49 bladder carcinoma models(138) and IL-17R−/− mice exhibited decreased tumor growth, when challenged with EL4 lymphoma, Tramp-C2 prostate cancer, or B16 melanoma tumor cells(70).

A role for IL-17 in attenuating the effect of inhibition of VEGF on tumor growth and metastasis was reported by others to result from IL-17 modulation of stromal cell activities including endothelial cells, tumor-associated macrophages, and cancer-associated fibroblasts(62). The knockdown of IL-17RA led to a decreased capability of B16F10 cells to form tumors in vivo analogous to that seen in IL-17-deficient mice and simultaneously increased antitumor immunity through augmentation of IFNγ-Th cells, not through Treg(134).

IL-17 stimulates CXCL2 and CXCL3 production from squamous esophageal cancer cells, which attracts myeloperoxidase+ IFN-γ+ antitumoral neutrophils in vivo and inhibits tumor growth(59). Similarly, IL-17 induces CCL2, CCL20, CXCL9, and CXCL10 production from esophageal squamous cancer cells that recruits and activates T cells, dendritic cells (DCs), and NK cells, correlating with an improvement in overall survival in 181 patients with esophageal squamous cell carcinoma(139). IL-17 also coaxes IL-6

production from a variety of cells in the tumor microenvironment, including macrophages and tumor cells. Ultimately, the role of IL- 17–induced IL-6 expression in antitumor immunity is rooted in the survival, proliferation, recruitment, and cytotoxicity of leukocytes(140). Thus, in established tumors, IL-17 both directly activates immune cells and indirectly nurtures a cytotoxic cytokine environment.

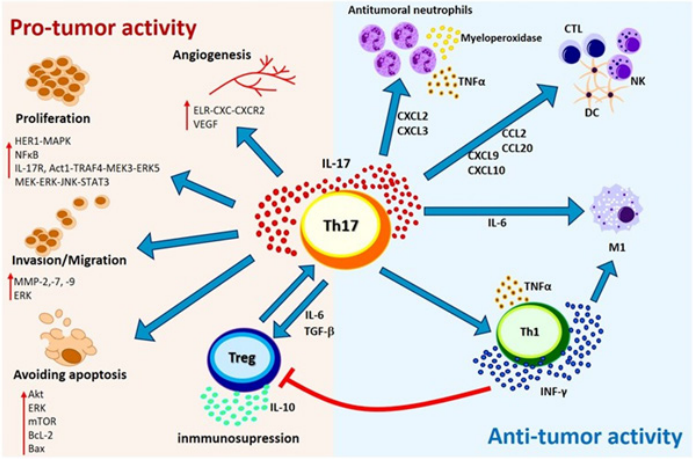

Figure 1: Th17 cells exhibit both pro and anti-tumoral activity. IL-17 production contributes to angiogenesis and recruitment to the TME. Moreover, TGF-13 might induce immunosuppression in Th17 cells by inducing ectonucleotidases expression. Inhibition of tumor growth can occur through recruitment/induction of immune effector cells within the tumor and by activation of tumor specific cytotoxic CD8+ T cells (CTL). There is evidence that Th17 cells can convert toward a Tregs cell phenotype in the TME in the (relative) absence of IL-6, while Th17 cell conversion to a Th1 cell phenotype results in IFN-γ and TNF-a production, tumor killing, and attenuation of Tregs function.

All the mechanisms mentioned in this section are summarized in Figure 1

The above evidence clearly demonstrates the importance of HIF-1α in the Th17/Tregs balance, mentioned before. This balance plays an important role in the pathogenesis of allergic asthma and cancer progression. Taking this into consideration, an important focus of our current investigation is HIF-1α, which we propose to be the crosslink protein between allergic response and cancer.

Immune response in allergic asthma and is correlation with cancer

Because allergic asthma is a complex inflammatory disorder of the respiratory system, it has been hypothesized that this chronic condition may affect the risk of cancer(8,9). A promising branch of this discipline is the emerging field of AllergoOncology, which focuses on Th2 and IgE-mediated immune responses in the cancer context, but this field has shown opposite results supported by two different theories and contradictory hypotheses. Several studies report an inverse association or protective effect between cancer an allergies, through the "immune surveillance theory", established by Burnet (1957)(141), that enounced that immune system can detect and eliminate malignant cells more effectively in a hypersensitive state such as allergy. Another complementary theory declares the protective role of allergic disorders in cancer development, is prophylaxis theory, which takes a Darwinian perspective, proposes that allergy symptoms themselves evolved by natural selection to serve a useful purpose: the expulsion of toxins, pathogens, and foreign particles before they, and any contained or adhering mutagens, will can initiate carcinogenesis(142,143), but in the other hand with inverse effect exits that explain the positive associations, McWhorter (1988)(144) proposed the "antigenic stimulation" hypothesis, which states that allergies cause chronic inflammation and stimulation of cell growth, which, in turn, increase the likelihood of mutations of actively dividing stem cells and malignant proliferation of aberrant clones. Indeed, the link between chronic inflammation and cancer occurrence is well established. Under the antigenic stimulation hypothesis, allergy symptoms directly increase risks of developing cancers in any tissue or organ system(141). Both theories are showed in the Figure 2.

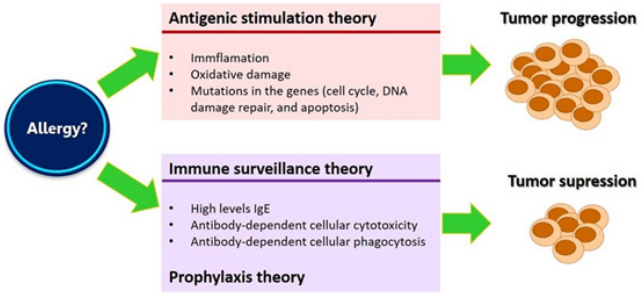

Figure 2: AllergoOncology Theories. Field of AllergoOncology, which focuses on Th2 and IgE-mediated immune responses in the cancer context, but this field, has shown opposite results supported by two different theories and contradictory hypotheses. First theory antigenic stimulation hypothesis, McWhorter (1988) that proposed which states that allergies cause chronic inflammation and stimulation of cell growth, which, in turn, increase the probability of mutations and malignant proliferation of aberrant clones, where the allergy symptoms directly increase risks of developing cancers in any tissue or organs, causing a pro-tumor or tumor growth effect; in the second place and with contradictory result exist the immune surveillance theory, by Burnet (1957), that immune system can detect and eliminate malignant cells more effectively in a hypersensitive state such as allergy obtain a tumor suppression or anti-tumor effect..

There is different epidemiological evidence that shows the complicated association between cancer and cancer risk, the clinical cases has been summarized in different meta-analyses, with inverse associations reported for several cancers including glioma, pancreatic cancer, and childhood leukemia (48,49). Most previous studies have relied on self-reported ascertainment of allergic status; these are typically limited, retrospective, and associated with potential biases. Emerging evidence come from prospective studies based on self-reported allergic history, which have reported inverse associations or protective effect in studies of colorectal cancer and breast cancer(1,145), but not in prostate cancers(1). A large scale study based on hospital discharge records reported an inverse association between allergy/atopy of at least 10 years in duration and incidence of brain cancer in a cohort of 4.5 million men(146). The case control studies reported inverse associations between borderline or elevated total IgE and glioma risk(147–149). One study reported an inverse trend between increasing blood eosinophil count and subsequent colorectal cancer risk (150). Another study reported that serum concentrations of soluble CD23/FceRII (sCD23) and soluble CD30 (sCD30) were positively associated with risk of non-Hodgkin's lymphoma(151).

Regard to clinical associations, several studies in large scale prospective using validated measures of self-reported allergy history and/or biomarkers of allergy is needed, including repeated evaluations over time. Sufficient latency with respect to the developing tumor, and detailed data(151,152) to confirm a possible

association between the allergic diseases or their components and cancer to considered in a future like possible immunotherapy against the cancer.

Experimentally there are different evidences in animal models that show the importance of the different molecules involved in allergic diseases and cancer, several studies have use one of the most characteristic molecules in allergic diseases, IgE antibody, targeting various tumor antigens in different models have shown that these immunoglobulins have significant anticancer activity while being well-tolerated. In fact, a tumor targeted murine IgE specific for either the major envelope glycoprotein (gp36) of mouse mammary tumor virus (MMTV)(153) or an antigenic determinant on the surface of human colon carcinoma cells(154) have shown anti-cancer effects in murine models. In addition, a mouse/human chimeric IgE (MOv18 IgE) specific for the human ovarian cancer antigen folate binding protein (FBP) demonstrated superior antitumor activity in murine models compared to a mouse/human chimeric IgG1 with the same variable regions (MOv18 IgG1)(155,156). Our work group demonstrated in the context of the immune response in our experimental model. Under allergic conditions and cancer develop, that both diseases share one molecule, TGF-β, that increase of cytokine by the allergy, can inhibit tumor growth, generating protect effect against cancer. In addition, we observed that Th17 might play an important protective role due to the induction of a cell-mediated response. Our results were the first to establish an inverse or protective relationship between allergic airway inflammation and tumor progression, in which TGF-β overexpression plays a direct and relevant role. We also show that the inhibition of tumor progression in our model depends on TGF-β, which is overexpressed in allergic airway inflammation and induces apoptosis of tumor cells in addition to inhibiting proliferation. Taken together, the results obtained in this study indicate that TGF-β generated in allergy is a potential target for antitumor therapy(157).

Other vision of several studies demonstrated that in cancer, an integral feature of inflammation is the activation, expansion and infiltration of diverse immune cell types, including CD4+ T cells. Within this T cell subset are immunosuppressive regulatory T (Treg) cells and pro-inflammatory T helper 17 (Th17) cells that act in a fine balance to regulate appropriate adaptive immune responses(49,158).

Conclusion

In this review, we have been able to analysis how allergy oncology tries to elucidate how two different diseases can pathologically coexist and share cellular and immunological agents to maintain a state of balance in the same organism, where the host has greater possibilities of fighting a disease as fatal as it is. However, we have also seen how adaptation, the response capacity of the organism and as a result the effect of this new adaptation depends a lot on the type of cancer. We present solid evidence to show that one of the main actors is the transcription factor HIF-1α, which plays an important role in human allergic airways. On the other hand, increased HIF-1 levels have been shown to be an independent predictor of mortality in several type of cancers. The hypoxic tumor microenvironment drives cancer progression largely by inducing HIF-1 activity, and the hypoxic status of cancer cells favors resistance to radiation therapy192 and chemotherapy162. In addition, our working group has established an inverse or protective relationship between allergic airway inflammation and tumor progression in a model of murine breast cancer, our study indicates that TGF-β is a potential target for antitumor therapy194,195. Taken together, in the present in this review, we show solid evidence to support that high activation of HIF1 during allergic disease can regulate and activate the Th17 balance. That induce a pro-tumor or anti-tumor response depending fundamentally of the balance of the existing cytokines and the transcriptional regulation of FoxP3 or RORγt that lead to promote or decrease tumor growth. See Figure 3.

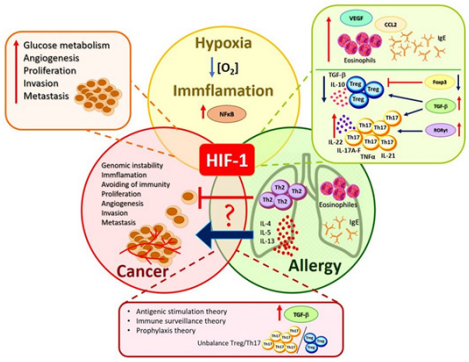

Figure 3: Summary of the Conclusions..

Further, when we prediction of the biological interaction between HIF-1and IL-17 (highlighted in light yellow line). The figure indicates the inferred GeneMANIA network program regulated by the HIF-1 (bright yellow) gene network. Additionally, other factors related to transcription (blue) were inferred. The pink factors are "master genes" or hubs that regulate at least three genes Figure 4. This analysis supports the possibility that the regulation of Th17 / Tregs through HIF1, and that this interaction could result in the development of an anti-tumor response between both pathologies when exist an overexpression and activation of HIF1α by asthma and cancer.

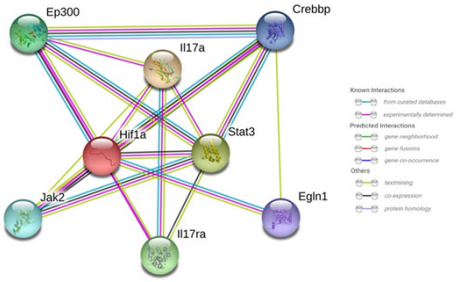

Figure 4: Prediction of interactions on the HIF1 a / Th17 axis. To demonstrate the possible interaction of HIFla with proteins and factors related to Th17, we checked the STRIG database (STRING CONSORTIUM 2020) available online at (https://string-db.org/), and found an important molecular relationship HIFI Awith stat3 and ILI 7.

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