Immunol Genet J, Vol. 4, No. 4, Dec 2021, pp.171-185 **DOI: https://doi.org/10.18502/igj.v4i4.12754**

Review Article

Cancer and Allergy; Molecular Association and Integrated Therapies

Sara Hemmati[1,2], Behnoud Baradaran Noveiry[1,3,4], Mahsa Keshavarz-Fathi[1,2,5*]

[1] *Cancer Immunology Project (CIP), Universal Scientific Education and Research Network (USERN), Tehran, Iran*
[2] *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Department of Medicine, Saint Mary's Hospital, Waterbury, CT, USA*
[4] *Cancer Immunology Project (CIP), Universal Scientific Education of Research Network (USERN), CT, USA*
[5] *Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*

Received: 16 September 2021; Accepted: 19 November 2021

Abstract

Both innate and adaptive arms of immune system play role in tumor development. Moreover, genetic and epigenetic alterations, widely demonstrated in cancer cells, result in disturbances in molecular pathways regulating cell growth, survival, and metastasis. Knowledge of molecular and cellular mechanisms involved in carcinogenesis leads to improvement of targeted treatments for cancers. Similarly, allergies are immune related entities and are treated according to the molecular mechanisms of hypersensitivity reactions. Some studies support the hypothesis of inverse association between cancer and susceptibility for allergies but the correlation is not simple and some demonstrate positive relation. For example, in some studies histamine released in response to allergens plays a role in tumor progression, probably through maintaining survival of myeloid derived suppressor cells (MDSCs). However, in other studies, the protective role of IgE against carcinogenesis have been reported. In this review, the role of immune system and specific molecular mechanisms in cancer and allergy will be discussed. Based on separately mentioned factors, interactions between these two seemingly disparate entities will also be presented. We conducted this review to illustrate potential molecular and cellular mechanisms underlying the association of cancer and allergy and make a basis for future interventions.

Keywords: Cancer; Allergy; Immune System; Hypersensitivity; Signaling Pathway; Epigenetics

***Corresponding Author:** Mahsa Keshavarz-Fathi, MD
School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

How to cite this article

Hemmati S, Baradaran Noveiry B, Keshavarz-Fathi M. Cancer and Allergy; Molecular Association and Integrated Therapies. Immunology and Genetics Journal, 2021; 4(4): 171-185. DOI: https://doi.org/10.18502/igj.v4i4.12754

Introduction

Cancer cells are normally recognized and destroyed by immune system in order to prevent tumor development. However, natural immune mechanisms may fail to keep up with the progression of cancer cells a part of which may be due to some immunity inhibiting cells enhanced in cancer patients such as myeloid derived suppressor cell (MDSC), regulatory T cells (Treg), etc (1). Indeed, cancer cells are self-cells with malignant alterations, hence, self-tolerance might play role in weakened immunity against cancer.(2) A number of molecular mechanisms underlying malignancy and uninterrupted proliferation of these cells have been investigated.

Being self-sufficient in growth signals and insensitive to growth-inhibitory signals can illustrate critical steps in transformation of normal cells into malignant cells (3). Continuous growth signaling can be an outcome of mutations in cell surface receptors or intracellular signal transducers, like the Epidermal Growth Factor (EGF) receptor (EGFR) and Phosphatidylinositol 3 kinase (PI3K) and some special pathways in Cancer Stem Cells (CSC) (4-6).

In addition, epigenetic, as the heritable changes in gene expression, which are not accompanied by changes in DNA sequence, including covalent modification of DNA and histone proteins, as methylation, plays an important role in inducing cancer (7). Environmental factors such as cigarette smoke in lung cancer as a chemical carcinogens, are reported to induce cancer through influencing epigenetic mechanisms of DNA methylation (8).

Aside from molecular researches on cancer itself, other studies have been conducted to define the correlation of cancers with other chronic diseases like allergies, yielding a new area of research known as “allergooncology" associated with the basic mechanisms of allergic diseases affecting specific cancers (9).

Considering immunologic factors and tolerance, the immune system often underreacts in cancer as cancer cells are originally normal cells with the previous antigenic feature and damaged DNA. However, in the case of allergies, the immune system becomes hyper-sensitive to a normally harmless substance, and immune cells overreact to that substance, resulting in inflammation and allergy symptoms. Different immunologic factors and immune tolerance underlying these two phenomena may explain how their genuine mechanism of disease can influence each other when they concomitantly occur or mimicked in therapies. On the other hand, multiple genetic and environmental factors are involved in both allergic reactions and cancers, in which mutual findings may illustrate how they are associated.

There are broad panel of molecular events before and during IgE mediated reactions. Before the initiation of reactions, processing allergen by antigen presenting cells (APC) and their subsequent secreted cytokines regulates transcription factors like Fork head box P3 (FOXP3) and GATA-binding protein 3 (GATA3). Regulation of these factors take part in determination of T cell subsets required for allergy induction (GATA3 for Th2) or suppression (Foxp3 in Treg cells). During the process, IgE priming on mast cells or basophils through Ig-E Fc portion receptor 1 (FcεR1) and signaling events followed by secondary exposure of allergens would trigger degranulation and release of mediators like histamines, leukotrienes (LTs), prostaglandins and ultimately anaphylaxis (10). Histamine affects target cells and subsequently, induces excess mucus production, vasodilation, vasopermeability and smooth muscle contraction (11).

Products of allergic reactions and associated cytokines can additionally participate in pathways involved in tumorigenesis, as both occur regarding the immune system dysfunction. Respiratory system cancers seem to exhibit clear associations with allergies as they occur in the principal site affected in asthma. Therefore, mechanisms discussed in separate sections are mainly focused on lung cancers and asthmatics allergies.

Important Molecular and Cellular Mechanisms of Cancer

Immune system and cancer

Both innate and adaptive immune reactions are important for antitumor responses (12). Natural killer (NK) cells, as a part of innate immune system, are reported to have important roles in clearance of lung tumor cells through interferon gamma (IFNγ) secretion or induction of apoptosis (13). In the adaptive immune system, T cells and their secreted cytokines play an essential role in immune system’s antitumor effects (14). Tumor cell death is usually mediated by CD8+ cytotoxic T cells and CD4+T helper (Th) cells via IFNγ secretion especially by Th1. Th17 also represents important antitumor responses by producing inflammatory cytokines like IL17 and associated tumor cell death (15). Enhancing the antitumor immunity by IL17 may be related to its role in increasing the generation of cytotoxic T cells (16). However, IL17 may also have

negative effects on tumor immune surveillance through inducing tumor vascularization. This tumorigenic function of IL17 contradicts disruptive effects of IFNγ on tumor's vasculature (17). Another important cytokine in cancer immunity is transforming growth factor-beta (TGF-β) which initially induces apoptosis in early stages of tumor. However, at later stages it demonstrates protumor activities due to the resistance of tumor cells to growth inhibitory signals by this cytokine (18). Increased TGF-β in tumor microenvironment leads to epithelial transition of cancer cells and consequent invasiveness and metastasis (19). However, some components of immune system may counteract the antitumor effects of immune system by protecting tumor cells or suppressing immune reactions. For example, a special subset of T cells called Tregs suppress immunity against tumors by inhibitory cytokines (20). Proliferation of Tregs cells are reported to be stimulated by TGF-β which indicates its immunosuppressive mechanism in tumor microenvironment (21). Another type of cells promoting tumor progression is MDSCs. MDSCs are very similar to monocytes and granulocytes. They are a kind of immature myeloid cells characterized by their potent immune suppressive activity, especially through inhibiting T-cell and proliferation of cytokine-producing cells (22). They might indurate immunotherapy of cancer as well as the natural immune responses against tumors(23). Abolition of MDSC in both preclinical and clinical settings has led to more effective immune responses. Surprisingly, a direct antitumor effect was observed in some studies as well. (22). The most substantial mechanisms of immunosuppressive activity of MDSC include contribution of arginase, nitric oxide (NO) and reactive oxygen species (ROS) (24).

Signaling pathways

Various molecular mechanisms are involved in tumor progression, and signaling pathways are major operators of initiation and maintenance of this malignant process. The most important pathways in cancer include Wnt and Notch in cancer stem cells, PI3K and ERK- MAPK which will be described herein. Cancer stem cells are a type of malignant stem cells in cancerous milieu, which share the characteristics of normal stem cells, specifically their pluripotent feature to produce all cell types (25). They have been found in a growing number of hematopoietic cancers and solid tumors and could be among the key factors of tumor survival (26). There are important pathways acting in renewable cells such as Wnt and Notch, which are related to extracellular ligands and receptors so that special transcription pathways can be activated. Similar pathways play role in cancer stem cells as well. Particular characteristic of Notch pathway is the enzyme γ-secretase, which can bind to the Notch Intracellular domain and be transferred to nucleus in order to activate or mutate some specific genes. Improper signaling pathway causes wide range of human genetic disorders and cancers. The other one, Wnt, is a paracrine signaling pathway active in cell growth and evolution. It functions through regulating a transcription co-activator "β-catenin". As the main role of Wnt is keeping stem cell pools in tissues, inappropriate activation of this signaling leads to tumor formation (25, 27).

PI3K PATHWAY The phosphatidylinositol 3-kinase (PI3K)/Akt pathway is proven to be activated in various cancers, including non-small cell lung cancer (NSCLC) (28). Activation occurs mostly in the helical or kinase domains of the alpha p110 catalytic subunit, PIK3CA, leading to increase in PIP3 levels. It induces mitosis, anti-apoptotic response, and phosphorylation of AKT which is a serine/threonine-specific protein kinase playing a key role in many cellular processes such as apoptosis, cell proliferation, transcription and cell migration. Other processes like higher protein translation are also induced as a subsequent event through mTOR activation, a phosphatidylinositol 3-kinase-related kinase protein family (29). Observations of PI3K in squamous cell cancer (SCC) and adenocarcinoma (AC) of lung showed alterations in this pathway according to the mutations in three genes – PIK-3CA, PTEN, and AKT. Most of the SCC cases are developed due to PIK3CA gene amplification rather than activating mutations (30).

Tumor suppressor PTEN, a lipid phosphatase and tensin homolog in which deletions or mutations result in a wide variety of tumors, downregulates the PI3K pathways activity through dephosphorylating PIP3 (28, 31). A study has demonstrated that a low level of PTEN expression does not necessarily lead to high activity of AKT. Logically, signaling from insulin like growth factor receptor (IGF1R) and other factors in PTEN-low cells affect AKT activation (32).
EGFR is a tyrosine kinase receptor activated by binding to growth factor ligands including epidermal growth factor (EGF). Subsequently, it activates downstream pathways including MAPK and PI3K and results in DNA synthesis and cell proliferation (33). It also participates in tumors

immune escaping and suppression of autophagy, illustrating clinical implications for immunotherapy (29). EGFR has been shown to be deregulated by different mechanisms including overexpression, amplification, and mutation in a variety of cancers. Activating mutations in tyrosine kinase domain of EGFR are proven to occur in NSCLC. There have been clinical trials indicating that patients treated with EGFR inhibitors show better results than ones treated only with standard cytotoxic chemotherapies (34).

Epigenetics

As environmental factors are increasingly studied, deregulation of the epigenome seems to have a common role in cancers. Epigenetics comprises several processes, such as DNA methylation, histone modifications and RNA interference (35). **SETD2** is a trimethyl transferase having a role in methylation of histone H3 on Lys36 (H3K36me3). During replication process, it ensures DNA mismatch repair (36).

CREBBP/CBP and EP300, histone acetyltransferase coactivators participating in many transcriptional and biological programs by acetylation of lysine residues on histones, are reported to be mutated in lymphoblastic leukemia (29).

KDM2A, histone H3 lysine 36 demethylase, is necessary for tumorigenesis and invasiveness of KDM2A-overexpressing NSCLC cells (37).

Some therapies use targeting epigenetic alterations. DNA methylation inhibitors, typically nucleoside analogs like 5-azacytidine and 5-aza, 2′-deoxycytidine that target DNA methyltransferases, lead to demethylation of DNA and gene re-expression. These molecules were found to be effective in the treatment of myelodysplastic syndromes and leukemia. Histone deacetylase (HDAC) inhibitors targeting acetyltransferases are also possible treatments for targeting genes (29, 38).

Molecular and cellular mechanisms of allergy

Development of T cells and associated cytokines

Cytokines can be categorized into two groups: pro-inflammatory and those that are essentially anti-inflammatory but may induce allergic responses. T lymphocytes are important sources of cytokines. These cells have antigen specific receptors on their surface to identify foreign pathogens presented on APCs like macrophages and dendritic cells (39). There are two main types of T lymphocytes according to their cell surface molecules known as CD4 and CD8. T lymphocytes expressing CD4 are also known as helper T cells being the most plentiful cytokine producers. When CD4 T cells receive IL-12 signals during their activation, Th1 cells are derived from them and the cytokines produced following this differentiation are known as Th1-type cytokines (40).

Interferon gamma (IFNγ), as one of the main Th1-type cytokines, produces the pro-inflammatory responses for killing parasites, which excessively result in tissue damage. In this case, Th2 responses have to counteract the Th1 mediated microbicidal action through excessive amounts of anti-inflammatory interleukin-10 (39, 41). Other Th2-type cytokines, comprising interleukins 4, 5, and 13 are associated with the promotion of IgE and eosinophilic responses as a prominent feature of allergic asthma (39).

Th17, Th9 and Th22 cells are differentiated from naïve CD4+ T cell depending on conditions at the time antigen is primarily introduced (42). Th9 cells secrete IL-9 which is regulated in the presence of IL-25 (43). IL-9 plays a role in the growth of mast cells. Inflammation in the lung and intestines, such as intestinal anaphylaxis can be induced under influence of IL-9 (44). This cytokine in combination with TGF-β acts as an inducer for development of Th17 cells (45).

Producing IL-17 and IL-22, Th17 cells increases recruitment of neutrophils and combat bacterial infections (46). IL-17 is also tracked in allergic conditions such as in patients with asthma, in association with neutrophils, and in the skin of patients with chronic atopic dermatitis (47). The other source of IL-22 production is Th22 cells (48). They only produce IL-22, a member of IL-10 cytokine family which shows immune activity through production of anti-microbial peptides and enhancement of survival of epithelial cells in skin, lung, and intestine. (49). However, IL-22 showed a role in the inflammation of skin in psoriasis (50). Similar to IL-17, high level of IL-22 is present in the skin of patients with atopic dermatitis (51).

CD4 Th cells are critical for organizing adaptive immune responses. During Th2 or Th1 cell differentiation, the expression of the transcription factor GATA3 is respectively up-regulated or down-regulated. GATA3 up-regulation is induced by IL-4–STAT6-mediated signaling. IL-4-independent GATA3 up-regulation is a sequel of low dose but not high dose of antigen stimulation through TCR (T cell receptors) and this also results in IL-4 production (52).

GATA3 suppresses IL-12–STAT4 signaling,

a pathway for Th1 cell differentiation (53). IL-12Rβ2(IL12 receptor β chain) is undetectable in naïve CD4 T cells but T-cell activation triggers its expression (54). In ectopic GATA3-expressing cells, the reduced IFN-γ production (which is related to a failure of T-box expressed in T cells, T-bet, up-regulation) could be explained by a failure to responding IL-12 because of GATA3 suppressing IL-12Rβ2 expression. However, increased GATA3 expression inhibits IFN-γ production even in developing Th1 with restored expression of IL-12Rβ2. Indeed, GATA3 exert this function through decreasing the expression of STAT4 as well as reduction in the expression of IL-12Rβ2. Expression of STAT4 is predominant in Th1 than in Th2 cells (55, 56). In the IL-12 signaling pathway, STAT4 plays a central role and promotes induction of Th1 cells. Owing to this fact, decrease in expression of STAT4, developed by increase in expression of GATA3 leads to failure in induction of Th1 cell despite the enforced expression of IL-12Rβ2. Inversely, GATA3 deletion during Th2 differentiation results in up-regulation of both STAT4 and IL-12Rβ2 (56).

Another mechanism through which GATA3 inhibits Th1 cell differentiation is by binding to Runx3 and therefore, blocking Runx3-mediated IFN-γ production in both CD4 and CD8 T cells. Interestingly, blocking Runx3 diminishes IFN-γ production in GATA3-deficient 'Th2' cells, indicating the role of Runx3 in IFN-γ- and IL-12-independent IFN-γ production. Runx3 has been reported to bind to the IFNγ promoter and multiple sites across the IFNγ gene locus some of which overlap with T-bet binding. These results imply that Runx3 can induce IFN-γ either by itself or by collaborating with T-bet family members to induce full levels of IFN-γ production (57).

As peripheral immune tolerance maintaining cell subsets, Tregs suppress the effector Th1, Th2, Th17 cells which is mediated by producing anti-inflammatory cytokines such as IL-10 and TGF-β (58). TGF-β inhibits the function of both Th1 and Th2 cells, and induces suppression of eosinophils, mast cells and basophils (59, 60). This accounts for an endogenous anti-allergy response.

There are two types of Tregs: the first one is called natural TReg (nTRegs) cells which make nearly 10-15% of blood cells lymphocytes (61). They're selected in the thymus as Foxp3+CD4+CD25+ TReg cells due to the effect of TGF-β on the conversion of naive CD4+CD25- T cells into CD4+CD25+ T cells mediated by the expression of Foxp3, a member of the fork head/winged-helix family of transcriptional regulators, crucial for differentiation of naïve T cell towards the Treg phenotype (62, 63). These cells control both pathogenic Th2 cells and Th1 cells, therefore prevent the development of autoimmune diseases (64). The number of local FOXP3+CD25+CD3+ cells in the nasal mucosa increases after allergen immunotherapy (65). Loss-of-function Foxp3 mutations can lead to severe allergic inflammation manifested as food allergy, asthma, atopic dermatitis, increased IgE levels and eosinophilia (61).

The other TReg cell type is produced after antigen exposure and is called inducible TRegs (iTRegs) cells. Inducible TRegs suppress and strict the function of Th2 cells, mast cells, basophils, eosinophils and dendritic cells. They inhibit mast cell degranulation and further pro-inflammatory cytokine release, by an OX40/OX40 Ligand interaction and IL10 production (61, 66, 67). IL-10 down-regulates T cells by blocking CD2, CD28 and inducible co-stimulator signaling (ICOS) (68). ITReg cells inhibit allergic eosinophilia and Th2 IL5 expression both through IL10 in murine lung as an indicator of its role in suppressing airway inflammation (69, 70). By producing IL-10 and TGF-β, they may also participate in IgA and IgG4 production and regulating allergen-specific-IgE (71).

Mast cells and allergy reaction

Mast cells are specialized cells defending against invading pathogens and are mostly located in mucosal and epithelial tissues near small blood vessels. The major growth factor for mast cells is stem-cell factor (SCF), which acts on the cell-surface receptor c-Kit (72). For development of allergic and anaphylactic reactions of type I hypersensitivity, mast cells play a central role. The high- and low-affinity IgE receptors (FcεRI and FcεRII) are targets for IgE binding via its Fc component expressed on mast cells and basophils. Release of histamine and IL-4 from the basophilic granules is the following event. The low-affinity FcεR, CD23, which is expressed in many types of immune cells such as lymphocytes, monocytes, and eosinophils, shows intricate function. However, CD23 coupled with IgE bring about presentation and transport of allergen, modulation of IgE synthesis, and cell-mediated effector functions (73-75). Bi- or multivalent antigen–IgE complex binding activates mast cells which leads to cross-linking of FcεRI and transducing an activating signal. Within minutes, mast

cells release preformed histamine, heparin, other proteoglycans, prostaglandins, several protease such as mast-cell chymase, tryptase and serine esterase for tissue destruction and cytoplasmic granule-associated cytokines such as IL-2, IL-4, IL-21, TNF, G-CSF and IL-13 which perpetuate the Th2 (76, 77). Cytokine and chemical mediator releasing leads to a second phase of allergic symptoms, also called late-phase reactions following immediate allergic reaction. This late response involves influx and activation of other effector cells contributing in the immune response, notably eosinophils, Th2 lymphocytes and basophils. Th2 activation results in accumulation of eosinophils in chronic inflammation. There is an interactive network between eosinophils, mast cells, and basophils (78). Major basic protein (MBP) released following the eosinophil degranulation, leads to another degranulation, this time from mast cells and basophils (73). Cytokines which are common growth factor for both eosinophils and basophils such as GM-CSF, IL-3, and IL-5 foster this interaction (79). Potentially, there is a reciprocal control of the stem-cell maturation into basophils or eosinophils. For example, TGFβ in the presence of IL-3 indicates suppression of eosinophil differentiation and enhancement in basophils'(78).

Mast cells also release high levels of tumor necrosis factor (TNF)-α either from its storage in cells or synthesis after activation. TNF-α promotes the influx of inflammatory leukocytes and lymphocytes into tissues through activation of endothelial cells and their increased expression of adhesion molecules (78, 80).

High levels of IgE can result in a dramatic increase in FcεRI on the surface of mast cells and resulted hypersensitivity of such cells to low concentrations of specific antigen. Ultimately, markedly increased IgE-dependent release of cytokines is noticeable (81).

Allergy & Epigenetic

Environmental factors and epigenetics, also play a role in deregulation of immune system resulting in allergy (82). For instance, air pollution can be a potential risk factor for asthma, although its role in the onset of the disease needs further studies (83). A study has shown increased DNA methylation of the FoxP3 transcription factor promoter and impaired T-regulatory (Treg) function in those patients, supporting the idea that methylation variations play a crucial role in T cell differentiation and plasticity (84). Chromatin remodeling in Th2 cytokine loci also shows a great importance. It was shown that mice undergone loss of histone H3-K4 methylation, general H3 acetylation and demethylation of the DNA in the Th2 cytokine locus, show marked reduction in the recruitment of leukocytes like eosinophils and decreased IgE levels and hyperreactivity mainly occurring in airways (85). Another study implies importance of HDAC for the development of Th2 cytokine production, allergic airway inflammation and early T-cell differentiation through binding to IL-4 gene locus (86). As mentioned, several common epigenetic features are noticeable in cancer and allergy which requires further studies to be investigated integratedly based on specific genes and their modifiers.

H3 methylation variations in both lung cancer (usually upregulated) and asthma (reported to be downregulated) may represent the epigenetic fundamental of associations between these two phenomena with enzymes like KDM2A and SETD2. Also, HDAC is supposed to be overexpressed in tumors, aside from its essential role for Th2 development and subsequent allergy induction (12).

Interactions of cancer and allergy

Histamine and tumor immune escape

Histamine can sustain NK cell function and indirectly promote clearance of malignant cells under conditions of phagocyte-induced oxidative stress mediated by these cells. These results suggested that histamine could be used in cancer immunotherapy protocols (87). However, another evidence indicated that histamine could augment proliferation of different normal and malignant cells. High histamine biosynthesis, linked to allergic reactions, infections, and tumor growth, together with histamine receptors have been reported in different human neoplasia including melanoma, colon and breast cancer, as well as in experimental tumors in which histamine has been considered as an important paracrine and autocrine proliferation regulator (88, 89).

Histamine acts on a variety of cell types with histamine receptors (HR1–4). Effects of histamine on cell growth, motility, phenotypic alterations and signaling mechanisms, are determined by the expression of specific HRs. Myeloid cells have been reported to express HRs and Histidine Decarboxylase (HDC), the enzyme required for histamine synthesis. Culturing monocytes with histamine can alter the cytokine production such as increase in IL-10 and inhibiting IL-12 which leads to Th2 immunity. It also alters signaling pathways important for MDSC accumulation and protects them against apoptosis; therefore, due

to higher levels of histamine in allergic asthma patients, they have more MDSCs in their bloodstream than non-allergic patients. Trafficking the MDSCs to tumors, as a site of inflammation, is mediated by their migration toward mast cells in tumor microenvironment. MDSCs have two subpopulations including monocytic and polymorphonuclear MDSC and this occurs mainly in monocytic subpopulations (11).

Allergy inducing components and cancer

IgE isotype class could show high tumoricidic efficacy in some passive immunotherapies performed with monoclonal antibodies of the IgM, IgG, IgA and IgE classes specifically against tumor-associated antigens. IgE is able to mediate high levels of the antibody-dependent cell-mediated cytotoxicity (ADCC). For example, folate receptor-α is a tumor target and biomarker in epithelial ovarian cancers with a role of delivering 5-methyltetrahydrofolate into the cell for DNA synthesis (90). Recombinant IgE antibodies targeting folate receptor-α revealed the FcεRI-dependent nature of ADCC by monocytes. Interdiction of IgE-FcεRI coupling on monocytes through applying a soluble α-chain of FcεRI or blocking monoclonal antibodies, subsequently decreased ADCC. The mechanism of reducing ADCC is upregulated upon incubation with IL-4 and IL-13. Moreover, CD23 on monocytic cells has the function to clear IgE–antigen complexes from the circulation (76, 91).

IgE can also involve a broad spectrum of effector cells in tumor defense, with a high cytotoxicity via binding to IgE receptors as well as restimulating the immune system through IgE-mediated facilitated antigen uptake and presentation. IgE effector cells like **Eosinophil** were described to be found in several cancer regions including malignancies of the head and neck, uterine, cervix, esophagus, and the gastro-intestinal tract. According to their IgE-mediated tumoricidic mechanisms, the term 'tumor-associated tissue eosinophilia' (TATE) was introduced (76).

Upon IgE activation, eosinophils can release cytotoxic mediators such as major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO). These proteins are also well investigated in their cytotoxic action in respiratory epithelium and cancer cells. EPO as a halo peroxidase enzyme catalyzing metabolites shows dual role at different levels. Although it is responsible for apoptotic or necrotic cell death through promotion of oxidative stress, it utilizes the tumor-associated receptor tyrosine kinase HER-2 for cell cycle progression and proliferation at non-cytotoxic levels (73, 76). Eosinophils also play role in cytotoxicity against colon cancer cells through release of TNF-α and granzyme A (92). These data support the idea of exploiting IgE for cancer immunotherapies. Aside from that, as IgE overproduction is considered to be a hallmark of allergic reactions, cross reactions of this immune component with some special tumor associated antigens may be related with cancer prognosis, as if the tumor antigen was formerly an allergic an antigen. Therefore, it may be intriguing to design an oral vaccine containing tumor antigens to induce IgE antibodies through an indigestible gastric passage (9).

Eosinophils also play a role in tissue remodeling in allergic and cancerous diseases through mediators such as basic fibroblast growth factor (b-FGF), platelet-derived growth factor (PDGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), TGF-β, IL-8 and IL-6. Therefore, they may demonstrate an ambivalent feature, which needs further studies with recombinant antitumor IgG vs IgE antibodies (76).

Mast cells, as IgE effector cells, were reported in tumor-surrounding tissues. Mast cell-specific serine protease-6 (MCP-6, tryptase) is an activator of tumor growth which exert the effect via coupling to protease-activated receptor-2 (PAR-2) expressed on the outside of carcinoma cells. Moreover, tryptase improved the growth of a colon adenocarcinoma cell line, DLD-1, through coupling to PAR-2 and involvement of mitogen-activated protein kinase (MAPK)

Proangiogenic effects can likewise stimulate the tumor growth. Mast cell-specific serine protease-4 (MCP-4, chymase) shows this effect through activation of progelatinase B. In vitro formation of blood vessels stimulated by MCP-6 is another proof for the effects of mast cells on the augmentation of angiogenesis and tumor growth (11, 76, 93, 94).

Of the cells in IgE-based immunotherapies are **basophils**. Basophils share many features with mast cells, whereas mast cells are located primarily in the tissue, basophils can be found in circulation as the least abundant immune cell population. As a consequence of being a main source of histamine, Basophils are of major concerns in passive immunotherapy of cancer with monoclonal IgE antibodies sensitizing FcεRI on them and could potentially be cross-linked by soluble tumor-associated antigens in the circulation, which are shed by tumors (76).

Allergy associated cytokines and tumor development

Some experimental studies observed attenuating effects of **Wnt overexpression** on allergic airway diseases like asthma. The probable mechanism is reduction in dendritic cell (DC) migration to lung draining lymph nodes in order to induce T cell activities (95). It has been reported that **Notch** signaling promotes **GATA3** in Th2 cells (with prominent effect on mast cells in allergy) through IL4-STAT6 independent mechanism (96). Another experimental study on asthmatic model of mice indicated reduced level of Th17/IL17 by blocking Notch signaling pathway through γ-secretase inhibitors, which can demonstrate an effective administration of these inhibitors for asthma patients as well as promoting antitumor effects through blocking the tumorigenic pathways in CSC (97, 98). Therefore, specific genetic mutations in cancer cells and administration of therapies like Wnt/Notch inhibitors in cancer may represent different prognosis in allergic patients.

TGF-β**,** produced by $Foxp3^+$ Treg cells for attenuating immune responses, is activated by retinoic acid and fibroblast growth factor-2 (FGF-2) in endothelial cells or by endotoxins and bleomycin in macrophages (99, 100). TGF-β is supposed to suppress effector cells in allergy such as mast cells, eosinophils and basophiles; however elevated levels of this factor may exacerbate the condition of allergic patients through other mechanisms such as airway structural changes in chronic asthma, which emanates from fibrogenicity and immunomodulating effects of this factor. Aside from tissue alterations, it mediates leukocyte chemotaxis to pulmonary tissues (101). Activation of the TGF-β receptor results in phosphorylation of serine/threonine residues, which induces phosphorylation of intracellular effectors (Smads). Smad proteins translocate to the nucleus and act as transcription factor of their target genes responsible for regulating various processes and cellular functions. TGF-β, through activating other non-Smad or Smad-independent signaling pathways such as p38, MAPK, PI3K-Akt, has an indirect role in apoptosis, mesenchymal-epithelial transition, migration, proliferation, differentiation, and extracellular matrix formation. Investigation on these activities can enhance the knowledge of TGF-β‘s role in both cancer and allergy. In advanced cancer, the ERK-MAPK pathway is activated by different growth factors including oncogenic RAS and TGF-β, which are frequently upregulated in cancer. Ambivalently, TGF-β acts as an antitumor agent in primary cancer stages probably through apoptosis of tumor cells (102). Moreover, TβRII and TβRI seem to be essential for activation of **PI3K-Akt signaling pathway** which was mentioned to be upregulated in NSCLC. Investigating precise role of TGF-β in mediating these mutual pathways, has the prospect of administering new therapeutic targets in cancer and allergy treatment. It also indicates that higher TGFβ in asthmatic patients have a prognosis of cancer development (99).

Atopic dermatitis (AD) is associated with immunologic responses, which make the most of the patients susceptible for asthma development. The condition is associated with elevated levels of Th17 and cytokine expression in peripheral blood, indicating the potential pathological role of this type of T helper cell. (103, 104). EGFR upregulation is also seen in inflammatory skin disorders, sharing a common feature with particular cancers like lung cancer and metastasis (105). This upregulation is hypothesized to have a protecting role as experimental studies have demonstrated that EGFR signaling suppresses Th17 cell differentiation and therefore, attenuates AD relapses. It’s been reported that cancer patients treated with EGFR tyrosine kinase inhibitor are prone to cutaneous inflammatory rash and associated increased IL17 serum level (106). These data can lead to a hypotheses that mechanisms involved in higher levels of EGFR signaling in AD patients may later participate in lung cancer development (107)(**Figure 1**).

Aside from associations of IL17 and TGF-β with tumorigenic pathways, these pleotropic cytokines could also influence components of immune system involved in both cancer and allergy. Enhanced levels of TGF-β in tumor microenvironment alternates the amount of antigen presentation and proliferation of Th1, cytotoxic T cells (CTL), etc. The effect of TGF-β on CTLs is shown to be mediated by IL17 secreting pathway as Th17 differentiation requires TGF-β (17). Therefore, allergic reactions to chemotherapies in cancer patients may be due to the high levels of IL17 which also exacerbates the tumor growth by inducing angiogenesis and cancer-associated inflammation. Angiogenesis in tumors can be inhibited by IFNγ secretion by NK cells, CTLs and Th1. But GATA3 overexpression (in allergy development) shunts the helper T cell differentiation from Th1 to Th2 cells. Therefore, decreased number of Th1 cells and their secreted IFNγ may result in defective antitumor responses and subsequent tumor progression (108-110)(**Figure 2**).

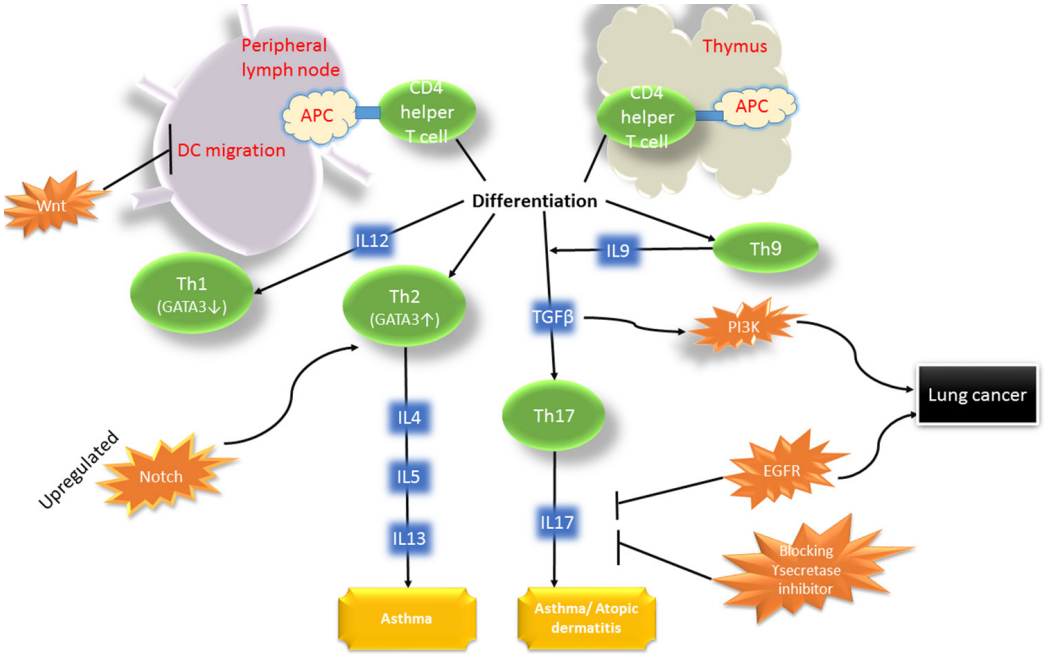

Figure 1. Interaction of allergy and tumorigenic pathways. Naïve CD4 T helper cells are activated through binding antigens presented on APCs. Sites of this activation could be in both thymus and peripheral lymph nodes. Migration of Dendritic cells to peripheral lymph nodes are required for antigen presentation. It has been studied that Wnt overexpression (A hallmark of specific cancers) could interfere with DCs' migration and T cell subsets differentiation. Activated CD4 T cells would differentiate to T helper subsets according to the cytokines they receive during activation. T helper cells, which receive IL12 would differentiate into Th1 cells due to the reduction in GATA3 expression. In the case of tissue damage resulted from Th1 excessive activity, GATA3 overexpression in helper T cells suppresses the effect of IL12 which would result in Th2 subset differentiation. Th2 are responsible for allergic responses due to the cytokines they produce (IL4, 5, 13). It has been studied that Notch pathway (an embryonic pathway upregulated in specific cancers) promotes GATA3 overexpression and subsequent Th2 differentiation and allergy developing. According to the time of antigen presentation, other subsets like Th9 and Th17 are also derived from Naïve CD4 T helper cells. Th9 secretes IL9 whose combination with TGFβ would induce Th17 differentiation and its IL17 secretion. IL17 is demonstrated to have roles in asthma and atopic dermatitis patients.
IL17 and TGFβ seem to bridge specific allergic diseases and cancers with multiple mechanisms. Overproduction of TGFβ and its receptors in advanced cancers could be responsible for upregulation of pathways involved in lung cancer such as PI3K-Akt. On the other hand, elevated levels of IL17 and Th17 in AD is hypothesized to be suppressed by EGFR pathway upregulation as a protective mechanism. Constant upregulation of this pathway may result in lung cancer in AD patients. Blocking embryonic pathways in cancer therapies like γ secretase inhibitors is reported to reduce levels of IL17; therefore, it attenuates allergy in these cancerous patients.

Conclusion

Determining a definite relationship between cancer and allergy on the basis of epidemiological studies is difficult because of interpersonal variations in cellular pathways and remarkable epigenetic differences in specific types of the allergy and cancers and methodological limitations. This can explain why epidemiological studies couldn't provide adequate data for significant association between these two diseases. Therefore, it will be more plausible to conduct further studies on biological mechanisms correlated between cancer and allergy concurrent with epidemiological studies which are still needed to be conducted. Examples of biological basis narrated in this article are cells and their associated molecules involved in allergic mechanisms, which also participate in some molecular pathways whose deregulation can lead to tumorigenicity such as TGF-β, important molecule in various immunologic events, effecting pathways like PI3K-Akt,

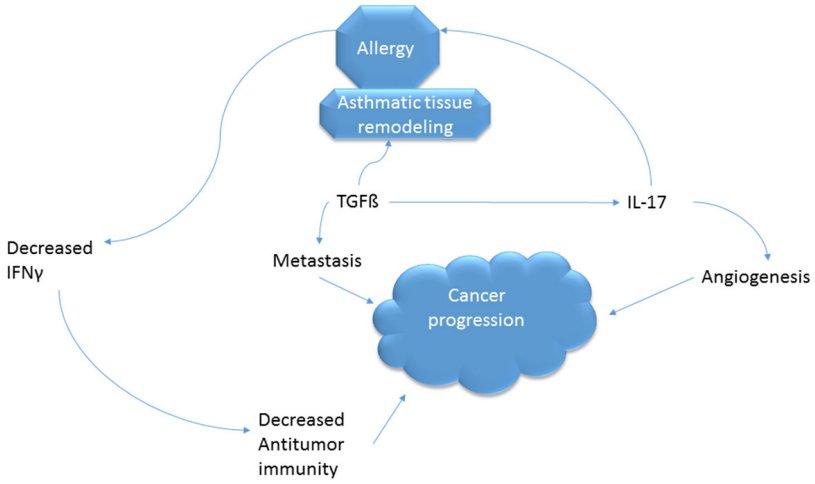

Figure 2. Associations of cytokines with allergy and cancer immunity. Several mechanisms are responsible for enhanced cancer progression such as metastasis, angiogenesis and reduced antitumor immunity. High levels of TGFβ leads to advanced cancer by inducing cancer cell invasiveness and metastasis. Another mechanism may be due to its role in inducing IL-17 secreting pathways and subsequent increase in angiogenesis by IL17. Increased levels of IL17 has also been reported to have pathological roles in allergy development. Aside from its cancer promoting roles, TGFβ participates in tissue remodeling in allergic patients like asthmatic differentiation of airway structures. Allergy development by these cytokines could result in defective IFNγ production. IFNγ has important roles in mediating immune responses against tumor cells. Therefore, decreased levels of IFNγ enhance cancer progression.

Wnt/Notch regulating T cell development and EGFR on Th17. Aside from that, environmental factors play a crucial role in occurrence of both cancer and allergy and this can be a basis of researches on mechanisms of correlation between these two phenomena. Due to the counteracting immune reactions, it has also been hypothesized that concurrence of these diseases may influence the prognosis of cancer in specific sites and its response to various targeted therapies as a result of allergic components or subsequent effects like accumulation of MDSCs.

Consequently, as there have been a lot of progresses in studying and understanding molecular mechanisms of allergy and cancer, understanding their exact interactions about how and up to what extent they influence each other can also help us to understand the diverse responses of patients to treatments, and clarify the role of various immune components in cancer immunotherapy.

Key issues

- Association of cancer with more easily diagnosed diseases like allergies can introduce new methods to detect cancer predisposing factors and prognosis in patients.
- Possible interactions of tumorigenic pathway deregulations and factors with concomitant allergies can lead to designing personalized therapies which consider the immunologic phenotype of patients which affects response to treatment and adverse events.
- Specific molecular and experimental researches through already hypothesized potential interactions need to be conducted to illustrate the effect of these two diseases on each other.

Conflict of Interest

The authors declare that they do not have any conflict of interests.

References

1. Blair GECook GP. Cancer and the immune system: an overview. Oncogene. 0000;7(45):5868-.
2. Makkouk AWeiner G. Cancer Immunotherapy and Breaking Immune Tolerance-New Approaches to an Old Challenge. Cancer res. 2015;75(1):5-10.
3. Hanahan DWeinberg RA. The Hallmarks of

Cancer. Cell.100(1):57-70.
4. Hatanpaa KJ, Burma S, Zhao DHabib AA. Epidermal Growth Factor Receptor in Glioma: Signal Transduction, Neuropathology, Imaging, and Radioresistance. Neoplasia. 2010;12(9):675-84.
5. Chang L, Graham P, Hao J, Ni J, Deng J, Bucci J, et al. Cancer stem cells and signaling pathways in radioresistance. Oncotarget. 2016;7(10):11002-17.
6. Liu P, Cheng H, Roberts TMZhao JJ. Targeting the phosphoinositide 3-kinase (PI3K) pathway in cancer. Nat Rev Drug Discov. 2009;8(8):627-44.
7. Feinberg APTycko B. The history of cancer epigenetics. Nat Rev Cancer. 2004;4(2):143-53.
8. Zhang Y, Elgizouli M, Schöttker B, Holleczek B, Nieters ABrenner H. Smoking-associated DNA methylation markers predict lung cancer incidence. Clin Epigenetics. 2016;8:127.
9. Jensen-Jarolim E, Achatz G, Turner MC, Karagiannis S, Legrand F, Capron M, et al. AllergoOncology: the role of IgE-mediated allergy in cancer. Allergy. 2008;63(10):1255-66.
10. Kumar S, Verma AK, Das MDwivedi PD. Molecular mechanisms of IgE mediated food allergy. Int Immunopharmacol. 2012;13(4):432-9.
11. Martin RK, Saleem SJ, Folgosa L, Zellner HB, Damle SR, Nguyen GKT, et al. Mast cell histamine promotes the immunoregulatory activity of myeloid-derived suppressor cells. J Leukoc Biol. 2014;96(1):151-9.
12. Sayour EJMitchell DA. Manipulation of Innate and Adaptive Immunity through Cancer Vaccines. J Immunol Res. 2017;2017:7.
13. He S, Yin T, Li D, Gao X, Wan Y, Ma X, et al. Enhanced interaction between natural killer cells and lung cancer cells: involvement in gefitinib-mediated immunoregulation. J Transl Med. 2013;11(1):186.
14. Du P, Xiong R, Li XJiang J. Immune Regulation and Antitumor Effect of TIM-1. J Immunol Res. 2016;2016:8605134.
15. Ivanova EAOrekhov AN. T Helper Lymphocyte Subsets and Plasticity in Autoimmunity and Cancer: An Overview. Biomed Res Int 2015;2015:327470.
16. Benchetrit F, Ciree A, Vives V, Warnier G, Gey A, Sautes-Fridman C, et al. Interleukin-17 inhibits tumor cell growth by means of a T-cell-dependent mechanism. Blood. 2002;99(6):2114-21.
17. Alshaker HAMatalka KZ. IFN-gamma, IL-17 and TGF-beta involvement in shaping the tumor microenvironment: The significance of modulating such cytokines in treating malignant solid tumors. Cancer Cell Int. 2011;11:33.
18. Yang L, Pang YMoses HL. TGF-beta and immune cells: an important regulatory axis in the tumor microenvironment and progression. Trends Immunol. 2010;31(6):220-7.
19. Lebrun J-J. The Dual Role of TGF in Human Cancer: From Tumor Suppression to Cancer Metastasis. ISRN Molecular Biology. 2012;2012:28.
20. Oleinika K, Nibbs RJ, Graham GJFraser AR. Suppression, subversion and escape: the role of regulatory T cells in cancer progression. Clin Exp Immunol. 2013;171(1):36-45.
21. Fu S, Zhang N, Yopp AC, Chen D, Mao M, Chen D, et al. TGF-beta induces Foxp3 + T-regulatory cells from CD4 + CD25 - precursors. Am J Transplant. 2004;4(10):1614-27.
22. Youn JIGabrilovich DI. The biology of myeloid-derived suppressor cells: The blessing and the curse of morphological and functional heterogeneity. Eur J Immunol. 2010;40(11):2969-75.
23. Parker KH, Beury DWOstrand-Rosenberg S. Myeloid-Derived Suppressor Cells: Critical Cells Driving Immune Suppression in the Tumor Microenvironment. Adv Cancer Res. 2015;128:95-139.
24. Gabrilovich DINagaraj S. Myeloid-derived-suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009;9(3):162-74.
25. Hu YFu L. Targeting cancer stem cells: a new therapy to cure cancer patients. Am J Cancer Res. 2012;2(3):340-56.
26. Keysar SBJimeno A. More than markers: biological significance of cancer stem cell-defining molecules. Mol Cancer Ther. 2010;9(9):2450-7.
27. Noori-Daloii MREbadi N. Pharmacogenomics and cancer stem cells. J Med Sci.

2015;25(1):1-15.
28. Cumberbatch M, Tang X, Beran G, Eckersley S, Wang X, Ellston RP, et al. Identification of a subset of human non-small cell lung cancer patients with high PI3Kbeta and low PTEN expression, more prevalent in squamous cell carcinoma. Clin Cancer Res. 2014;20(3):595-603.
29. Shtivelman E, Hensing T, Simon GR, Dennis PA, Otterson GA, Bueno R, et al. Molecular pathways and therapeutic targets in lung cancer. Oncotarget. 2014;5(6):1392-433.
30. Yamamoto H, Shigematsu H, Nomura M, Lockwood WW, Sato M, Okumura N, et al. PIK3CA mutations and copy number gains in human lung cancers. Cancer Res. 2008;68(17):6913-21.
31. Chalhoub NBaker SJ. PTEN and the PI3-Kinase Pathway in Cancer. Annu Rev Pathol. 2009;4:127-50.
32. Curry NL, Mino-Kenudson M, Oliver TG, Yilmaz OH, Yilmaz VO, Moon JY, et al. Pten-null tumors cohabiting the same lung display differential AKT activation and sensitivity to dietary restriction. Cancer Discov. 2013;3(8):908-21.
33. Akbay EA, Koyama S, Carretero J, Altabef A, Tchaicha JH, Christensen CL, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov. 2013;3(12):1355-63.
34. Inoue A, Kobayashi K, Usui K, Maemondo M, Okinaga S, Mikami I, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol. 2009;27(9):1394-400.
35. Handy DE, Castro RLoscalzo J. Epigenetic Modifications: Basic Mechanisms and Role in Cardiovascular Disease. Circulation. 2011;123(19):2145-56.
36. Li F, Mao G, Tong D, Huang J, Gu L, Yang W, et al. The histone mark H3K36me3 regulates human DNA mismatch repair through its interaction with MutSalpha. Cell. 2013;153(3):590-600.
37. Wagner KW, Alam H, Dhar SS, Giri U, Li N, Wei Y, et al. KDM2A promotes lung tumorigenesis by epigenetically enhancing ERK1/2 signaling. J Clin Invest. 2013;123(12):5231-46.
38. Lockwood WW, Wilson IM, Coe BP, Chari R, Pikor LA, Thu KL, et al. Divergent genomic and epigenomic landscapes of lung cancer subtypes underscore the selection of different oncogenic pathways during tumor development. PLoS One. 2012;7(5):e37775.
39. Berger A. Th1 and Th2 responses: what are they? Bmj. 2000;321(7258):424.
40. Bettelli EKuchroo VK. IL-12– and IL-23–induced T helper cell subsets: birds of the same feather flock together. J Exp Med. 2005;201(2):169-71.
41. Maspi N, Abdoli AGhaffarifar F. Pro- and anti-inflammatory cytokines in cutaneous leishmaniasis: a review. Pathog Glob Health. 2016;110(6):247-60.
42. Yuan M-L, Tong Z-H, Jin X-G, Zhang J-C, Wang X-J, Ma W-L, et al. Regulation of CD4+ T Cells by Pleural Mesothelial Cells via Adhesion Molecule-Dependent Mechanisms in Tuberculous Pleurisy. PLOS ONE. 2013;8(9):e74624.
43. Kaplan MH. Th9 cells: differentiation and disease. Immunol Rev. 2013;252(1):104-15.
44. Goswami RKaplan MH. A Brief History of IL-9. J Immunol. 2011;186(6):3283.
45. Coquet JM, Rausch LBorst J. The importance of co-stimulation in the orchestration of T helper cell differentiation. Immunol Cell Biol. 2015;93(9):780-8.
46. Jin WDong C. IL-17 cytokines in immunity and inflammation. Emerg Microbes Infect. 2013;2(9):e60-.
47. Agache IAkdis CA. Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine. Allergol Int 2016;65(3):243-52.
48. Sugita S, Kawazoe Y, Imai A, Kawaguchi T, Horie S, Keino H, et al. Role of IL-22- and TNF-alpha-producing Th22 cells in uveitis patients with Behcet's disease. J Immunol. 2013;190(11):5799-808.
49. Belkaid YHand Timothy W. Role of the Microbiota in Immunity and Inflammation. Cell. 2014;157(1):121-41.
50. Brembilla NC, Dufour AM, Alvarez M, Hugues S, Montanari E, Truchetet M-E, et al. IL-22 capacitates dermal fibroblast respons-

es to TNF in scleroderma. Ann Rheum Dis. 2016;75(9):1697.
51. Cesare AD, Meglio PDNestle FO. A Role for Th17 Cells in the Immunopathogenesis of Atopic Dermatitis? J Invest Dermatol. 2008;128(11):2569-71.
52. Yagi R, Zhu JPaul WE. An updated view on transcription factor GATA3-mediated regulation of T(h)1 and T(h)2 cell differentiation. Int Immunol. 2011;23(7):415-20.
53. Zhu JPaul WE. Peripheral CD4 T cell differentiation regulated by networks of cytokines and transcription factors. Immunol Rev. 2010;238(1):247-62.
54. Solomou EE, Keyvanfar KYoung NS. T-bet, a Th1 transcription factor, is up-regulated in T cells from patients with aplastic anemia. Blood. 2006;107(10):3983-91.
55. van Hamburg JP, de Bruijn MJ, Ribeiro de Almeida C, van Zwam M, van Meurs M, de Haas E, et al. Enforced expression of GATA3 allows differentiation of IL-17-producing cells, but constrains Th17-mediated pathology. Eur J Immunol. 2008;38(9):2573-86.
56. Yagi R, Junttila IS, Wei G, Urban JF, Jr., Zhao K, Paul WE, et al. The transcription factor GATA3 actively represses RUNX3 protein-regulated production of interferon-gamma. Immunity. 2010;32(4):507-17.
57. Yagi R, Zhu JPaul WE. An updated view on transcription factor GATA3-mediated regulation of Th1 and Th2 cell differentiation. International Immunology. 2011;23(7):415-20.
58. Burt TD. Fetal Regulatory T Cells and Peripheral Immune Tolerance in. Am J Reprod Immunol. 2013;69(4):346-58.
59. Maggi E. T cell responses induced by allergen-specific immunotherapy. Clin Exp Immunol. 2010;161(1):10-8.
60. Gorelik L, Constant SFlavell RA. Mechanism of Transforming Growth Factor β–induced Inhibition of T Helper Type 1 Differentiation. J Exp Med. 2002;195(11):1499-505.
61. Rachid RUmetsu DT. Immunological mechanisms for desensitization and tolerance in food allergy. Semin Immunopathol. 2012;34(5):689-702.
62. Chen WJ, Jin W, Hardegen N, Lei K, Li L, Marinos N, et al. Conversion of Peripheral CD4(+)CD25(−) Naive T Cells to CD4(+) CD25(+) Regulatory T Cells by TGF-β Induction of Transcription Factor Foxp3. J Exp Med. 2003;198(12):1875-86.
63. Workman CJ, Szymczak-Workman AL, Collison LW, Pillai MRVignali DAA. The Development and Function of Regulatory T Cells. Cell Mol Life Sci. 2009;66(16):2603-22.
64. Zozulya ALWiendl H. The role of regulatory T cells in multiple sclerosis. Nat Clin Pract Neuro. 2008;4(7):384-98.
65. Radulovic S, Jacobson MR, Durham SRNouri-Aria KT. Grass pollen immunotherapy induces Foxp3-expressing CD4+ CD25+ cells in the nasal mucosa. J Allergy Clin Immunol. 2008;121(6):1467-72, 72.e1.
66. Ganeshan KBryce PJ. Regulatory T cells enhance mast cell production of IL-6 via surface-bound TGF-beta. J Immunol. 2012;188(2):594-603.
67. Taylor A, Verhagen J, Blaser K, Akdis MAkdis CA. Mechanisms of immune suppression by interleukin-10 and transforming growth factor-β: the role of T regulatory cells. Immunology. 2006;117(4):433-42.
68. Akdis CAAkdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. World Allergy Organ J. 2015;8(1).
69. Oral HB, Kotenko SV, Yilmaz M, Mani O, Zumkehr J, Blaser K, et al. Regulation of T cells and cytokines by the interleukin-10 (IL-10)-family cytokines IL-19, IL-20, IL-22, IL-24 and IL-26. Eur J Immunol. 2006;36(2):380-8.
70. Zhang H, Kong H, Zeng X, Guo L, Sun XHe S. Subsets of regulatory T cells and their roles in allergy. J Transl Med. 2014;12(1):125.
71. Meiler F, Klunker S, Zimmermann M, Akdis CAAkdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. Allergy. 2008;63(11):1455-63.
72. El-Koraie AF, Baddour NM, Adam AG, El Kashef EHEl Nahas AM. Role of stem cell factor and mast cells in the progression of chronic glomerulonephritides. Kidney Int. 2001;60(1):167-72.
73. Stone KD, Prussin CMetcalfe DD. IgE, Mast Cells, Basophils, and Eosinophils. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S73-80.
74. Galli SJTsai M. IgE and mast cells in allergic

disease. Nat Med. 2012;18(5):693-704.
75. Hibbert RG, Teriete P, Grundy GJ, Beavil RL, Reljic R, Holers VM, et al. The structure of human CD23 and its interactions with IgE and CD21. J Exp Med. 2005;202(6):751-60.
76. Singer JJensen-Jarolim E. IgE-based immunotherapy of cancer: challenges and chances. Allergy. 2014;69(2):137-49.
77. Daines MO, Zornes PAKhurana Hershey GK. Signaling Interactions Between IL-4 or IL-13 and Leukotrienes in Allergic Inflammation. J Allergy Clin Immunol.119(1):S288.
78. Janeway CA Jr TP, Walport M immunobiology: The Immune System in Health and Disease. 5 ed. New York: Garland Science; 2001.
79. Allen JS, Eisma R, Leonard GKreutzer D. Interleukin-3 interleukin-5, and granulocyte-macrophage colony-stimulating factor expression in nasal polyps. Am J Otolaryngol. 1997;18(4):239-46.
80. Ala A, Dhillon AHodgson H. Role of cell adhesion molecules in leukocyte recruitment in the liver and gut. Int J Exp Pathol. 2003;84(1):1-16.
81. Yamaguchi M, Lantz CS, Oettgen HC, Katona IM, Fleming T, Miyajima I, et al. IgE Enhances Mouse Mast Cell FcεRI Expression In Vitro and In Vivo: Evidence for a Novel Amplification Mechanism in IgE-dependent Reactions. J Exp Med. 1997;185(4):663-72.
82. Tezza G, Mazzei FBoner A. Epigenetics of allergy. Early Hum Dev. 2013;89 Suppl 1:S20-1.
83. Jerrett M, Shankardass K, Berhane K, Gauderman WJ, Kunzli N, Avol E, et al. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. Environ Health Perspect. 2008;116(10):1433-8.
84. Lovinsky-Desir SMiller RL. Epigenetics, Asthma, and Allergic Diseases: A Review of the Latest Advancements. Curr Allergy Asthma Rep. 2012;12(3):211-20.
85. Koh BH, Hwang SS, Kim JY, Lee W, Kang MJ, Lee CG, et al. Th2 LCR is essential for regulation of Th2 cytokine genes and for pathogenesis of allergic asthma. Proc Natl Acad Sci U S A. 2010;107(23):10614-9.
86. Grausenburger R, Bilic I, Boucheron N, Zupkovitz G, El-Housseiny L, Tschismarov R, et al. Conditional deletion of histone deacetylase 1 in T cells leads to enhanced airway inflammation and increased Th2 cytokine production. J Immunol. 2010;185(6):3489-97.
87. Martner A, Wiktorin HG, Lenox B, Ewald Sander F, Aydin E, Aurelius J, et al. Histamine Promotes the Development of Monocyte-Derived Dendritic Cells and Reduces Tumor Growth by Targeting the Myeloid NADPH Oxidase. J Immunol. 2015;194(10):5014-21.
88. Kennedy L, Hodges K, Meng F, Alpini GFrancis H. Histamine and histamine receptor regulation of gastrointestinal cancers. Transl Gastrointest Cancer. 2012;1(3):215-27.
89. Medina VARivera ES. Histamine receptors and cancer pharmacology. Br J Pharmacol. 2010;161(4):755-67.
90. Kelemen LE. The role of folate receptor alpha in cancer development, progression and treatment: cause, consequence or innocent bystander? Int J Cancer. 2006;119(2):243-50.
91. Josephs DH, Spicer JF, Karagiannis P, Gould HJKaragiannis SN. IgE immunotherapy: A novel concept with promise for the treatment of cancer. MAbs. 2014;6(1):54-72.
92. Prizment AE, Vierkant RA, Smyrk TC, Tillmans LS, Lee JJ, Sriramarao P, et al. Tumor eosinophil infiltration and improved survival of colorectal cancer patients: Iowa Women's Health Study. Mod Pathol. 2016;29(5):516-27.
93. de Souza Junior DA, Santana AC, da Silva EZ, Oliver CJamur MC. The Role of Mast Cell Specific Chymases and Tryptases in Tumor Angiogenesis. Biomed Res Int. 2015;2015:142359.
94. Yoshii M, Jikuhara A, Mori S, Iwagaki H, Takahashi HK, Nishibori M, et al. Mast cell tryptase stimulates DLD-1 carcinoma through prostaglandin- and MAP kinase-dependent manners. J Pharmacol Sci. 2005;98(4):450-8.
95. Reuter S, Martin H, Beckert H, Bros M, Montermann E, Belz C, et al. The Wnt/beta-catenin pathway attenuates experimental allergic airway disease. J Immunol. 2014;193(2):485-95.
96. Wan YY. GATA3: A master of many trades in immune regulation. Trends Immunol. 2014;35(6):233-42.
97. Purow B. NOTCH INHIBITION AS A

PROMISING NEW APPROACH TO CANCER THERAPY. Adv Exp Med Biol. 2012;727:305-19.
98. Zhang W, Zhang X, Sheng A, Weng C, Zhu T, Zhao W, et al. γ-Secretase Inhibitor Alleviates Acute Airway Inflammation of Allergic Asthma in Mice by Downregulating Th17 Cell Differentiation. Mediat Inflamm. 2015;2015:7.
99. Tirado-Rodriguez B, Ortega E, Segura-Medina PHuerta-Yepez S. TGF-β: An Important Mediator of Allergic Disease and a Molecule with Dual Activity in Cancer Development. J Immunol Res. 2014;2014:15.
100. Kubiczkova L, Sedlarikova L, Hajek RSevcikova S. TGF-β – an excellent servant but a bad master. J Transl Med. 2012;10:183.
101. Makinde T, Murphy RFAgrawal DK. The regulatory role of TGF-beta in airway remodeling in asthma. Immunol Cell Biol. 2007;85(5):348-56.
102. Schuster NKrieglstein K. Mechanisms of TGF-beta-mediated apoptosis. Cell Tissue Res. 2002;307(1):1-14.
103. Koga C, Kabashima K, Shiraishi N, Kobayashi MTokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. J Invest Dermatol. 2008;128(11):2625-30.
104. Buffery D. The 2015 oncology drug pipeline: Innovation drives the race to cure cancer. Am Health Drug Benefits. 2015;8(4):216-22.
105. Bethune G, Bethune D, Ridgway NXu Z. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. J Thorac Dis. 2010;2(1):48-51.
106. Zhang Z, Xiao C, Gibson AM, Bass SAKhurana Hershey GK. EGFR signaling blunts allergen-induced IL-6 production and Th17 responses in the skin and attenuates development and relapse of atopic dermatitis. J Immunol. 2014;192(3):859-66.
107. Hagströmer L, Ye W, Nyrén OEmtestam L. Incidence of cancer among patients with atopic dermatitis. Arch Dermatol. 2005;141(9):1123-7.
108. Sun T, Yang Y, Luo X, Cheng Y, Zhang M, Wang K, et al. Inhibition of tumor angiogenesis by interferon-gamma by suppression of tumor-associated macrophage differentiation. Oncol Res. 2014;21(5):227-35.
109. Zhu J, Yamane HPaul WE. Differentiation of Effector CD4 T Cell Populations. Annu Rev Immunol. 2010;28:445-89.
110. Chung F. Anti-inflammatory cytokines in asthma and allergy: interleukin-10, interleukin-12, interferon-gamma. Mediat Inflamm. 2001;10(2):51-9.