Immune Boosters and Immunotherapy in Allergic Diseases and in Cancer Management

Abstract

Allergy and cancer are immune-mediated diseases presenting substantial clinical challenges. Immunotherapy, exploiting the immune system for therapeutic intervention, holds immense potential in their management. This review scrutinizes the immunotherapeutic landscape of allergic diseases and cancer, emphasizing their shared immunological underpinnings and therapeutic implications. Allergy manifests as exaggerated immune responses to innocuous antigens, culminating in inflammation and tissue damage. Immunotherapy for allergies aims at inducing immune tolerance to allergens, thereby alleviating symptoms and improving disease outcomes. Conversely, cancer employs multifaceted immune evasion mechanisms to evade immunosurveillance and propagate malignancy. Immunotherapeutic strategies in cancer endeavor to reinvigorate antitumor immunity and eradicate neoplastic cells. Notably, immune checkpoint inhibitors have emerged as a cornerstone in cancer immunotherapy, unleashing the immune system's potential to recognize and eliminate malignant cells. This review elucidates the intricate immunological mechanisms underlying allergy and cancer pathogenesis and delineates the diverse immunotherapeutic strategies employed in each context. It underscores the convergence of immunological principles and clinical applications in shaping the therapeutic landscape of allergic diseases and cancer. By synthesizing fundamental immunology with clinical insights, immunotherapy offers transformative prospects for personalized medicine. Recent advancements, including immune checkpoint blockade and adoptive cell therapy, have revolutionized the treatment paradigm in cancer.

Keywords: Allergy, Cancer, Immunotherapy, Immune boosters

1. Introduction

Introduction to Immune System Regulation

The immune system maintains homeostasis through a complex network of regulatory mechanisms. Following pathogen clearance, it shifts into a regulatory phase to prevent overactivity and ensure balanced immune responses (1). This regulatory phase is orchestrated by a multitude of checkpoint molecules and specialized immune cells, including regulatory T cells (Tregs), regulatory B cells (Bregs), regulatory dendritic cells (DCregs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages. These cells secrete immunomodulatory mediators such as interleukin-10 (IL-10) and transforming growth factor beta (TGFβ) to modulate immune responses and restore equilibrium (2).

Overview of Innate and Adaptive Immune Systems

The immune system comprises innate and adaptive components, each playing distinct roles in host defense. The innate immune system serves as the first line of defense against pathogens, utilizing innate immune cells and soluble factors at barrier sites such as the skin, respiratory tract, and gastrointestinal tract. Cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) orchestrate communication between immune cells and tissues, and targeting these cytokines holds promise for treating autoimmune diseases (2). The adaptive immune system, characterized by T and B lymphocytes, confers antigen-specific immune memory and mounts tailored responses to pathogens. Memory T and B cells provide long-lasting protection against reinfection and represent potential therapeutic targets for autoimmune disorders (2).

Immunological Mechanisms in Allergic Diseases

Allergic diseases result from dysregulated immune responses to innocuous environmental antigens, driven by aberrant Th2 cell activation and IgE-mediated hypersensitivity. Dysfunctional immunoregulatory mechanisms fail to suppress these exaggerated responses, exacerbating allergic symptoms. Allergen immunotherapy (AIT) aims to induce immune tolerance by promoting the expansion of regulatory T cells (Tregs) and the secretion of anti-inflammatory cytokines such as IL-10 and TGFβ. AIT also modulates B cell class switching towards allergen-specific IgG4 and IgA antibodies, attenuating allergic reactions (2).

Immune Modulation in Cancer Progression

In cancer, the interplay between tumor cells and the immune system dictates disease progression and treatment outcomes. Initially, the immune system mounts anti-tumor responses, eliminating nascent tumor cells. However, cancer cells employ various immune evasion strategies, including the recruitment of regulatory immune cell subsets such as regulatory T cells (Tregs), regulatory B cells, dendritic cells (DCregs), and M2 macrophages. These cells secrete immunosuppressive factors like IL-10 and vascular endothelial growth factor (VEGF), promoting immune tolerance and tumor progression (2). Tumor cells also contribute to immune suppression by producing IL-10 and enhancing metastatic potential.

Despite immune infiltration in tumors, the suppressive tumor microenvironment impedes effective anti-tumor immunity. Checkpoint inhibitor immunotherapy aims to counteract tumor-induced immune suppression by blocking inhibitory pathways and reinvigorating anti-tumor immune responses (2).

Mechanisms of Action of Immunotherapy

Allergen Immunotherapy (AIT): As discussed in section 3, AIT exploits several mechanisms to induce immune tolerance in allergic diseases. These include the expansion of Tregs, modulation of cytokine production, and a shift in B cell class switching (3).

Checkpoint Inhibitor Immunotherapy: This approach targets specific molecules on immune cells or tumor cells that normally put the brakes on immune responses. By blocking these checkpoints, immunotherapy unleashes the body's T cells to recognize and attack cancer cells.

CTLA-4 Blockade: CTLA-4 is a checkpoint molecule expressed on T cells that inhibits their activation. Drugs like ipilimumab block CTLA-4, allowing T cells to become more active and target cancer cells. Mechanism: Increases T cell activation and proliferation in the tumor microenvironment (Table 1).

PD-1/PD-L1 Blockade: PD-1 is another checkpoint molecule expressed on T cells, while PD-L1 is its ligand expressed on tumor cells and some immune cells. PD-1/PD-L1 interaction inhibits T cell activity. Drugs like pembrolizumab and nivolumab block this interaction, allowing T cells to recognize and attack cancer cells. Mechanism: Prevents T cell exhaustion and restores anti-tumor T cell activity (4) (Table 1).

Table 1. Checkpoint Inhibitor Drugs and their Targets

Checkpoint Molecule	Targeted Cell Type	Checkpoint Inhibitor Drug	Mechanism of Action
CTLA-4	T cells	Ipilimumab	Increases T cell activation and proliferation in the tumor microenvironment.
PD-1	T cells	Pembrolizumab, Nivolumab	Prevents T cell exhaustion and restores anti-tumor T cell activity

2. Approaches for Managing Immune Tolerance Therapeutically

Immunoregulating Allergens to Achieve Tolerance

Promoting immune tolerance through allergen immunotherapy (AIT) involves eliciting regulatory T and B cell responses, along with regulatory dendritic cells, which can produce the immunomodulatory cytokine IL-10. AIT induces the emergence of allergen-specific IgG1 and anti-inflammatory IgG4 antibodies (5). These IgGs act as blocking antibodies by intercepting allergens before crosslinking with allergen-specific IgE, interact with the inhibitory IgG receptor FcγRIIb to downregulate IgE-mediated signaling, or induce the differentiation of tolerogenic M2b macrophages (6). Despite advancements, the specific mechanisms underlying

immune tolerance induction and potential biomarkers for predicting clinical responses to AIT remain elusive (7).

Insights into Disrupting Tolerance in Cancer

Tumor cells and infiltrating immune cells create a tolerogenic microenvironment conducive to tumor growth and metastasis (8). Disrupting tumor tolerance has garnered interest, particularly with the clinical success of checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1 antibodies in melanoma treatment. CTLA-4 and PD-1 are crucial checkpoint molecules that limit T cell activation and promote immunological tolerance in cancer (9). Checkpoint inhibitors mitigate T cell inhibition, leading to enhanced anti-tumor immune responses (10). Clinical trials have demonstrated significant improvements in metastatic melanoma treatment with checkpoint inhibitors, including ipilimumab, nivolumab, and pembrolizumab. However, adverse autoimmune reactions underscore the risks associated with immune regulation interference (11). Ongoing clinical investigations explore the efficacy and safety of checkpoint inhibitors in various malignant diseases, with promising outcomes observed in non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), and classical Hodgkin lymphoma (cHL) among others (12, 13).

3. Navigating Immune Tolerance: Unveiling Molecular Insights from Allergy to Cancer

IgG4 Antibodies

In Allergy: Induced during allergen immunotherapy, IgG4 antibodies act as blocking antibodies, inhibiting allergen crosslinking with IgE, and interact with the inhibitory FcγRIIb receptor, dampening allergic responses.

In Cancer: Overexpression of IgG4 antibodies is observed in certain malignancies, often derived from intra-tumoral regulatory B cells (Bregs), and correlates with disease progression.

IgE and IgG Repertoires

In Allergy: IgE serves as the primary effector antibody in immediate-type allergies, binding to FcεRI receptors on mast cells and basophils, leading to allergic reactions. IgE clones exhibit increased persistence and are associated with other switched isotypes and larger clonal families.

In Cancer: Monoclonal IgE and IgG populations are observed in myelomas, and in B cell leukemia, small sub-clones re-emerge at relapse alongside dominant clones, suggesting clonal evolution dynamics.

Free Light Chains (FLC)

In Allergy: Elevated polyclonal FLC levels activate mast cells, contributing to allergic responses.

In Cancer: Elevated FLC levels serve as a prognostic biomarker for poor prognosis in basal-like breast cancer.

Regulatory Cytokines and Chemokines:

In Allergy: IL-10 and TGF-β play pivotal roles in establishing tolerance to allergens, while the CCL1:CCR8 axis is crucial in immune regulation.

In Cancer: IL-10 and TGF-β derived from both immune and cancer cells shape the immunosuppressive tumor microenvironment and correlate with disease progression. Chemokines such as CCL3, CCL4, and CCL5 from intratumoral myeloid-derived suppressor cells (MDSCs) can recruit regulatory T cells (Tregs) (14).

Mast Cell Mediators and Receptors:

In Allergy: Mast cells secrete mediators and cytokines supporting allergy and acute inflammation by interacting with IgE and other isotypes.

In Cancer: Mast cells exhibit a controversial role, with some mediators promoting tumor growth and neovascularization, while others inhibit tumor growth, induce apoptosis, and inhibit metastasis (15).

Lipocalins (LCN):

In Allergy: LCN sequesters iron, and its levels decrease in allergy; some allergens belong to the lipocalin family.

In Cancer: LCN and iron levels are upregulated in cancer, forming complexes with matrix metallopeptidase 9 (MMP-9), potentially contributing to tumor progression (9, 16).

4. CONCLUSION

Recent research highlights shared immune mechanisms in allergen immunotherapy and cancer immunology. Dendritic cells (DCs) and mast cells play crucial roles in both conditions, influencing immune tolerance and tumor microenvironment. Tumor-specific IgE disrupts DC-mediated tolerance, while regulatory immune cells and cytokines contribute to immunosuppression in cancer.

To strengthen immunity against allergies, maintaining optimal nutrition, managing stress, and incorporating immune-boosting compounds like zinc and vitamins are essential. Allergy shots and natural interventions aid in allergy management. Similarly, vitamins B, C, and glutathione support immune health and cancer management strategies.

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Conflicts of Interest

The authors declare no conflict of interests.

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