Mini Review

Immune Boosters and Immunotherapy in Allergic Diseases and in Cancer Management

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ABSTRACT

Allergy and cancer are immune-mediated diseases that present substantial clinical challenges, and immunotherapy, which exploits the immune system for therapeutic intervention, holds immense potential in their management. This review scrutinises the immunotherapeutic landscape of allergic diseases and cancer, emphasising their shared immunological underpinnings and therapeutic implications. Allergy manifests as exaggerated immune responses to innocuous antigens, culminating in inflammation and tissue damage. The therapeutic objective in the context of allergy is to induce 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 endeavour to reinvigorate antitumor immunity and eradicate neoplastic cells. A notable development in this field is the emergence of immune checkpoint inhibitors as a cornerstone in cancer immunotherapy, unleashing the immune system's potential to recognise 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 synthesising fundamental immunology with clinical insights, immunotherapy offers transformative prospects for personalised medicine, as evidenced by recent advancements, including immune checkpoint blockade and adoptive cell therapy, which have revolutionized the treatment paradigm in cancer.

Keywords: Allergy, Cancer, Immunotherapy, Immune Boosters.

1. Introduction

1.1. Introduction to Immune System Regulation

The immune system is responsible for maintaining homeostasis through a complex network of regulatory mechanisms. Following the clearance of pathogens, the immune system shifts into a regulatory phase with the aim of preventing overactivity and ensuring balanced immune responses (1). This regulatory phase is orchestrated by a multitude of checkpoint molecules and specialised 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).

1.2. Overview of Innate and Adaptive Immune Systems

The immune system is comprised of two distinct components: the innate and adaptive. The innate system serves as the primary line of defence against pathogens, utilising innate immune cells and soluble factors at barrier sites such as the skin, respiratory tract, and gastrointestinal tract. Cytokines, such as tumour necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6), orchestrate communication between immune cells and tissues, and the targeting of these cytokines holds promise for the treatment of autoimmune diseases (2).The adaptive immune system, characterised by T and B lymphocytes, confers antigen-specific immune memory and mounts tailored responses to pathogens. Memory T and B cells have been shown to provide long-lasting protection against reinfection and thus represent potential therapeutic targets for the treatment of autoimmune disorders (2).

1.3. Immunological Mechanisms in Allergic Diseases

Allergic diseases are the result of immune responses to innocuous environmental antigens which are dysregulated, driven by aberrant Th2 cell activation and IgE-mediated hypersensitivity. Dysfunctional immunoregulatory mechanisms fail to suppress these exaggerated responses, exacerbating allergic symptoms.The aim of allergen immunotherapy (AIT) is 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, thereby attenuating allergic reactions (2).

1.4. Immune Modulation in Cancer Progression

In the context of cancer, the dynamic interplay between tumour cells and the immune system is a pivotal factor determining both disease progression and treatment outcomes. Initially, the immune system mounts anti-tumour responses, resulting in the elimination of nascent tumour cells. However, cancer cells have developed 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, including IL-10 and vascular endothelial growth factor (VEGF), which promote immune tolerance and tumour progression (2).Tumour cells also contribute to immune suppression by producing IL-10 and enhancing metastatic potential. Despite immune infiltration in tumours, the suppressive tumour microenvironment impedes effective anti-tumour immunity. Checkpoint inhibitor immunotherapy aims to counteract tumour-induced immune suppression by blocking inhibitory pathways and reinvigorating anti-tumour immune responses (2).

1.4. Mechanisms of Action of Immunotherapy

Allergen Immunotherapy (AIT): As discussed in section 3, AIT employs various mechanisms to induce immune tolerance in allergic diseases, including the expansion of Tregs, the 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 tumour cells that normally inhibit immune responses. By blocking these checkpoints, immunotherapy unleashes the body's T cells to recognise 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 tumour microenvironment (Table 1). The PD-1/PD-L1 blockade is another mechanism that has been identified. Programmed cell death protein 1 (PD-1) is another checkpoint molecule expressed on T cells, while its ligand, programmed cell death protein 1 ligand 1 (PD-L1), is expressed on tumour cells and some immune cells. The PD-1/PD-L1 interaction is known to inhibit T cell activity. Drugs such as pembrolizumab and nivolumab have been developed to block this interaction, thereby allowing T cells to recognise and attack cancer cells. Mechanism: This results in the prevention of T cell exhaustion and the restoration of anti-tumour T cell activity (4) (Table 1).

2. Approaches for Managing Immune Tolerance Therapeutically

2.1. Immunoregulating Allergens to Achieve Tolerance

The promotion of immune tolerance through allergen immunotherapy (AIT) is achieved by the elicitation of regulatory T and B cell responses, in addition to regulatory dendritic cells, which have the capacity to produce the immunomodulatory cytokine IL-10. AIT has been demonstrated to induce the emergence of allergen-specific IgG1 and anti-inflammatory IgG4 antibodies (5). These immunoglobulins act as blocking antibodies by intercepting allergens before crosslinking with allergen-specific IgE, interacting with the inhibitory IgG receptor FcγRIIb to downregulate IgE-mediated signalling, or inducing the differentiation of tolerogenic M2b macrophages (6). Despite significant advancements in the field, the specific mechanisms underlying immune tolerance induction and

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

potential biomarkers for predicting clinical responses to AIT remain elusive (7).

2.2. Insights into Disrupting Tolerance in Cancer

The presence of tumour cells and infiltrating immune cells in the microenvironment fosters a tolerogenic state, which is conducive to tumour growth and metastasis (8).The disruption of tumour tolerance has garnered significant interest, particularly in the context of the clinical success of checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1 antibodies, in the treatment of melanoma.CTLA-4 and PD-1 represent pivotal checkpoint molecules that modulate T cell activation and promote immunological tolerance in cancer (9). Checkpoint inhibitors have been shown to mitigate T cell inhibition, thereby enhancing anti-tumour immune responses (10). Clinical trials have demonstrated significant improvements in metastatic melanoma treatment with checkpoint inhibitors, including ipilimumab, nivolumab, and pembrolizumab. However, the potential risks associated with immune regulation interference, as highlighted by adverse autoimmune reactions, underscore the need for careful consideration of benefits versus risks in the therapeutic decision-making process (11). Ongoing clinical investigations are exploring 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

3.1. IgG4 Antibodies

3.1.1. In Allergy

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

3.1.2. In Cancer

The present study has demonstrated that the expression of IgG4 antibodies is elevated in certain malignancies, frequently arising from intra-tumoral regulatory B cells (Bregs). This finding is indicative of a correlation between the expression of IgG4 antibodies and the progression of the disease.

3.2. IgE and IgG Repertoires

3.2.1. In Allergy

IgE is the principal effector antibody in immediate-type allergies. It binds to FcεRI receptors on mast cells and basophils, thus inducing allergic reactions. IgE clones demonstrate increased persistence and are linked with other switched isotypes and larger clonal families.

3.2.2. In Cancer

Monoclonal IgE and IgG populations have been observed in myelomas, and in B cell leukaemia, small sub-clones re-emerge at relapse alongside dominant clones, suggesting clonal evolution dynamics.

3.3. Free Light Chains (FLC)

3.3.1. In Allergy

Elevated polyclonal FLC levels have been demonstrated to activate mast cells, thus contributing to allergic responses.

3.3.2. In Cancer

Elevated FLC levels have been identified as a prognostic biomarker for basal-like breast cancer, indicating a poor prognosis for patients affected by this condition.

3.4. Regulatory Cytokines and Chemokines

3.4.1. In Allergy

IL-10 and TGF-β have been demonstrated to play pivotal roles in establishing tolerance to allergens, while the CCL1:CCR8 axis has been shown to be crucial in immune regulation.

3.4.2. In Cancer

It has been established that IL-10 and TGF-β, which are derived from both immune and cancer cells, shape the immunosuppressive tumour microenvironment and correlate with disease progression. Furthermore, chemokines such as CCL3, CCL4, and CCL5, which are derived from intratumoral myeloid-derived suppressor cells (MDSCs), have been shown to recruit regulatory T cells (Tregs) (14).

3.5. Mast Cell Mediators and Receptors

3.5.1. In Allergy

Mast cells are responsible for the secretion of various mediators and cytokines, which play a crucial role in the development of allergic responses and acute inflammation. These cells interact with various isotypes of immunoglobulins, including IgE, to facilitate these processes.

3.5.2. In Cancer

The role of mast cells is a contentious one, with some mediators promoting tumour growth and neovascularization, while others inhibit tumour growth, induce apoptosis, and inhibit metastasis (15).

3.6. Lipocalins (LCN)

3.6.1. In Allergy

LCN has been demonstrated to sequester iron, and its levels have been observed to decrease in allergy; some allergens have been found to belong to the lipocalin family.

3.6.2. In Cancer

Levels of LCN and iron are increased in cancer, forming complexes with matrix metallopeptidase 9 (MMP-9), which may contribute to tumour progression (9, 16).

4. Conclusion

Recent research has highlighted the presence of shared immune mechanisms in the domains of allergen immunotherapy and cancer immunology. Dendritic cells (DCs) and mast cells have been shown to play crucial roles in both conditions, influencing immune tolerance and the tumour microenvironment. Disruption of DC-mediated tolerance has been observed as a consequence of tumour-specific IgE, while regulatory immune cells and cytokines have been identified as contributing factors to immunosuppression in cancer. In order to strengthen immunity against allergies, it is essential to maintain optimal nutrition, manage stress, and incorporate immune-boosting compounds such as zinc and vitamins. Allergy immunotherapy and natural interventions are effective in the management of allergies, while vitamins B, C, and glutathione have been shown to support immune health and cancer management strategies.

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Authors' Contribution

Study concept and design: M.Y.N, Z.S, M.R.N.
Acquisition of data: M.R.N, S.A, Z.S, M.Y.N
Analysis and interpretation of data: G.M, A.B, M.A
Drafting of the manuscript: M.Y.N, Z.S, M.R.N
Critical revision of the manuscript for important intellectual content: M.R.N, Z.S, M.Y.N
Administrative, technical, and material support: M.R.N, Z.S S.A, M.Y.N

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare no conflict of interests.

Data Availability

The data that support the findings of this study are available on request.

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