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Personalized medicine: Harnessing the allergy cascade to disrupt solid tumors

Michael John Dochniak *

Alleamit Corporation, Minnesota, and the United States of America.

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Abstract

Harnessing the allergy cascade to target the extracellular matrix of solid tumors represents a frontier in immuno-oncology. Building upon advances in allergen-specific immunoglobulin E monoclonal antibodies and hyperallergenic skin creams, this approach leverages targeted degranulation to remodel the tumor microenvironment, enhance immune cell infiltration, and induce tumor cytotoxicity. This review examines the mechanistic rationale and emerging evidence for Passive Degranulation Cancer Immunotherapy.

Keywords: Allergy Cascade; Degranulation; Extracellular Matrix; Ige Monoclonal Antibodies; Tumor Microenvironment; Personalized Medicine

1. Introduction

Research on the extracellular matrix (ECM) is a vital and dynamic area of study in the field of solid tumors. Previously considered an inert scaffold, the ECM is now understood to be a crucial element of the tumor microenvironment. It plays an active role in driving cancer progression, metastasis, and treatment resistance [1].

Research focusing on the ECM explores the process of breaking down its physical barrier [2]. Collagen, glycoprotein, and proteoglycan are major non-cellular components of fibroblasts that remodel the ECM in solid tumors [3]. There is a potential for immunoglobulin E (IgE) antibodies to induce an “allergic” inflammatory response to these components based on the presence of IgE receptor-expressing immune effector cells in the tumor microenvironment [4]. Allergy-assisted cancer immunotherapy explores the use of forced atopy and the allergy cascade to alter the tumor microenvironment of solid tumors [5].

Advancements in the development of IgE monoclonal antibodies [6,7] and hyperallergenic skin creams [8] may make it possible to induce targeted degranulation in the ECM of solid tumors. Monoclonal antibodies are vital for patients who are immunocompromised or have a genetic predisposition to resist allergic reactions.

Passive degranulation cancer immunotherapy (PDCI) is an experimental approach that leverages allergic inflammation to disrupt the ECM. PDCI involves intratumoral injection of allergen-specific IgE monoclonal antibodies into solid tumors. Monoclonal antibodies can be chosen to have increased cross-reactivity to epitopes present on the non-cellular components of the ECM. Then, specific allergen exposure from hyperallergenic skin creams promotes a localized inflammatory response within the ECM. This cascade of events may compromise the ECM and inhibit the solid tumors' support structure, growth, and progression.

* Corresponding author: Michael John Dochniak

2. Description

2.1. Human IgE Monoclonal Antibodies

Monoclonal antibodies are vital for patients with severe malnutrition [9] or those with a genetic predisposition to resist allergic reactions [10].

Priming the ECM for allergic degranulation involves injecting human IgE monoclonal antibodies (hIgE mAb**)** into the solid tumor. The synthesis of hIgE mAb is possible because atopic individuals produce elevated levels of IgE in response to allergens, and techniques exist to cultivate allergen-specific hIgE mAb [11]. The hIgE mAb may be generated through advanced laboratory methods, such as human hybridoma technology [12] and single-cell sequencing [13]. hIgE mAb reduces the risk of developing FcεRI-mediated type I hypersensitivity because IgE-secreting plasma cells are not present [14]. The final product is an ultra-pure therapeutic protein, and any host cells used during manufacturing are removed during the extensive purification process [15].

Allergen-specific hIgE mAb may cross-react [16] with homologous epitopes on the non-cellular components of the ECM. The three major non-cellular components of the ECM are collagen, glycoproteins, and proteoglycans [17]. The allergen selected to produce the allergen-specific hIgE mAb may increase its affinity and avidity to the non-cellular component. Examples of non-cellular components and allergens that have homologous epitopes.

- Collagen; Bovine allergen [18], porcine allergen [19], and marine allergen [20].
- Glycoproteins: Alpha-gal allergen [21] and Horseradish peroxidase allergen [22]
- Proteoglycans: Proteoglycan allergen [23].

Solid tumors may contain the structural epitope amyloid-beta (Aβ). Research shows a complex relationship between amyloid proteins and cancer development. The presence of Aβ epitopes is in several types of solid tumors, like glioblastomas, melanomas, breast cancer, and pancreatic cancer. Two major non-cellular components of the ECM that have Aβ epitopes are extracellular amyloid fibrils and heparin sulfate proteoglycans [24]. Allergens with Aβ epitopes may be selected to produce allergen-specific hIgE mAb. For example, Research has shown that rubber elongation factor (Hev b 1) exhibits characteristics of an amyloid protein, with a high propensity for aggregation and a structure containing amyloid-beta sheets. Amyloid proteins are known for their propensity to misfold and aggregate into fibrils [25].

2.2. Hyperallergenic Skin Cream

The hyperallergenic skin cream has allergens with structural (Aβ) and linear epitopes [26]. After the solid tumor is injected with allergen-specific hIgE mAb, a hyperallergenic skin cream is applied. The allergens are absorbed through the skin and migrate into the solid tumor, triggering the allergy cascade and targeted degranulation. Optionally, the allergens can be injected directly into the solid tumor to accelerate targeted degranulation [27].

2.3. Mechanistic Rationale of PDCI

PDCI is a developing concept that works in two main steps

2.3.1. Step 1: Antibody Priming

Intratumoral injection of allergen-specific human IgE monoclonal antibodies (hIgE mAb) primes mast cells and basophils in the TME by binding FcεRI receptors. These antibodies are engineered to recognize epitopes homologous to ECM components such as collagen, glycoproteins, and proteoglycans

2.3.2. Step 2: Allergen Activation

Application of the hyperallergenic skin cream delivers a controlled dose of allergens systemically. Upon reaching the primed tumor site, the allergens bind to IgE-armed effector cells, triggering the release of mediators. For accelerated responses, allergens can also be delivered intratumorally by injection.

2.4. Tumor Microenvironment Remodeling

2.4.1. Physical barrier disruption

In solid tumors, a dense, stiff ECM forms a physical barrier that prevents immune cells from entering and effectively attacking cancer cells. Degranulation releases proteases, like tryptase and chymase, which may break down the ECM and reduce its stiffness. This "debulking" helps normalize the vascular network and makes the tumor more accessible to immune cells and therapeutics [28, 29]

2.4.2. Anti-tumor messaging

The degradation of the ECM also releases "matrikines," or protein fragments, that may promote anti-tumor functions and angiogenesis inhibition (new blood vessel formation) [30].

2.5. Direct Tumor Cell Cytotoxicity

2.5.1. Direct killing

The mediators released during targeted degranulation may be directly toxic to tumor cells. For instance, mast cells may release tumor necrosis factor-alpha, which may induce apoptosis (cell death) in certain cancer cells [31].

2.5.2. Anti-tumor mediators

Mast cells may be engineered to release anti-tumorigenic cytokines, effectively polarizing them into cytotoxic agents that directly attack tumor cells [32].

2.6. Enhanced Immune Cell Infiltration

2.6.1. Recruitment

The localized inflammatory response acts as a powerful signal to attract a range of anti-tumor immune cells to the TME. Mast cells may release chemokines such as CXCL10, CCL3, and CCL5, which help recruit cytotoxic CD8+ T cells and natural killer cells [33].

2.6.2. Repolarization

Allergy-induced degranulation may help overcome the immunosuppressive nature of ECM by altering the function of other immune cells. For example, it may shift the balance away from suppressive T regulatory cells toward anti-tumor effector T cells [34].

2.7. Frontier Opportunities for Synergy

2.7.1. Checkpoint Inhibitors

Combining PDCI with PD-1/PD-L1 or CTLA-4 inhibitors may enhance T-cell activation and tumor eradication [35].

2.7.2. Tumor Vaccines and CAR-T Cells

Leveraging ECM disruption may increase accessibility for tumor-targeted CAR-T therapies and neoantigen vaccines [36].

2.7.3. Microbiome Modulation

Emerging data suggest that tumor-resident microbiota shape immune responses; integrating microbiome profiling could further personalize PDCI [37].

2.8. Safety, Risks, and Regulatory Pathway

While PDCI offers targeted activity, risks such as systemic hypersensitivity and anaphylaxis must be mitigated through dose titration, rapid-response protocols, and real-time monitoring [38]. Regulatory classification will likely position hIgE mAb as a biologic under FDA CBER guidance, with combination-device oversight for the skin cream delivery system [39].

3. Conclusion

Immune-modulating skin cream and PDCI framework represent a frontier approach in oncology, merging precision immunology with patient-centric technology. By targeting the ECM through controlled IgE-mediated degranulation, this platform opens new avenues for enhancing immune infiltration, overcoming resistance mechanisms, and personalizing solid tumor therapy.

Compliance with ethical standards

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Michael John Dochniak (Co-Founder) of Alleamit Corporation, Minnesota, and the United States of America.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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