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(REVIEW ARTICLE)

Diet and mast cell recycling in AllergoOncology

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Abstract

Allergy-assisted cancer immunotherapy (AACI) leverages the body's allergy cascade to target and disrupt solid tumors. This approach involves injecting allergen-specific immunoglobulin E (IgE) antibodies and their pro-IgE macromolecules (allergens) directly into the tumor, thereby provoking a targeted acute allergic reaction. Maximal degranulation causes the tumor-associated mast cells to release a potent array of inflammatory and cytotoxic mediators to disrupt the tumor's stroma. Subsequently, these mast cells undergo an energy-demanding process of regranulation, enabling them to recycle and compete with tumor cells for nutrients. This review explores how macronutrients and micronutrients may affect tumor-associated mast cell recycling during AACI.

Keywords: AllergoOncology; Cancer immunotherapy; Maximal Degranulation; Diet; Macronutrients; Mast cells; Micronutrients; Regranulation

1. Introduction

Allergy-assisted cancer immunotherapy (AACI) [1] is an emerging experimental approach for treating solid tumors. AACI intentionally induces an acute allergic response within the tumor microenvironment by directly injecting allergen-specific IgE antibodies and their corresponding allergens into the tumor. This process degranulates tumor-associated mast cells (TAMCs), releasing potent mediators that can disrupt tumor integrity.

Upon maximal degranulation, TAMCs release high concentrations of bioactive mediators stored within their secretory granules. These mediators include chemokines (e.g., CCL3, CCL5, MCP-3, MCP-4), enzymes (such as chymase and granzyme-B), cytokines (IL-1, IL-4, IL-6, IL-9, TNF-α, XCL10), growth factors (colony-stimulating factor), proteins (cystatin-C), and other molecules (granulocyte-macrophage factors, heparin, reactive oxygen species) [2]. Collectively, these substances may disrupt the tumor stroma and weaken the tumor's structural integrity. Following degranulation, TAMCs undergo regranulation, replenishing their granules and enabling repeated cycles of activation. This process may deplete tumor resources and recruit additional immune cells to attack cancer cells. Supporting mast cell recycling through targeted nutritional interventions could enhance the effectiveness of AACI. Specific macronutrients (carbohydrates, fatty acids, amino acids) and micronutrients (minerals) may facilitate mast cell recovery and function during therapy.

The current standard of care for solid tumors includes surgery, chemotherapy, radiation therapy, and a growing array of immunotherapies such as checkpoint inhibitors and CAR T-cell therapy [3]. While these treatments have improved survival and quality of life for many patients, solid tumors frequently develop resistance or respond inadequately, especially in advanced diseases. Most established immunotherapies rely on T-cell- or antibody-mediated mechanisms and do not harness the acute allergic response or the unique biology of mast cells within the tumor microenvironment. Despite advances in cancer therapy, several unmet needs and persistent challenges remain in the treatment of solid tumors. Notably, the efficacy of current immunotherapies is often constrained by tumor resistance [4], immune

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suppression within the tumor microenvironment, and a lack of strategies that leverage alternative immune pathways—such as the response of TAMCs.

AACI is significant because it harnesses the body's acute allergic response to potentially overcome resistance to conventional treatments and improve outcomes for individuals with malignant solid tumors. This AllergoOncology strategy may pave the way for novel immunotherapies and deepen our understanding of how immune and cancer cells compete for nutrients. If validated, AACI could offer more targeted cancer therapies with fewer side effects. Furthermore, investigating how dietary interventions influence TAMC recycling may yield new insights into the biology of solid tumors and immune responses.

2. Discussion

2.1. Allergy-Assisted Cancer Immunotherapy

Allergy-assisted cancer immunotherapy (AACI) is an experimental approach that seeks to harness the body's acute allergic response [5] to target and eliminate malignant tumors. This emerging field, often referred to as AllergoOncology, explores the "paradoxical" relationship between allergies and cancer, where the overactive immune surveillance seen in allergic individuals may help protect against tumor development [6]. Passive monoclonal IgE antibodies can be used during AACI to reduce systemic allergic reactions [7]. The core mechanism of AACI is to cause TAMCs to degranulate and release inflammatory mediators within the tumor microenvironment. By triggering degranulation of TAMCs within or near a tumor, the resulting acute inflammation can disrupt tumor vasculature, induce cell death (apoptosis), and recruit additional immune cells to attack the cancer [8]. Subsequently, these degranulated TAMCs undergo an energy-demanding process of regranulation, enabling them to compete with tumor cells for vital nutrients. Dietary intervention may improve AACI by enhancing TAMCs recycling. When TAMCs degranulate, they release substances that can damage the tumor by disrupting the stroma. Afterward, these spent TAMCs regranulate—refilling their storage granules—so they can repeat the allergy cascade process. TAMCs' recycling can drain the solid tumor's resources and attract other immune cells to help fight cancer. Select macronutrients (carbohydrates, fatty acids, amino acids) and micronutrients (minerals) may be used to aid mast cell recycling during AACI.

2.2. Macronutrients

2.2.1 Carbohydrates

Foods low in carbohydrates may benefit AACI.

Carbohydrates are broken down in the body into glucose, which is then used by solid tumors as their primary energy source for growth and division. Cancer cells have a unique, highly active metabolism (the Warburg effect) that requires excessive glucose, often converting it to lactate even when oxygen is available [9].

Research confirms that glucose metabolism is essential for mast cell activation, serving as the primary energy source (ATP) for degranulation and regranulation. Glucose availability in the tumor stroma may directly affect the release of inflammatory mediators [10, 11].

In the core of solid tumors, intratumoral glucose levels are typically decreased. This occurs because cancer cells consume glucose at exceptionally high rates—often 20–30 times faster than normal cells—to fuel rapid proliferation [12]. TAMCs have evolved specific mechanisms to survive glucose scarcity. The transporter Slc37a2 enables them to scavenge metabolic intermediates (such as G6P) from the environment to fuel granule formation when pure glucose is low [13].

A ketogenic diet low in carbohydrates may be helpful during AACI, as TAMCs' recycling may compete for glucose, thereby reducing cancer cell metabolism and proliferation. Foods low in carbohydrates include meat, fish, eggs, butter, oils, avocados, and coconut. Low-carbohydrate beverages include coconut water, sugar-free soft drinks, and wine. It is recommended that carbohydrates make up 5% to 10% of daily calories [14].

2.2.2 Fatty Acids

Foods high in Omega-6 polyunsaturated fatty acids (PUFAs) may benefit AACI.

The fatty acid composition of the mast cell membrane directly regulates its sensitivity and the intensity of its inflammatory response. By altering the biophysical properties of the membrane—such as its fluidity and lipid raft

structure— PUFA (Arachidonic Acid) can prime mast cells to enhance degranulation/regranulation. Once TAMCs are triggered, a membrane rich in PUFA provides the raw material for a "pro-inflammatory storm" of leukotrienes and prostaglandins [15].

Leukotrienes

Leukotriene B4 (LTB4) is a potent lipid chemoattractant. LTB4 signaling via the BLT1 receptor is essential for recruiting cytotoxic CD8+ T cells into solid tumors. Research indicates that without this leukotriene signal, T cells may fail to infiltrate the tumor, potentially leading to immunotherapy failure [16].

Prostaglandins

During granular exocytosis, the release of prostaglandin E2 (PGE2) promotes angiogenesis (new blood vessel growth) in solid tumors. Solid tumors and angiogenesis are known to significantly increase the number of TAMCs [17]. These mast cells accumulate at the solid tumor boundary, where AACI can repurpose TAMCs to escalate stroma disruption. During granular endocytosis, Omega-6s are the primary precursors used by mast cells to produce PGE2.

Foods that are high in PUFA include refined vegetable oils, safflower oil, sunflower oil, corn oil, cottonseed oil, grapeseed oil, walnuts, almonds, sunflower seeds, cashews, pistachios, peanut butter, store-bought eggs, poultry, and pork. During AACI, it is recommended that foods high in Omega-6 make up 65% to 85% of daily calories.

2.2.3 Amino Acids

TAMCs regranulation (the resynthesis of granules after emptying) typically takes 24–48 hours and depends on the availability of specific building blocks and metabolic switches [18]. Several amino acids are critical for the overall biogenesis, maintenance, and regulation of TAMCs' granules. Consuming proteins rich in amino acids glutamine, arginine, and glycine may benefit AACI.

L-Glutamine serves as a critical metabolic fuel that supports TAMCs' degranulation/regranulation. During AACI, L-glutamine may increase mast cell protease II, histamine, and prostaglandin D2 (PGD2) [19]. L-glutamine-rich foods include beef, chicken, sardines, cod, eggs, dairy yogurt, and cottage cheese. Plant-based options include red cabbage, tofu, beans, almonds, walnuts, pistachios, hazelnuts, Brazil nuts, peanuts, and lentils.

Arginine is a critical amino acid for maintaining TAMC functional integrity, specifically by regulating TAMC granule proteases, such as tryptase and chymase [20]. L-arginine-rich foods include pumpkin seeds, peanuts, walnuts, almonds, turkey breast, chicken breast, soybeans, chickpeas, salmon, and spirulina.

Glycine is a critical component of serglycin, the dominant proteoglycan found in the secretory granules of TAMCs. Serglycin helps create a pro-angiogenic environment by regulating the secretion of growth factors, such as Vascular Endothelial Growth Factor and Hepatocyte Growth Factor, which promote the formation of new blood vessels, and by enhancing TAMC expression and its recycling in solid tumors. Glycine-rich foods include gelatin powder, pork skin snacks, chicken skin, beef brisket, beef chuck roast and shank, bone broth, mollusks, yellowfin tuna, and salmon. During AACI, it is recommended that amino acid-rich proteins account for 10% to 35% of daily calories.

2.3. Micronutrients

Minerals are not synthesized biochemically by living organisms [21]. The degranulation and subsequent regranulation of TAMCs are supported by the availability of specific minerals that affect signaling processes.

2.3.1 Minerals that Promote Degranulation

Degranulation requires a rapid influx of extracellular ions to trigger mediator release.

Calcium (Ca2+) is the most critical mineral for TAMCs' degranulation. Stimulation of specific receptors leads to calcium release from the endoplasmic reticulum, followed by a subsequent influx of extracellular calcium, which serves as the "obligatory signal" for granule exocytosis [22]. Foods high in calcium include dairy products (milk, yogurt, cheese), fortified beverages (soy/almond milk, orange juice), and canned fish with bones (such as sardines and salmon). Leafy greens like kale and collard greens, as well as chia seeds and tofu prepared with calcium sulfate, are also excellent sources. The recommended daily calcium intake is about 1,000–1,300 mg [23].

Zinc has complex, dose-dependent roles that can promote mast cell degranulation and regranulation. Zinc (Zn^{2+}) is essential for the translocation of granules to the plasma membrane. Zinc deficiency impairs TAMC activation, and specific zinc transporters (such as ZnT1 and ZnT5) are crucial for proper signaling and cytokine production. The recommended daily intake of zinc is about 11 mg for men and 8 mg for women. Foods high in zinc include meat, shellfish, and legumes [24].

Barium (Ba^{2+}) and strontium (Sr^{2+}) are divalent cations that may substitute for calcium in supporting mediator release from TAMCs [25]:

Foods high in barium (Ba^{2+}) include Brazil nuts, potatoes, onions, lettuce, wheat bran, and fish. The World Health Organization (WHO) and the U.S. EPA have established an oral reference dose of 0.2 mg/kg/day; and

Foods high in strontium (Sr^{2+}) include oysters, scallops, milk, yogurt, cheddar cheese, Brazil nuts, wheat bran, carrots, peas, lettuce, spinach, seaweed, cabbage, legumes, and peanuts. The recommended daily intake of strontium is approximately 1.9 mg [26].

2.3.2 Minerals that Inhibit TAMCs' Degranulation

Certain minerals can inhibit degranulation; therefore, supplemental magnesium and zinc should be avoided during AACI.

Magnesium (Mg^{2+})—including forms such as magnesium chloride ($MgCl_2$), magnesium sulfate ($MgSO_4$), magnesium glycinate, and magnesium orotate—acts as a natural calcium antagonist [27]. Elevated magnesium levels can stabilize mast cell membranes and significantly reduce degranulation by blocking calcium influx. Foods rich in magnesium include hemp seeds, chia seeds, black beans, edamame, dark chocolate, avocados, and bananas [28]. The recommended daily intake is about 310–420 mg. Magnesium typically stays in the body for 12 to 48 hours.

Zinc has complex, dose-dependent roles that can inhibit mast cell degranulation. Zinc [29], including zinc oxide nanoparticles [30,31], can inhibit TAMC degranulation by interfering with calcium entry through channels such as TRPM7. Foods high in zinc include oysters and crab. The recommended daily intake is 8–11 mg [32]. Zinc stays in the body for about 25 hours to two weeks.

Selenium supplementation, particularly through selenoproteins like glutathione peroxidase, suppresses the release of inflammatory mediators—including prostaglandin D2, beta-hexosaminidase, and histamine—by reducing oxidative stress and lowering reactive oxygen species (ROS) levels [33].

2.3.3 The Paradox

Research reveals a paradoxical role for zinc in mast cell biology. While zinc is essential for proper TAMC activation and granule translocation, it also serves as a potent mast cell stabilizer at higher concentrations. Both magnesium and zinc exhibit dose-dependent inhibition of degranulation, but zinc is far more effective at lower concentrations. For example, in vitro experiments show that significant degranulation reduction occurs with magnesium chloride only at concentrations above 50 mM, whereas zinc chloride achieves similar inhibition at just 25 μM [34]. Consequently, while zinc (and magnesium) supplementation should be avoided during AACI to ensure robust mast cell degranulation, higher levels of these minerals may be beneficial after AACI to promote TAMC stability and regranulation.

3. Conclusion

Allergy-assisted cancer immunotherapy (AACI) represents a novel and promising approach to treating solid tumors. By harnessing the acute allergic response and targeting tumor-associated mast cells within the tumor microenvironment, AACI addresses some major limitations of established cancer therapies, including immune evasion and therapeutic resistance. The integration of nutritional strategies to support mast cell recycling introduces a new dimension to immunotherapy, with the potential to further improve therapeutic outcomes. Ongoing research into AACI and the impact of dietary interventions will be crucial to optimizing this approach and developing more effective, less toxic cancer treatments. Ultimately, AACI may expand the therapeutic arsenal against solid tumors and improve patient survival and quality of life.

Compliance with ethical standards

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Grammarly was used for grammar, spelling, and punctuation throughout the review article preparation process. The tool (Grammarly, version 14.1271.0, Grammarly Inc., San Francisco, CA) was used to review and edit the entire review article for grammatical accuracy, clarity, and readability. Grammarly's AI-powered writing assistant provided suggestions on sentence structure, word choice, and tone consistency, which the author reviewed and selectively incorporated. The tool was not used to generate original scientific content, data analysis, or research conclusions. The author takes full responsibility for the integrity of all content generated and presented in this review article.

Disclosure of conflict of interest

The author claims no conflict of interest.

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