GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

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Superallergen-Assisted passive cancer immunotherapy and tertiary lymphoid structures

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GSC Advanced Research and Reviews, 2026, 27(01), 055-058

Publication history: Received on 27 February 2026; revised on 04 April 2026; accepted on 07 April 2026

Article DOI: https://doi.org/10.30574/gscarr.2026.27.1.0084

Abstract

Superallergen-assisted cancer immunotherapy (SAPCI) is an emerging AllergoOncology approach that harnesses the high-affinity binding properties of superallergens and passive immunoglobulin E (IgE) antibodies to induce targeted anti-tumor inflammation. The SAPCI protocol involves intratumoral administration of human IgE monoclonal antibodies—derived either from atopic donors or produced recombinantly—followed by the localized, controlled introduction of superallergens at the tumor site. This sequence triggers a robust acute inflammatory response, marked by mast cell and basophil degranulation and the release of potent anti-tumor mediators. These mediators orchestrate remodeling of the tumor vasculature, support the development of high endothelial venules, and promote recruitment of naïve T and B lymphocytes—processes essential for the maturation of tertiary lymphoid structures (TLS). Mature TLSs function as intratumoral immune hubs, fostering localized adaptive immune responses and correlating with improved outcomes in diverse solid tumor types. SAPCI faces translational hurdles, including the potential for anaphylaxis from superallergen dissemination and the need to precisely optimize dosing and delivery methods. This review examines the mechanistic basis for SAPCI's ability to promote mature TLS formation in solid tumors, offering a strategy to convert immunologically "cold" tumors into "hot" ones.

Keywords: Immunoglobulin E (IgE); Inflammation; Superallergens; Mast cells; Tertiary lymphoid structures (TLS); Tumor microenvironment (TME)

1. Introduction

Superallergen-assisted passive cancer immunotherapy (SAPCI) aims to bypass the limitations of a cancer patient's own immune system, particularly in cases of low immunogenicity or a highly immunosuppressive tumor microenvironment (TME).

Cancer immunotherapy has undergone a rapid transformation over the past decade, driven by breakthroughs in our understanding of tumor immunology and the complexities of the tumor microenvironment (TME). Immune cell-based therapies have achieved significant clinical success; however, many solid tumors remain resistant to these approaches, in part due to insufficient local immune activation [1].

Most significantly, immunoglobulin E (IgE) mediated allergic responses have been recognized as relevant to cancer inhibition [2]. Emerging evidence supports this paradigm, suggesting that the unique immunological properties of IgE—including its exceptionally high affinity for Fc epsilon receptor-I (FcεRI) receptors and capacity to activate potent effector cells such as mast cells and basophils—can be therapeutically harnessed [3].

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Recent research underscores the critical importance of tertiary lymphoid structures (TLS)—organized aggregates of immune cells that resemble secondary lymphoid organs—in orchestrating effective anti-tumor immunity within the TME. TLS acts as a local hub for antigen presentation, B and T cell activation, and the generation of high-affinity tumor-specific antibodies, and their presence correlates strongly with improved patient outcomes [4].

SAPCI builds on these insights, employing the passive transfer of human IgE antibodies [5] and localized exposure to superallergens that bind to the variable regions of immunoglobulin E (IgE) antibodies [6,7] and trigger targeted acute inflammation within the tumor milieu. This cascade may break local immunosuppression, remodel the TME, and promote the maturation of TLS, thus enhancing the breadth and efficacy of anti-tumor immunity.

This review explores the mechanistic rationale for SAPCI's potential to promote the formation of mature TLS within solid tumors. It emphasizes intratumoral injections of human IgE antibodies and superallergens/superantigens to amplify a localized allergic response. The review also examines how SAPCI may transform immunologically "cold" tumors into "hot" tumors. Finally, it highlights key unanswered questions and outlines future research directions for the safe and effective clinical implementation of SAPCI.

2. Discussion

2.1. Mechanistic Rationale

SAPCI functions via two sequential steps. First, human immunoglobulin E (IgE) antibodies—sourced from atopic donors or generated as recombinant monoclonal IgE—are injected directly into the tumor. Second, a superallergen is administered intratumorally to provoke an acute, localized inflammatory response through degranulation. This process activates tumor-associated effector cells such as mast cells, basophils, and macrophages that express FcεRI receptors. When exposed to the superallergen, the IgE-primed effector cells undergo degranulation, releasing a diverse array of anti-tumor mediators, including TNF-alpha, GM-CSF, IL-1, and IL-18 [8].

2.2. Mechanistic Hurdle

Limiting "superallergens" to the tumor site to prevent systemic IgE cross-linking. Intratumoral delivery is a strategic method to confine superallergens within the tumor microenvironment (TME), maximizing their therapeutic concentration while minimizing the risk of life-threatening systemic allergic reactions. This localized approach is designed to prevent systemic IgE cross-linking, which occurs when allergens enter the bloodstream and trigger mast cells or basophils throughout the body.

2.3. Mature Tertiary Lymphoid Structures

SAPCI may promote the formation of mature tertiary lymphoid structures by triggering a robust, localized cytokine storm—characterized by mediators such as IFN-gamma, TNF-alpha, and IL-4/IL-13—within the tumor microenvironment (TME). This acute inflammatory milieu may convert immunologically "cold" tumors into "hot" ones. The ensuing response may accelerate TLS maturation by coordinating lymphocyte recruitment [9], driving B-cell follicle organization [10], remodeling vasculature into high endothelial venules, and maintaining the structural integrity of the niche [11], and superallergen amplification that can engage a massive, polyclonal pool of IgE-sensitized mast cells and basophils. [12].

2.4. Safety Considerations

A key concern is the safety of deliberately inducing a localized acute allergic response in cancer patients, many of whom may be immunocompromised or particularly susceptible to adverse events [13].

The potential for systemic anaphylaxis and off-target effects necessitates thorough evaluation in preclinical and early-phase clinical trials. Furthermore, determining the most effective superallergens, dosing regimens, and delivery methods remains essential to maximize therapeutic benefit while minimizing risk [14].

Another important area of research is the characterization and monitoring of tertiary lymphoid structure (TLS) formation and function within cancerous solid tumors. Although TLS presence correlates with improved outcomes across several cancer types, the mechanisms underlying their contribution to anti-tumor immunity remain incompletely understood [15]. Progress in imaging, biomarker identification, and single-cell analysis will be vital for developing non-invasive tools to monitor TLS dynamics and predict response to therapy [16].

The heterogeneity of tumor microenvironments among cancer types and patient populations poses a significant translational challenge. Variables such as tumor mutational burden, baseline immune infiltration, and the prevalence of immunosuppressive cells may affect SAPCI efficacy. Personalized strategies incorporating comprehensive tumor and immune profiling will likely be required to identify patients who stand to benefit most from this therapy [17].

Ethical and regulatory considerations will also be crucial as SAPCI advances toward clinical implementation. Rigorous clinical trial design, robust informed consent procedures, and diligent post-marketing surveillance are paramount for safeguarding patient safety and maintaining public trust [18].

3. Conclusion

Superallergen-assisted passive cancer immunotherapy offers promising potential to broaden the scope of cancer immunotherapy. Its successful translation will demand multidisciplinary collaboration, ongoing mechanistic research, and rigorous safety and efficacy assessment. Overcoming these challenges could enable the development of novel immune-based therapies for patients with refractory solid tumors.

Compliance with ethical standards

Acknowledgments

Artificial intelligence technology was used in the preparation of this review article. Gemini AI (version 2.5 Pro, Google LLC, Mountain View, CA) was used during the research period of March 2026.

Grammarly was used for grammar, spelling, and punctuation throughout the preparation of the review article. 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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