



Cholera toxin and breast cancer: Immunological insights and therapeutic opportunities

Zahra Keshvari¹, Raheleh Sheikhi^{2*} 

1. Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
2. Department of Microbiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

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Despite major advances in diagnosis and treatment, breast cancer continues to represent one of the most prevalent malignancies and a leading cause of cancer-related morbidity and mortality worldwide [1]. Growing recognition of the pivotal role of anti-tumor immunity has stimulated interest in unconventional immunomodulatory agents [2]. Among these, cholera toxin (CT) and its non-toxic B subunit (CTB) have re-emerged as promising biotools because of their capacity to modulate antigen presentation, target GM1 gangliosides on cell membranes, and function as delivery scaffolds for immunogens or therapeutic payloads [3].

Recent mechanistic studies provide a compelling rationale for the use of CTB as an immunological adjuvant. Tepale-Segura et al. demonstrated that CTB induces trained immunity in dendritic cells by enhancing TNF- α production, LDH expression, and co-stimulatory activity following secondary stimulation. Moreover, CTB-trained dendritic cells exhibited improved antigen-presenting capacity and promoted enhanced proliferation and functional activity of CD8⁺ T cells. In a murine melanoma model, CTB-induced trained immunity significantly reduced tumor growth and increased tumor-free survival through enhanced infiltration of activated dendritic cells and reinvigoration of exhausted CD8⁺ T cells [4]. In addition, studies evaluating CTB derivatives as adjuvants have demonstrated augmented anti-tumor immune responses together with reduced melanoma and breast cancer metastasis, thereby highlighting the translational promise of toxin-derived immunomodulatory platforms [5].

Preclinical carcinogenesis studies further suggest that CT may influence mammary tumor biology. Afaloniati et al. reported that peri-weaning CT exposure suppressed overall tumor incidence and multiplicity, with variable efficacy across different cancer types, while also improving survival in mice [6]. Similarly, Argyris et al. demonstrated that early-life oral administration of CT reduced mammary cancer incidence and was associated with alterations in bone morphogenetic protein (BMP) and Notch signaling pathways, both of which are critically involved in mammary epithelial homeostasis and tumorigenesis, thereby providing a plausible mechanistic basis for CT-mediated modulation of carcinogenic processes [7].

Although these findings are derived from animal models, they support the hypothesis that CT/CTB may reshape tumor-promoting niches through both immune-related and developmental signaling pathways. Population-level observations provide an additional epidemiological perspective.

*Corresponding Author(s):

Raheleh Sheikhi, PhD

Address: Department of Microbiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

Tel: +98 13 33690099

E-mail: sheikhirahele@gmail.com



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Zheng et al. reported an association between post-diagnostic cholera vaccination and improved survival outcomes among patients with breast cancer in a large cohort study [8]. While residual confounding limits definitive causal interpretation, this association is consistent with a potential immunomodulatory effect of CT-containing vaccines that warrants further investigation. From a translational perspective, high affinity of CTB for GM1 gangliosides, which are frequently enriched within lipid rafts of malignant cells, offers a rational targeting strategy for the selective delivery of immunogens or cytotoxic cargoes [9]. Furthermore, CTB has previously been utilized as a neuronal tracer and as a targeting component in preclinical delivery systems, emphasizing its versatility as a modular scaffold for tumor-directed therapeutic approaches [10].

Taken together, mechanistic, preclinical, and epidemiological evidence suggests that cholera toxin and its subunits may represent versatile and multifunctional platforms with potential applications in breast cancer therapy, including use as adjuvants, targeting ligands, or components of combinatorial immunotherapeutic strategies. Nevertheless, prior to clinical translation, comprehensive evaluation of safety profiles, dose-response relationships, and potential off-target GM1 interactions remains essential. We therefore urge the oncology and immunology communities to prioritize translational studies aimed at clarifying the biological effects of CT/CTB within the breast tumor microenvironment and assessing their feasibility for early-phase clinical evaluation.

Declaration of artificial intelligence (AI) in the writing process

The authors declare whether AI or AI-assisted technologies were used during the preparation of this manuscript. If used, AI tools were employed solely to improve language quality, grammar, readability, and organizational structure. The authors carefully reviewed and edited all AI-generated content and take full responsibility for the accuracy, integrity, and originality of the final manuscript. No AI tool was used to generate, analyze, or interpret scientific data or images, or to draw scientific conclusions. The use of AI-assisted technologies complies with current publication ethics recommendations and journal policies.

Authors' contributions

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Conflict of interest

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