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Trained Immunity in Cancer: Pathways, Strategies and Emerging Therapies

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ABSTRACT

Cancer immunotherapy has revolutionized oncological treatment; yet, its efficacy is compromised by the immunosuppressive Tumor Microenvironment (TME) and limited T-cell responses. Trained immunity, a newly recognized feature of the innate immune system characterized by memory-like functional reprogramming, offers a viable supplementary approach to enhance immune responses against cancers. Unlike adaptive immunity, which relies on specific antigen recognition, trained immunity augments the readiness of innate immune cells via epigenetic and metabolic reprogramming, facilitating more vigorous responses to subsequent stimuli. Innate immune cells, including as monocytes, macrophages, and natural killer (NK) cells, are essential to this phenomenon. Their enhanced functional state, achieved through exposure to microbial ligands or immunomodulatory agents such as BCG or β-glucans, results in increased cytokine production, elevated phagocytic activity, and greater cytotoxicity in subsequent encounters with infections or tumor antigens. These trained responses are transient but can be maintained through the reprogramming of Hematopoietic Stem and Progenitor Cells (HSPCs), hence promoting long-term enhancement of innate immunity. This review comprehensively analyzes the molecular and cellular mechanisms behind trained immunity, including its induction via histone modifications, DNA methylation, and shifts in cellular metabolism. We examine the therapeutic relevance of trained immunity in cancer treatment, particularly its role in enhancing the efficacy of existing medicines, such as immune checkpoint inhibitors and cancer vaccines. We highlight novel approaches employing nanoparticles for the direct delivery of therapeutics that stimulate trained immunity within the tumor microenvironment, thereby improving treatment efficacy and minimizing systemic toxicity. Integrating trained immunity into cancer immunotherapy frameworks is a viable strategy to tackle critical challenges such as immune evasion, antigen heterogeneity, and resistance to conventional medicines. Trained immunity can alter the innate immunological environment, potentially promoting a more robust, sustained, and personalized anti-tumor immune response.

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Introduction

The immune system is essential for detecting and eliminating cancerous cells. Immunological memory has conventionally been seen as a defining feature of adaptive immunity, mediated by T and B cells. Recent discoveries have altered this paradigm by identifying "trained immunity," a concept that refers to the memory-like behavior of innate immune cells, such as monocytes, macrophages, dendritic cells (DCs), and natural killer (NK) cells [1]. Unlike the antigen-specific memory of the adaptive immune system, trained immunity is characterized by its antigen independence and is marked by enhanced responsiveness upon repeated activation, predominantly driven by epigenetic and metabolic reprogramming [2,3].

This tendency was first seen following BCG vaccination, during which monocytes exhibited heightened cytokine production upon subsequent exposure to unrelated illnesses [4]. Trained immunity involves molecular alterations in histones, DNA methylation, and a metabolic shift towards glycolysis, enhancing the ability of innate cells to produce a more robust inflammatory response. These modifications not only protect against subsequent infections but have also demonstrated potential in cancer, where immune system evasion is a key feature [5].

Given that malignancies often manipulate the Tumor Microenvironment (TME) to suppress T-cell responses and elude immune detection, strategies that utilize the adaptability of innate immune cells may provide a broader, antigen-independent aspect of immunosurveillance. Trained immunity enhances the effectiveness of innate cells, and its integration into cancer immunotherapy may mitigate the issues of antigen heterogeneity and immune evasion mechanisms [6].

The discovery that Hematopoietic Stem and Progenitor Cells (HSPCs) can retain acquired traits and pass them to their progeny underscores the potential for lasting enhancement of the innate immune response [7].

This study examines the molecular basis of trained immunity, assesses its clinical relevance in cancer immunotherapy, and explores novel ways, such as nanoparticle-based delivery systems, to improve its anti-tumor effectiveness.

Immunological memory has traditionally been attributed solely to adaptive immune cells. However, research accumulated over the past decade has challenged this notion by revealing that innate immune cells can exhibit memory-like traits through a phenomenon termed "trained immunity" [8]. Unlike adaptive memory, trained immunity is antigen-independent and involves

lasting functional alterations in innate cells triggered by initial exposure to microbial ligands or danger signals. These alterations enhance resilience in responding to future challenges, regardless of the specific stimulus.

Trained immunity is enabled via epigenetic reprogramming and metabolic reconfiguration in monocytes, macrophages, dendritic cells, and natural killer cells. This potential has profound implications for cancer immunotherapy, particularly in malignancies that evade adaptive immune responses. Employing trained immunity can alleviate immune suppression within the tumor microenvironment and bolster enduring anti-tumor responses [9].

Mechanisms of Trained Immunity

Epigenetic and Metabolic Reprogramming

Trained immunity is activated by alterations in gene expression influenced by histone methylation (e.g., H3K4me3), DNA methylation, and variations in chromatin accessibility. A metabolic transition from oxidative phosphorylation to aerobic glycolysis (the Warburg effect) occurs concurrently, augmenting energy generation and biosynthetic activity [9].

The essential physiological mechanisms involved include the mTOR and HIF-1α signaling pathways, which promote glycolysis, while persistent epigenetic markers maintain an increased transcriptional state despite the lack of the initial stimulus. Upon restimulation, these trained cells exhibit an enhanced cytokine response and increased effectiveness in eradicating infections or malignancies [8].

Role of Hematopoietic Stem and Progenitor Cells (HSPCs)

Despite the brief lifespans of several innate immune cells, trained immunity can endure owing to reprogramming at the level of bone marrow hematopoietic stem and progenitor cells (HSPCs). Agents such as BCG and β-glucan modify HSPCs to produce progeny with enhanced characteristics. This guarantees a continuous reservoir of activated innate cells that can swiftly respond to tumor-associated signals [9,10].

Tissue-Specific Training with Interferon-Gamma

Interferon-Gamma (IFN-γ) is essential not only as an effector cytokine in immune responses but also as a significant modulator of trained immunity in a tissue-specific context. Recent investigations have shown that IFN-γ can activate innate immune cells, including macrophages and natural killer cells, resulting in improved functional responses following further stimulation. The priming impact is contingent upon the tissue microenvironment, which affects the epigenetic and metabolic reprogramming that constitutes trained immunity [11,12]. Exposure to IFN-γ in lung-resident macrophages can elicit an enhanced state of vigilance, hence augmenting host defense against respiratory infections [2]. Furthermore, IFN-γ-mediated conditioning has been demonstrated to influence hematopoietic stem and progenitor cells in the bone marrow, resulting in enduring systemic immunological modifications [7]. Comprehending the tissue-specific impacts of IFN-γ is crucial for therapeutically utilizing trained immunity, especially regarding infectious illnesses and cancer immunotherapy.

Clinical Utilization in Cancer Immunotherapy

BCG in Non-Muscle-Invasive Bladder Carcinoma (NMIBC)

BCG remains the standard for the management of NMIBC. It functions by provoking both adaptive and Trained innate reactions. Intravesical BCG stimulates enhanced production of TNF and IL-1β, mediated via the epigenetic reprogramming of monocytes. Clinical correlations demonstrate improved disease-free survival in patients displaying stronger innate memory signatures [2,12,13].

Additional Inducers: β-Glucans and Muramyl Dipeptides

In addition to conventional stimuli such as Bacillus Calmette-Guérin (BCG), other inducers such β-glucans and Muramyl Dipeptides (MDPs) have been identified as effective modulators of trained immunity. β-Glucans, polysaccharides sourced from fungal cell walls, activate innate immune cells via pattern recognition receptors like Dectin-1, resulting in increased cytokine production and epigenetic reprogramming that provides enduring protection against future infections [14,15]. Likewise, muramyl dipeptides, constituents of bacterial peptidoglycan, engage nucleotide-binding oligomerization domain-containing protein 2 (NOD2) receptors to elicit metabolic and transcriptional alterations that maintain the trained immune phenotype [16,17]. The supplementary inducers broaden the range of substances that might provoke trained immunity, providing valuable resources for vaccination adjuvant advancement and immunotherapeutic strategies.

Induction of Trained Immunity by Nanoparticle-Based Approaches

Nanotechnology has presented innovative methods for inducing trained immunity. Metallic nanoparticles (MNPs), including iron oxide, silver, and gold, can reprogram immune cells by directly administering immuno-stimulatory agents to the Tumor Microenvironment (TME). Significant effects include: M1 polarization of macrophages, activation of the STING pathway and generation of IFN-β, enhanced NK cell cytotoxicity, and T-cell recruitment. Ferritin-based nanoparticles and PEGylated carriers have shown efficacy in improving antigen distribution and facilitating trained immune activation in preclinical breast cancer models. Furthermore, nanoparticle platforms diminish systemic toxicity while promoting localized immune activation [18].

Recent studies have emphasized the burgeoning function of nanoparticles in regulating trained immunity, presenting potential opportunities for innovative treatment techniques. Magadán et al. (2021) presented a thorough examination of the interactions between diverse nanoparticles and the innate immune system, highlighting their capacity to elicit trained immunity and subsequently augment immune responses in a regulated fashion [19]. Zarenezhad et al. (2023) investigated metallic nanoparticles, illustrating their ability to induce trained immune mechanisms that could enhance breast cancer immunotherapy efficacy [18]. Furthermore, Pan et al. (2022) demonstrated that β-glucan-conjugated superparamagnetic iron oxide nanoparticles efficiently elicit trained immunity in mouse models, leading to enhanced protection against sepsis, hence highlighting the therapeutic potential of nanoparticle-mediated immune training [20]. Van Leent et al. (2022) examined the extensive applications of nanomedicine in modulating trained immunity, highlighting the precise engineering of nanomaterials to modulate innate immunological memory [21]. The findings indicate that nanotechnology-based modulation of trained immunity is a promising advancement in immunotherapy and the management of infectious diseases.

Trained Immunity Beyond Infection: Implications in Non-Communicable Diseases

Initially characterized in relation to host defense against infections, trained immunity has become a significant element in the pathophysiology of various non-communicable inflammatory and autoimmune disorders. These encompass atherosclerosis,

rheumatoid arthritis, Systemic Lupus Erythematosus (SLE), and metabolic problems including diabetes mellitus [22,23].

Trained immunity plays a well-defined function in chronic disease, particularly in atherosclerosis, where the exposure of monocytes and macrophages to endogenous Damage-Associated Molecular Patterns (DAMPs) or microbial ligands elicits enduring pro-inflammatory responses. Epigenetically modified macrophages demonstrate enhanced secretion of IL-6, TNF, and IL-1β, which facilitates the development and instability of atherosclerotic plaques. Exposure to oxidized Low-Density Lipoprotein (oxLDL) has been demonstrated to elicit trained immunity responses in human monocytes, facilitated by histone changes like H3K27ac and H3K4me3 [22].

In autoimmune and rheumatic illnesses, trained immunity fosters persistent inflammation despite the lack of continuous antigenic stimulation. In Rheumatoid Arthritis (RA), synovial macrophages exhibit epigenetic reprogramming indicative of a trained phenotype. This results in continuous release of pro-inflammatory mediators and the recruitment of lymphocytes to the inflamed joint. In systemic lupus erythematosus, evidence indicates that early-life viral or microbial exposures may epigenetically modify innate immune progenitors, subsequently amplifying IFN-α and IL-6 responses in later life [23]. In addition to the cardiovascular and autoimmune systems, trained immunity may potentially aggravate chronic metabolic illnesses (Riksen, 2019) [24]. In type 2 diabetes, innate immune cells are continuously subjected to metabolic stresses, including elevated glucose and free fatty acids, resulting in a trained phenotype characterized by heightened NLRP3 inflammasome activation and augmented IL-1β production [22].

These data collectively suggest that although trained immunity can confer protection in infectious scenarios, its sustained activation in non-infectious environments may contribute to the chronic low-grade inflammation associated with numerous non-communicable disorders. Therefore, treatment approaches designed to modulate trained immunity must be meticulously calibrated to prevent prolonged inflammatory repercussions.

Challenges and Future Outlook

The therapeutic application of trained immunity is fraught with difficulties, despite its enormous potential:

- Potential for systemic inflammation or autoimmune activation
- Tumor heterogeneity and varied immune cell infiltration
- Requirement for accurate biomarkers to assess training responses

Moreover, several nascent issues necessitate additional scrutiny. The durability of trained immunity in non-communicable diseases generates apprehensions about its prolonged pro-inflammatory consequences [22]. The overactivation of innate responses may enhance chronic inflammation or worsen autoimmunity, especially in individuals prone to these disorders [23].

Furthermore, tumor-associated myeloid populations demonstrate considerable plasticity and may respond differently to training cues. The reprogramming of MDSCs or TAMs to a pro-inflammatory state may not consistently manifest across various tumor types or stages, hence constraining the generalizability of such therapies [25]. From a translational standpoint, inter-individual variability in the epigenetic and metabolic profiles of innate immune cells poses a considerable challenge. In the absence of reliable biomarkers, forecasting or assessing the effectiveness of therapies based on trained immunity is challenging [26,27]. Future initiatives should emphasize combinatorial strategies that merge trained immunity with adaptive immune modulation, personalized assessment of patient immunological profiles, and the creation of nanoformulations designed for specific tumor types [9,18].

Conclusion

Trained immunity is a substantial advancement in cancer immunotherapy. Utilizing the inherent memory-like capabilities of the innate immune system can improve tumor surveillance, reduce immunosuppression, and promote enduring treatment outcomes. In contrast to adaptive immune responses that specifically target antigens and can be circumvented by tumors via mechanisms like antigen loss or MHC downregulation, trained immunity offers a more generalized, non-specific immune defense that may enhance early responses prior to the activation of adaptive immunity [1,26].

Furthermore, approaches using trained immunity present potential solutions to the significant limitations of existing immunotherapeutics. This encompasses inadequate immune cell infiltration in specific tumor forms, resistance to immune checkpoint drugs, and the existence of an immunosuppressive tumor microenvironment. Epigenetically modified monocytes, macrophages, and NK cells can be reprogrammed to maintain prolonged anti-tumor activity, hence enhancing response rates to conventional therapy when administered simultaneously [8,9].

The utilization of nanotechnology to elicit trained immunity offers novel opportunities for precision medicine. Nanoparticles can transport immunostimulatory agents directly to the tumor location, augmenting local immune activation while reducing systemic toxicity. Moreover, the capacity of some trained immunity inducers, including β-glucans and BCG, to reprogram hematopoietic stem and progenitor cells (HSPCs) indicates potential lasting therapeutic advantages beyond temporary immune activation [7].
For therapeutic purposes, better biomarkers are needed to assess trained immunity and identify responsive patients. Immunology, oncology, systems biology, and bioengineering must collaborate to optimize trained immunity for cancer therapy [28-30].

In conclusion, trained immunity could be a good addition to or replacement for current cancer immunotherapies. It helps innate immune cells become ready and work better, which helps get rid of tumors and provide long-lasting protection. Researchers aim to create new drugs that are more effective, more accessible, and tailored for cancer patients. Trained immunity is a big step forward in cancer immunotherapy. Tumor monitoring, immunosuppression reduction, and extended treatment benefits are achievable by harnessing the memory-like properties of the innate immune system.

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