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Mini Review

Listeria Monocytogenes-Based Cancer Vaccines: Importance of Pathogen Interplay with Host's Cell Death Machinery

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Abstract

The efficacy and potency of Listeria monocytogenes (LM)-based cancer vaccines are intricately influenced by the dynamic interplay between the host and pathogen. LM has evolved sophisticated mechanisms to engage with the host's immune system and these molecular interactions exert considerable influence over the vaccine's ability to provoke a robust immune response against cancer cells. The host's immunological status plays a crucial role, with prior exposure to LM, pre-existing immunity, and overall health status all impacting the vaccine-triggered immune response. Individuals with compromised immune function, such as newborns, elderly individuals, and pregnant women, or those undergoing cancer treatment or suffering from immunodeficiency disorders may experience reduced effectiveness of LM-based vaccines. Importantly, the host's genetic background also significantly shapes the magnitude and nature of the immune response elicited by the vaccine. Variations in key host genes involved in immune recognition, antigen presentation, cytokine or cell death signalling pathways can have profound implications for vaccine efficacy. Therefore, the sophisticated interplay between host genetics and immunophenotype underscores the complexity of immune responses elicited by LM-based vaccines and highlights the necessity for additional research and the advancement of personalized strategies to enhance therapeutic results.

Keywords: Listeria monocytogenes; Cancer vaccines; CD8 T lymphocytes

Abbreviations: LM: Listeria monocytogenes; RIPK3: Receptor-Interacting Protein Kinase 3; IL-1β:interleukin-1β; IL-18: Interleukin-18; MLKL: Mixed Lineage Kinase Domain-like Pseudokinase; GSDMD: Gasdermin D; TSAs: Tumor-Specific Antigens; TAAs: Tumor-Associated Antigens; MDSCs: Myeloid-Derived Suppressor Cells; TCR: T Cell Receptor; TAP: Transporter Associated with Antigen Processing

Introduction

Cancer remains a significant and pressing health issue globally, posing formidable challenges to both individuals and healthcare systems worldwide. Despite enormous advances in basic science, medical approaches, and treatment schemes, cancer still imposes a significant burden, claiming millions of lives annually and profoundly impacting the quality of life for those affected [1]. One promising avenue in cancer research is the development of cancer vaccines. Cancer vaccines are designed to stimulate the immune system to recognize and attack cancer cells exclusively, offering a targeted and potentially less toxic therapy [2-4]. These vaccines can be engineered to express tumor-specific antigens (TSAs), or antigens associated with cancer stem cells, enhancing their specificity and efficacy in targeting malignant cells while sparing healthy tissues [4,5].

In the last decade, there has been growing interest in harnessing the unique properties of Listeria monocytogenes (LM) for the

development of cancer vaccines [6-8]. LM is well known for its ability to infect and replicate within host cells, particularly professional antigen-presenting cells (APCs), such as dendritic cells and macrophages, thereby inducing robust cellular immunity [9,10]. In addition, because LM can also infect tumor-infiltrating myeloid-derived suppressor cells (MDSCs), LM remains protected from the host immune response and accumulates inside the tumor microenvironment where it can also directly kill tumor cells [11]. These characteristics make LM particularly well-suited for targeting tumors that are resistant to conventional therapies.

Importantly, the level and duration of the immune response against LM can significantly impact the effector and memory responses against recombinant proteins engineered in LM-based vaccines [12]. Prolonged antigen presentation [13] and systemic inflammation [14] induced by LM may enhance the generation of memory T cells specific to the encoded antigens, thereby conferring long-lasting immunity against the target tumor cells. On the other hand, excessive immune responses against LM may have detrimental effects on the efficacy of LM-based vaccines [15]. Hyperactivation of inflammatory pathways induced by LM infection could lead to immunosuppression, compromising the overall effectiveness of the vaccine [16,17].

Control of LM Infection by Regulated Necrotic Cell Death Programs

The host's cell death machinery is crucial for protection against LM and other pathogens [18,19]. Two prominent necrotic/inflammatory cell death programs involved in this process are necroptosis and pyroptosis.

Necroptosis is an inflammatory form of regulated cell death triggered by receptor-interacting protein kinase 3 (RIPK3) activation in response to various stimuli, including bacterial infections. Activation of necroptosis leads to cell swelling, membrane rupture, and the release of cellular contents, ultimately resulting in the demise of the infected cell and the containment of bacterial replication [18,20,21]. Similarly, pyroptosis is another inflammatory form of cell death involved in protection against intracellular pathogens, which is initiated by the activation of caspase-1 or caspase-11 in the context of multimolecular platforms called inflammasomes [18,22,23]. Upon detection of intracellular pathogens such as LM, so-called canonic inflammasomes are assembled, leading to the activation of caspase-1 and the subsequent cleavage of interleukin-1β (IL-1β), interleukin-18 (IL-18), and gasdermin D (GSDMD). GSDMD cleavage triggers the formation of membrane pores, causing cell swelling and lysis and the release of the pro-inflammatory cytokines IL-1β and IL-18 [4,24].

In the context of LM infection, necrotic/inflammatory cell death takes on particular significance due to the bacterium's ability to induce both traditional necrosis and regulated necrotic forms of cell death [19]. LM expresses listeriolysin O (LLO), a pore-forming toxin that can trigger traditional necrosis by disrupting cellular integrity. Despite regulatory mechanisms evolved by LM to limit LLO toxicity, excessive LLO activity can lead to host cell death, potentially aiding bacterial dissemination [25]. Recent studies have highlighted the involvement of LM in inducing necroptosis, suggesting a finely tuned interplay between bacterial virulence factors and host cell death pathways. For instance, it was shown that the activation of the RIPK3-MLKL pathway in infected cells restricts intracellular LM replication [26]. Interestingly, RIPK3 phosphorylates MLKL, but the LM-infected cells do not undergo necroptosis, suggesting a RIPK3-dependent, necroptosis-independent mechanism of LM control. Essentially, the authors found that MLKL can directly bind to LM in the cytosol and obstruct its replication [26]. Regarding the role of pyroptosis in the control of LM infection, it is generally considered that inflammasome activation is protective even though LM has evolved strategies to evade this response to maintain its virulence [16,27]. Interestingly, recombinant LM strains designed to specifically induce necrosis, pyroptosis, or apoptosis yield impaired protective immunity [15].

Despite the growing evidence on the role of cell death regulatory and effector molecules on LM restriction, the precise interplay between these molecules and their impact on the adaptive immune responses against recombinant proteins engineered in LM-based vaccines remains unclear.

Do Defects in Host Necroptosis/Pyroptosis-Related Molecules Downgrade LM-Based Vaccines?

Recombinant LM expressing "surrogate" tumor antigens such as ovalbumin (OVA), tetanus toxoid (TT) melanoma antigen gene (MAGE), among others, induces strong tumor-specific CD8+ T cell responses in a variety of experimental setups [28-30]. The induction of robust CD8+ T cell responses is key to the effectiveness of LM-based vaccines and depends, among other features, on pathogen interplay with the host's cell death machinery [19,31].

RIPK3 and Caspase-1/11 play pivotal roles in orchestrating the immune response elicited by recombinant LM infection, particularly concerning CD8+ T cell-mediated immunity against both pathogens and tumors. Caspase-1/11 is essential for facilitating LM clearance and enhancing the production of proinflammatory cytokines, including IL-18 and IFN-γ, which are crucial for mounting effective immune responses against LM and tumor antigens [32]. Using recombinant WT LM (10403S) expressing ovalbumin (LM-OVA) we observed that both Caspase-1/11 and RIPK3 are important for priming and induction of optimal OVA-specific CD8 T cell responses, although only Caspase-1/11 deficiency negatively interfere with the ability of mice to clear bacteria [28]. Moreover, we showed that the combined deficiency of Casp-1/11 and RIPK3 limit the early initiation of antigen-specific CD8+ T cell memory response [28]. Our results differ from those obtained by Morrow and Sauer, who recently found no difference in LM-induced T-cell responses in Caspase-1/11 and WT mice [33]. It is important to note that these authors used an attenuated strain of LM that is rapidly cleared from the mice (2-3 days), whereas we used a WT strain that persists for a longer period (at least 7 days) post-infection/vaccination. Differential activation of inflammasomes in our experimental systems may account for the discrepancies observed by our groups

and highlight the importance of further addressing how necroptosis and pyroptosis regulatory and effector molecules contribute to the efficiency of each individual vaccine configuration. Indeed, live vaccine vectors differentially interact with the host's cell death machinery [18,19,31]. Interestingly enough, when we changed the vaccine vector carrying the ovalbumin gene to recombinant human adenovirus 5 (rhAd5-OVA), we observed no significant differences in OVA-specific CD8+ T cell differentiation and effector response in WT, Caspase-1/11-KO, and RIPK3-KO backgrounds. Taken together, data in the literature largely support the importance of considering the live vector interplay with the host's cell death machinery, to better design LM-based cancer vaccines.

Conclusion and Future Directions

Recombinant LM-based cancer vaccines are considered an encouraging immunotherapeutic strategy for the treatment of cancer. A robust yet balanced immune response against LM vectors, characterized by the regulation of the host cell death machinery, the proper activation of antigen-presenting cells, the recruitment and activation of effector T cells, and the production of pro-inflammatory cytokines is crucial for generating effective immune responses against the encoded antigens (Figure 1). Despite the challenges ahead, including safety considerations and immune evasion mechanisms, ongoing research efforts hold the potential to unlock the full therapeutic potential of recombinant LM-based cancer vaccines. Ongoing work in our laboratory is addressing the relative impact of IL-1, IL-18, and GSDMD individual deficiencies on the development of optimal LM-OVA-triggered CD8 T cell responses. Also, single-cell and/or multiparametric flow cytometry analysis of tumor-infiltrating cells in WT and deficient mice should further shed light on how the host regulatory and effector cell death molecules contribute to the efficiency of LM-based cancer vaccines.

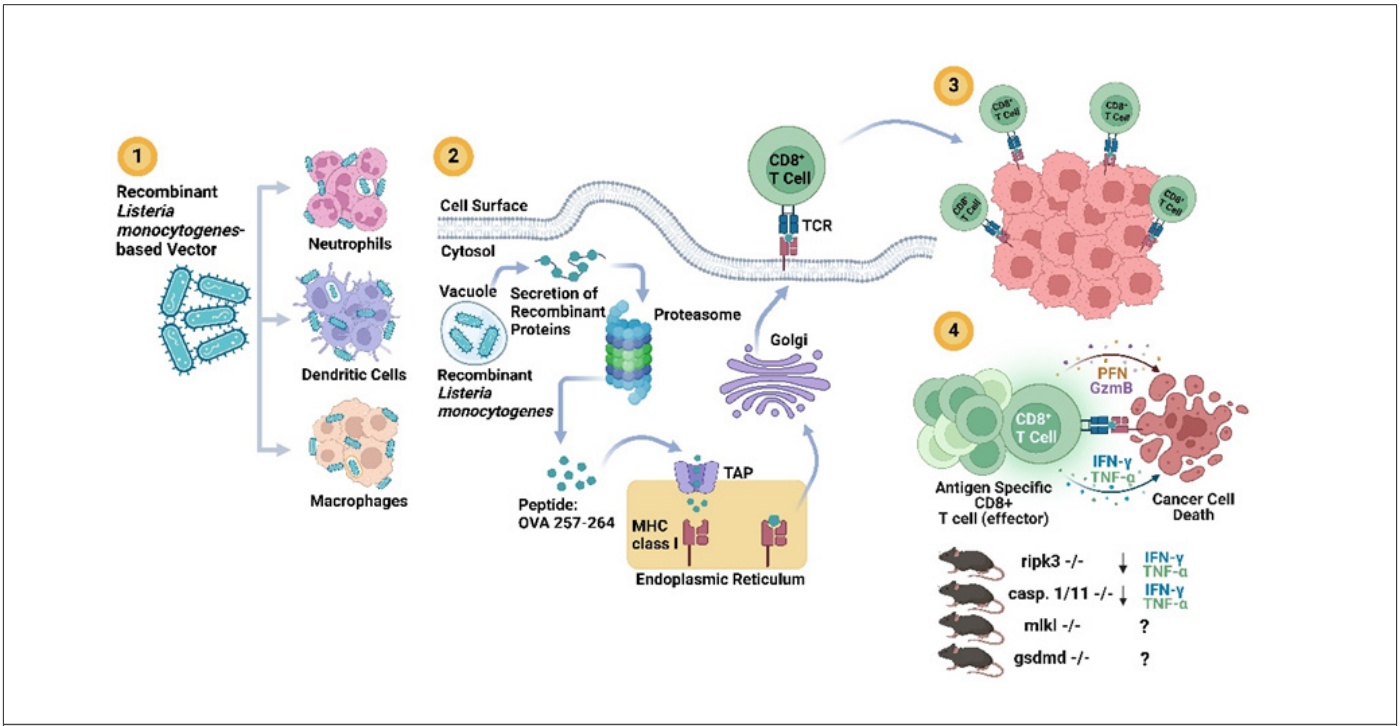

Figure 1: Recombinant *Listeria monocytogenes* (LM)-based vaccine interacts with the host immune system. (1) The recombinant LM vector, upon infection, interacts with host innate immune cells such as neutrophils, dendritic cells, and macrophages. (2) Recombinant peptides, such as OVA 257-264, are produced via proteasome-mediated degradation of LM-derived proteins (i.e., ovalbumin) and are presented to CD8+ T cells via MHC class I molecules. (3) Antigen-specific CD8+ T cell activation results in an effective adaptive immune response that lead to antigen (OVA)-expressing cancer cell death through the release of cytotoxic granules containing perforin and granzymes and the action of effector cytokines (IFN-γ and TNF-α). (4) Mice deficient of *casp. 1/11-/-* or *ripk3-/-* display reduced IFN-γ and TNF-α production as well as lesser antigen-specific CD8+ T cell killing [28]. The potential role of other inflammatory cell death mediators, such as mixed lineage kinase domain-like protein (MLKL) and Gasdermin D (GSDMD), in the modulation of antigen-specific CD8+ T cells generated by recombinant LM-based vectors are under investigation in our laboratory. Figure is generated by BioRender (*https://www.biorender.com/*).

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Conflict of Interest

The authors declare no conflict of interest.

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