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Review Article

An Overview on Listeria Monocytogenes as a Versatile Vector for Cancer Immunotherapy

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ABSTRACT

Listeria monocytogenes, Gram-positive anaerobic bacteria, is gaining popularity as a vector for immunotherapy of cancer. Vaccines based on modified Listeria have been created to stimulate immune responses against several types of cancer. Many clinical trials evaluating Lm cancer vaccines are now ongoing, providing insight into their potential use in cancer immunotherapy.

Overview

The ability of the immune system to recognize and eliminate cancer cells is known as the immuno-surveillance [1]. Failure of immuno-surveillance promotes the clinical progression of cancer, motivating the quest for methods to restore efficient immune responses to malignant cells. One such effort is to produce a cancer vaccine [2]. In this approach, a bacterium has become a prominent common vector for cancer treatment.

Bacteria's capacity to trigger innate immune responses and generate antitumor responses was initially discovered over 100 years ago, when a scientist called William Coley identified cases of spontaneous cancer regression in persons suffering from sarcoma who got bacterial skin infections. [3].

One such bacteria is Listeria monocytogenes. Over fifty years ago, George Mackaness revealed Mice given sublethal dosages of Lm produced immunological reactions that last for a long time and do not require antibodies that protected against a subsequent Listeria monocytogenes challenge administered at deadly doses. [4]. These & other results subsequently resulted in the research of Lm as a vaccination vector with the purpose of generating comparable cell-mediated immune responses against foreign antigens. Paterson and colleagues applied this approach by inducing a cytotoxic lymphocyte response against cancer cells expressing β-galactosidase antigen [5]. Generally, cancer vaccines are built up of antigens found in tumour cells, also known as tumor-associated antigens (TAA), linked with adjuvants aimed to induce an immune response. Cancer vaccine-induced antigen-specific T-cell responses likely to cause focused eradication of cancer cells than usual chemotherapy and result in enduring memory responses capable of preventing disease recurrence [2,6]. A Gram positive, facultative anaerobic bacterium, Listeria monocytogenes is growing in a major common vector for the treatment of cancer [7]. The severe illness induced by these bacteria is relatively unusual,

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because the immune system of human generates powerful innate & acquired immune responses have a potential of regulating infections of Listeria [8]. Furthermore, this infection stimulates CD8 T cell responses, which serve a critical role in curing Lm during the initial infection and providing protective immunity towards repeated infections [9]. There are several methods for immunotherapy of cancer. As alternate vectors can be stopped by neutralising Ab, Listeria infection causes relatively mild humoral responses that are unable to prevent repeated infection [10, 5]. As a result, Lm-based vectors are administered repeatedly to patients in order to increase T-cell responses. Bacteria substantially stimulate innate & acquired immune responses. Keeping all this in mind, Several Lm vaccines have been developed for the treatment of different cancers. Until today, chemotherapy, radiation & surgical excision were the three basic methods for treatment of cancer that directly eliminate or attack the cancer cells. Furthermore, cancer therapy that induce innate or acquired immune activity in humans need to be intensively researched [11].

Because the wild type Listeria strain is highly infective & unsuitable for medical application, significant effort needed to be devoted to increase safety of Listeria monocytogenes. There have been several techniques to generate attenuated strain, including as,

1. Deletion of Virulence genes.
2. Episomal Replacement of Virulence or Metabolic genes.
3. Killed but Metabolically Active genes. [2]

To present, approximately 30 clinical studies including ten distinct Lm cancer vaccines have begun. Two businesses are at the precursor of developing vaccines for Lm via clinical trials and each using various tactics [12]. Although Lm has been frequently provided combined with typical chemotherapies, there is a lot of interest in researching Lm in combining with alternative immune-therapies & radiation treatment. Combining immune control point drugs with therapeutic Lm vaccination is a reasonable step in improving effectiveness of vaccine. Example - Combining TAA-expressing Lm vaccination with α-PD-1 antibody resulted in total tumour regression in 20% of mice with HPV-positive TC-1 tumours, compared to no cure with either alone while a comparable method eliminated all tumours in a breast cancer model [13].

A question arises that, How actually Listeria monocytogenes work as a vector for cancer treatment?

1. First, Listeria monocytogenes has tumor-homing capabilities & particularly creates tropism in primary & metastatic tumours, which may lead to direct death of tumour cells [14].

2. Second, Listeria monocytogenes causes a robust innate inflammatory immunological response, which is crucial for generation of powerful adaptive immunity & effectiveness of Listeria monocytogenes as a vector for cancer vaccine [15].

3. Third, Lm stimulates strong CD8 T cell responses. Furthermore, recent investigations revealed that antigens derived from Listeria monocytogenes are digested & presented with better capability than autogenous synthesised viral antigens, support the use of Listeria monocytogenes as a vaccine vector to induce strong CD8 T cell responses [16].

4. Fourth, Listeria monocytogenes induced CD8-T cells may render resistance to antigens associated with tumour giving justification to use Listeria monocytogenes as a vector of vaccine for immune-therapy of cancer [14].

5. Fifth, cancer vaccines based on Listeria monocytogenes been demonstrated to diminish the number & suppressive function of regulatory T cells & myeloid-determine suppressor cells in the micro-environment of tumour [17].

6. Sixth, Listeria monocytogenes vaccinations could be given repeatedly to maximise effectiveness because antibodies do not seem to be enough to prevent elevation [18].

Overall, the foregoing properties make Listeria monocytogenes one of the most encouraging vectors of vaccine for immunotherapy of cancer & may produce Lm-based vaccines based on Listeria monocytogenes against infections that has proved hard to immunise against like HIV.

Despite preclinical models have revealed substantial therapeutic advantages of Listeria monocytogenes vaccinations, no Listeria monocytogenes vaccines are currently licensed by the FDA [19].

Indeed, following early clinical studies using Listeria monocytogenes showed a single tumor antigen, Listeria monocytogenes vaccine technology have expanded to incorporate vaccines exhibiting numerous tumour antigens. Indeed, Lm vaccines focusing on proteins associated with mour, such as CD105 & VEGFR2, have exhibited inhibition of tumor development and also the capacity to generate secondary anticancer immune responses through spreading of epitope. While promising, these vaccinations have not yet been clinically tested. Other trials will expect examine methods based on combination employing Listeria monocytogenes vaccinations with radiation, chemotherapy, immune checkpoint inhibitors & other medicines [20].

Conclusion

The development of cancer immunotherapy employing Lm as a vaccine vector, as well as other microbes like Salmonella for treatment, is under progress, and numerous researchers and scientists are exploring them for the enhancement of the health-care system. This study has shed light on how Lm-based vaccinations have demonstrated therapeutic advantages to cancer patients.. Unfortunately, there is not a single Lm-based vaccination that is FDA-approved, but the study and development of more and more such vaccines is currently ongoing. These vaccinations were injected in cancer patients where they have showed excellent benefits, but in other cases, the patients have also suffered the worst. More than 30 clinical studies investigating ten distinct Lm cancer vaccines have been launched. The research is anticipated to establish and develop the application of Lm-based vaccines in new immunotherapies for the treatment and benefit of cancer patients.

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