Essay

How Virulence of *Listeria monocytogenes* Can Be Harnessed to Develop an Immunotherapeutic Agent

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How Virulence of *Listeria monocytogenes* Can Be Harnessed to Develop an Immunotherapeutic Agent

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Abstract

Listeria monocytogenes (Lm) is a Gram-positive, facultative intracellular bacterium traditionally known as a foodborne pathogen but increasingly recognized as a promising vector for cancer immunotherapy. Its unique virulence factors—such as listeriolysin O (LLO), internalins, phospholipases, and ActA—enable robust activation of cell-mediated immunity, making Lm-based vaccines superior to conventional treatments and other bacterial vectors. This review discusses the mechanisms by which recombinant Lm induces antitumor responses, including antigen presentation via MHC I and II pathways, and outlines strategies to attenuate pathogenicity while preserving immunogenicity, such as gene deletions, partial restoration of PrfA, and killed-but-metabolically-active strains. Furthermore, we examine key clinical trials evaluating Lm-based vaccines in HPV-associated cancers, prostate cancer, and HER-2-positive malignancies, highlighting their safety, tolerability, and efficacy in improving survival outcomes. The versatility of Lm-based immunotherapies positions them as a novel and effective approach in oncology, with ongoing trials paving the way for future therapeutic applications.

Keywords: listeria monocytogenes; cancer immunotherapy; bacterial vaccine vectors; listeriolysin O (LLO); ActA protein; internalins; attenuated strains; killed but metabolically active (KBMA); tumor-associated antigens; CD8 T-cell immunity; AXAL (ADXS11-001); HPV-associated cancers; prostate cancer; HER-2 positive malignancies; clinical trials; immune checkpoint inhibitors

Introduction

Listeria monocytogenes is a Gram-positive, non-capsulated, non-spore-forming, facultative anaerobic, intracellular food-borne pathogen, responsible for different diseases in humans. It shows motility by polar flagella at 10°C to 25°C. (Farber and Peterkin, 1991) Listerial disease is not comprised a severe disease in an immunocompetent individual, and it is only characterized by gastroenteritis and fever. However it is a fatal disease in immunocompromised individuals and the average mortality rate in listeriosis is 20-30%. (Schuchat, Swaminathan and Broome, 1991) In recent years *L. monocytogenes* is used to produce immunotherapeutic agents in cancer therapies and vaccination due to the unique properties of its virulence factors like listeriolysin (LLO), internalins, phospholipases, ActA etc. These virulence factors make *Listeria* an influential vector for cancer immunotherapies than other bacteria like *Salmonella, Mycobacterium, Clostridium, Bacillus, and Bifidobacterium*. (Bernardes *et al*, 2010) Moreover, immunotherapies are superior to conventional treatments in malignancy like surgery, chemotherapy and radiotherapy. The bacterial vaccines provide precise and long-term antitumor immunity than monoclonal antibodies, oncolytic virus and donor-active lymphocytes. (Page, Fusil and Cosset, 2020; Marhelava *et al*, 2019)

A study conducted in 1962 by G.B Mackaness showed that the mice developed a long-term, antibodyindependent immune response exposed *to L. monocytogenes* and provided further protection to the mice against *L. monocytogenes* infection. (MACKANESS, 1962) Unlike other bacterial vaccine vectors, L. monocytogenes provides cell-mediated immunity by CD8 T-cells. (Wood and Paterson, 2014) In 1890 at New York Memorial Hospital, surgeon William Coley observed the sarcoma regression after erysipelas by activating innate immunity. (Coley, 1991) All these properties made

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Listeria monocytogenes unique to use as vaccine vectors. This review essay aims to discuss the virulence factors of *Listeria monocytogenes* and their application to produce immunotherapeutic agents.

Mechanism of Recombinant *Listeria monocytogenes* (Lm) as an Immunotherapeutic Agent

Firstly, as an immunotherapeutic agent recombinant *L. monocytogenes* are administered into the host via the parenteral route (Intravenous) rather than enteral. After traversing through blood *L. monocytogenes* enter into the phagocytic and non-phagocytic cells by internalin (InlA and InlB) through receptor-mediated endocytosis, (Pizarro-Cerdá, Kühbacher and Cossart, 2012) and it is encapsulated into the phagosome.

After internalization, most of the *L. monocytogenes* are killed by the fusion of phagosome with the lysosome and the degraded bacterial products are presented to the T-helper cells via MHC II. (Wood and Paterson, 2014) Few bacteria can survive within the cells and express PrfA, which encodes all the virulence factors of *L. monocytogenes*. (de las Heras *et al*, 2011) Listeriolysin (LLO), and phospholipases (PlcA and PlcB) are produced. *L. monocytogenes* escaped from the phagosome to the cytosol by a barrel-shaped pore produced by the oligomerization of LLO (Köster *et al*, 2014), and hydrolytic dissolution of phagosomal membrane by phospholipases. (Tattoli *et al*, 2013) Here in the cytoplasm *L. monocytogenes* is degraded by proteasomes and bacterial products with tumor-associated antigens are presented to the cytotoxic Tcells via MHC I pathway. (Wood and Paterson, 2014)

Another virulence factor, actin assembly-inducing protein (ActA) is produced in response to PrfA is responsible for the polymerization of host cell actin. This comet-like structure pushes the bacteria and *L. monocytogenes* enters the adjacent cell resulting in the spread of the infection. (Lambrechts *et al*, 2008)

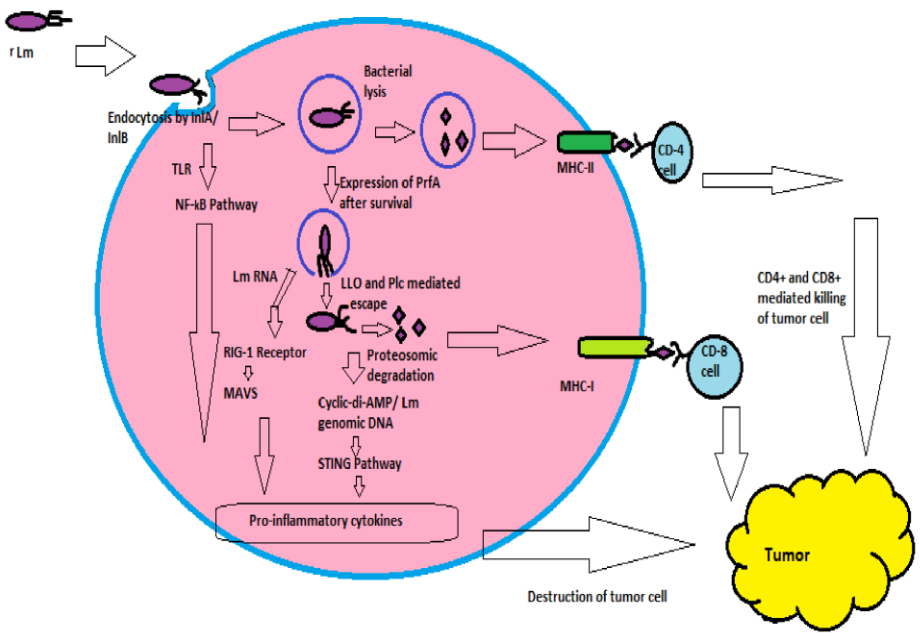

Figure 1. Recombinant *Listeria monocytogenes* (rLm) with tumor-associated antigen acting as an immunotherapeutic agent. Here, bacteria is endocytosed into the host by internalins, during this process toll-like receptors (TLR) recognize the bacteria and NF-κB pathway is activated for production of cytokines. Most of the bacteria undergo lysosomic degradation and are presented to CD4+ cell by MHC-II. Remaining bacteria

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produces listeriolysin (LLO) and phospholipases and escape from the phagolysosome. Within the host cell's cytoplasm they are degraded by proteasome and presented to CD8+ cell via MHC-I. Bacterial RNA, genomic DNA and secreted cyclic-di-AMP also produces the proinflammatory cytokines. All these combined effects alter the tumor microenvironment and regress the tumor.

Activation Innate Immunity by *Listeria monocytogenes* (Lm)

When *Listeria monocytogenes* enters the host it activates the chemotaxis of polymorphs and macrophages as a first-line defense. (Zenewicz and Shen, 2007) During cellular attachment and within the cytosol, toll-like receptors TLR-2 and TLR-5 recognize Lm and lead to production of pro-inflammatory cytokines by activating the NF-κB pathway. (Aubry *et al*, 2012) Moreover, Lm RNA activates the retinoic acid-inducible gene receptor I (RIG-I), which stimulates the mitochondrial antiviral signaling (MAVS) pathway and leading to production of IFN. (Hagmann *et al*, 2013) Also *Listeria* can stimulate the STING pathway for interferon production by secreting cyclic di-adenosine monophosphate (cyclic-di-AMP) (Woodward, Iavarone and Portnoy, 2010) or genomic DNA of Listeria can produce cyclic GAMP by activating cyclic GMP-AMP synthase enzyme. (McFarland *et al*, 2017)Type-I interferon provides tumor immunity by cell cycle arrest, apoptosis, lysis of tumor cell by CD-8 and NK cells. (Musella *et al*, 2017) (Fuertes *et al*, 2011)

L. monocytogenes as Vaccine Vector

All these properties of *Listeria monocytogenes* discussed above made it unique to use it as a therapeutic vaccine vector. However, the wild-type of *Listeria monocytogenes* is responsible for encephalitis, meningitis even death in non-pregnant immunocompromised individuals, so attenuated strain should be used by reducing the pathogenicity and increasing the immunogenicity. These methods are described below:

1. **Complete deletion of virulence factor:** *Listeria monocytogenes* has a wide range of cellular tropism like hepatocytes, epithelial cells, endothelial cells, fibroblast, etc., mediated by InlB. (Vázquez-Boland *et al*, 2001) Deletion of InlB will limit the infection only to the phagocytic cells, which is the desired action. Furthermore, deleting ActA will limit the infection only into the cytoplasm and hinder the spread of the infection. The mutants lacking ActA are 1000-fold less virulent than the wild type, as their LD-50 is 1000-fold more or higher than the wild strains. (Starks *et al*, 2004)
   The strain that lacks both InlB and ActA is more selective and has lesser adverse effects than the wild type of Lm. Also this strain is widely used in different clinical trials, known as the live attenuated double deleted vaccine (LADD) produced by Aduro Biotech Company in the USA. Mutants lacking ActA and PlcB used in hepatocellular carcinoma in different clinical trials found highly immunogenic. (Chen *et al*, 2012)
2. **Partial restoration of virulence gene:** As mentioned earlier, PrfA is the master transcription factor that encodes for the majority of the virulence factors. So deletion of PrfA would definitely make *Listeria monocytogenes* less pathogenic. However, the bacteria would be unable to escape from phagolysosome due to the absence of LLO and phospholipases, resulting in Lm less immunogenic. Partial restoration of PrfA by plasmid was the solution that was used in XFL-7 used in prostate cancer, and breast cancer was more immunogenic and attenuated than wild type. (Gunn *et al*, 2001; Singh *et al*, 2005; Shahabi *et al*, 2008)
3. **Killed but metabolically active strain:** The above-mentioned attenuated vaccines can be reactivated in an immunocompromised host and might cause listeriosis. For example, ADXS11001 systemic listeriosis was observed in few patients. (Sacco *et al*, 2016) To minimal this adverse effect, heat-killed vaccines can be used. Nevertheless, these killed vaccines are poorly immunogenic as they cannot induce cytotoxic T-cell mediated immune response by escaping into the host cytoplasm.
   Killed but metabolically active (KBMA) bacteria is produced by UV radiation, where the DNA of L. monocytogenes is irreversibly damaged, and it is incapable of replication. (Brockstedt *et al*, 2005)
   Listerial proteins using as adjuvants:

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To increase the effectiveness of the cancer vaccines by enhancing immune response, the following listerial proteins are used as adjuvants:

1. **Truncated listeriolysin (t-LLO):** In 2001, scientist George R. Gunn demonstrated that LLO could be used as an adjuvant. In his study, two groups of recombinant *Listeria monocytogenes* were produced as therapeutic vaccine. One of them was able to secret E7 (Human Papilloma Virus-16 associated cervical cancer protein) alone, and another group secreted E7 along with t-LLO (LLO deficient of hemolytic property). E7 was injected to the experimental mice and on day 7 there was 4-5mm palpable tumor was found on mice. A group of mice was treated with Lm-E7 another group was treated with Lm-LLO-E7. The result showed a 75% regression of tumor size in the second group, whereas there was no change in the tumor size in the first group. (Gunn *et al*, 2001) This study proved that t-LLO is responsible for escaping from phagolysosome and ultimately increases the cytotoxic T cell-mediated antitumor immunity by increased presentation of tumor antigen by MHC-I.
2. **ActA:** In 2010, similar study was conducted by Laurence M. Wood by treating two different groups of mice; those were injected with E7 and treated one group with Lm-E7 and another group with Lm-ActA-E7. The tumor size dramatically shrunk in the second group after vaccination, as well there was little or no evidence of lung metastasis in the second group. Nevertheless, the first group showed gross lung metastasis. (Wood *et al*, 2010)

Lm Based Vaccine on Cancer Immunotherapy

After studying the Lm vaccine on animal models, different clinical trials are conducted. A few of them are discussed below:

1. **Safety trial with empty Lm vaccine:** In 2002, Angelakopoulos conducted the first human trial with an empty Lm vaccine strain, where *L. monocytogenes* were deficient of ActA and PlcB. Here twenty healthy individuals were chosen, and 25ml of saline with the Lm vaccine escalating dose from 1×10^{6} to 1×10^{9} CFU was administered orally. Only two individuals had a transient increase in liver enzymes. Apart from that, no adverse effect was noted. Fifteen volunteers had detectable shedding of bacteria in the stool for four days. Lm based T-cell response was detected by the increased level of IFN-γ, but there no or was minimal level of the humoral immune response. (Angelakopoulos *et al*, 2002)
2. **Trials with HPV-associated cancer:** Human Papilloma Virus has been identified as a definite carcinogen for cervical, vulval, anal, oropharyngeal, penile, and vaginal cancer. In the year 2008, the total number of malignant cases was 12.7 million, among them 610,000 (5%) were due to HPV infection (mainly by the high-risk group 16, 18). (Forman *et al*, 2012) Viral oncoprotein E6 and E7 is responsible for forming the tumor by inhibition of tumor-suppressor gene p53 and RB (Roden and Stern, 2018) Axalimogene filolisbac clinical trial or AXAL or ADXS11-001 is an Lm-based vaccine that secrets E7 from HPV-16 along with tLLO.

- **Phase I:** In 2009, 15 individuals with invasive cervical cancer, which was unresponsive to traditional treatments were chosen to assess the safety of the ADXS11-001; the exclusion criteria was the previous history of listeriosis. They were divided into three groups, member of each group received 2 doses of ADXS11-001 vaccine intravenously every 21day either in 1×10^{9} or 3.3×10^{9} or 1×10^{10} CFU. The dose-limiting toxicity was found in those who received the highest dose; (most common was pyrexia, others were vomiting, nausea, tachycardia, headache, musculoskeletal pain) due to the innate immune response after vaccination. Two deaths were recorded during the study period, unrelated to the trial. (Maciag, Radulovic and Rothman, 2009)
- **Phase II:** After successfully completing the first trials, multiple phase II trials have been conducted in India and the USA. In 2010, a trial was conducted in India where 110 patients with invasive cervical cancer were chosen for the study. The study population were divided

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into different two groups; one group received three doses of 1×10^9 CFU of AXAL and another group received four doses of 1×10^9 CFU of AXAL along with Cisplatin (Chemotherapeutic agent). The overall survival rate was increased in both cases up to 1.5 to 2 folds. The ADXS11-001 was well-tolerated by the study population. However, the adverse effects were more in those who received cisplatin along with ADXS11-001. (Basu *et al*, 2018)

Another open-label, multicenter, dose determination and expansion cohort trial was started in 2013 for ADXS11-001 along with immune checkpoint inhibitor anti-PD-L1 named 'durvalumab' in fifteen patients with metastatic carcinoma of cervix or HPVassociated metastatic squamous cell carcinoma of head and neck region and dose determination is completed already. Here cohort 1 received 1×10^9 CFU of AXAL along with 3mg/mg of durvalumab and cohort 2 received 10mg/mg of durvalumab along with 1×10^9 CFU of AXAL and there were no dose-related toxicities observed in both cohort. (Clinical trial govt. identifier: NCT02002182)

- **Phase III (AIM2CERV):** A phase III double-blinded, placebo-controlled randomized clinical trial was started in September 2016. Around 450 participants who have locally advanced cervical carcinoma and have already completed the cisplatin-based concurrent chemoradiotherapy and have a higher risk of recurrence. This is the only phase III trial Lm based vaccine till now and the estimated date of completion of the study is October 2024 (Clinical trial govt. identifier: NCT02853604)

ADXS11-001 is on clinical trial for anal cancer, lung cancer, and oropharyngeal cancer.(Flickinger, Rodeck and Snook, 2018)

1. **Trials with carcinoma of the Prostate:** Prostate cancer is the second leading cause of death to the men in the USA after skin cancer and around 14% of men develop prostate cancer during their life time. (Jemal *et al*, 2007) Prostate-specific antigen (PSA) is widely expressed in adenocarcinoma of the prostate and it has been using as a tool for immunotherapeutic agents. (Cunha *et al*, 2006) In 2008, a study conducted with Lm based vaccine along with PSA (Lm-LLO-PSA) was injected into the mice with TPSA-23 tumor and the tumor showed 80% of regression from the initial. (Shahabi *et al*, 2008) Based on this study, a phase l/II trial has been started with Lm-based vaccine (ADXS31-142), where the strain is attenuated (LmddA) by deletion of *dal* and *dat* gene (responsible for the synthesis of D-alanine which is required for the bacterial cell wall synthesis) and deletion of ActA. This LmddA strain secrets PSA along with tLLO. This is an open-label, randomized, multicenter, dosedetermination trial of ADXS31-142 as a monotherapy or combination therapy with immune checkpoint inhibitor Pembrolizumab (anti PD-1 monoclonal antibody) in metastatic, castrationresistant carcinoma of the prostate in 37 patients. And the study determined the dose level of Lm vaccine which is 1×10^9 CFU, and for Pembrolizumab it is 200mg IV every 3 weeks up to 24 months or disease progression. There were some minor treatment related adverse effects recorded in around 10% of the study population (Pyrexia, chills, nausea, vomiting, hypotension, tachycardia etc.) The PSA level declined in 40.5% of patients and 59% had stable disease. (Stein *et al*, 2020)
2. **Trials with HER-2 associated cancer:** Human epidermal growth factor-2 (HER-2) is a protooncogene or receptor tyrosine kinase. Overexpression of this gene responsible for several malignancies in the breast, salivary glands, bone, ovary, stomach, esophagus, etc. (Scotlandi *et al*, 2005; Omar, Yan and Salto-Tellez, 2015)

   An Lm-based vaccine of LmddA strain secreting tLLO with human HER-2 (containing immunogenic region of two extracellular domains and one intracellular domain) has developed named ADXSHER2 or ADXS31-164. (Seavey *et al*, 2009) This is the only Lm-based vaccine granted by FDA (Food and Drug Administration) as a therapeutic vaccine in non-metastatic canine osteosarcoma which prevents or delays the metastasis and increases the overall survival rate of dogs along with carboplatin

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treatment. The treatment-related adverse effects were pyrexia, fatigue, lethargy, diarrhea etc. (Musser *et al*, 2021)

After the historical success of ADXS31-164 in canine osteosarcoma, it has undergone the phase II open-label, multicenter, single arm human trial is going on with patients of completely resected osteosarcoma (Age limit 12-39 years) to estimate the safety and tolerability of the vaccine, evaluation of overall survival rate of the patients in 2017 is yet to complete. (advaxis.com/her2associated-cancers)

3. **ADXS-NEO (Clinical trial govt. identifier NCT0365080):** Advaxis has taken another project (Phase I) on the Lm vaccine known as ADXS-NEO, based on personalized medicine. It is a patient-specific immunotherapy for different malignancies. Following the histopathological examination, the neoepitope (MHC-bounded peptides resulting from tumor-associated mutations) (Leclerc *et al*, 2019) is identified from the primary or metastatic tumor. Later on, the neoepitope is integrated with LLO of live, attenuated *L. monocytogenes*. This vaccine is produced on the hypothesis of destruction of tumor cells by *Listeria* mediated cytotoxic T cells response and depletion of regulatory T-cells and myeloid-derived suppressor cells in the tumor microenvironment. (Wallecha, Singh and Malinina, 2013) As T-reg and myeloid-derived suppressor cells are responsible for tumor immunosuppression. (Plitas and Rudensky, 2020) The objective of this ongoing open-label, multicenter, non-randomized trial is to assess the safety, tolerability, clinical and immunological potency of ADXS-NEO as monotherapy or as combination therapy with immunological checkpoint inhibitor (anti PD-1 antibody) in different cancers (metastatic non-small cell carcinoma of the lung, squamous cell carcinoma of head and neck region, microsatellite stable colorectal cancer, urothelial cancer, melanoma etc.) (advaxis.com/neo-program)

Conclusions

Although several adverse effects of the Lm-based vaccination, they are mainly mild. However, two patients had developed systemic listeriosis after administration of CRS-207 (Lm vaccine which expresses mesothelin with modified ActA) (Le *et al*, 2012) which was treated with ampicillin and gentamycin. (Denham *et al*, 2018) Hence, listeriosis is a matter of consideration while administration of the Lm vaccine in immunocompromised patients and should be monitored carefully. Despite of these adverse effects of the attenuated vaccine, virulence factors of *Listeria monocytogenes* has made this bacteria an ideal vaccine vector. The prospects of Lm vaccine are up-and-coming. It can be used as a single immunotherapeutic agent or combined with chemotherapy, radiotherapy and immunological checkpoint inhibitors to treat different primary or secondary malignancies. Years have taken to develop the model of Lm-based vaccine by harnessing the virulence factors, and it is believed that it will be widely used in clinical practices for the benefit of the patients in the upcoming years.

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