ADVAXIS PLATFORM TECHNOLOGY ABSTRACTS

Primary publications and presentations

ADXS-HPV (ADXS11-001)

CLINICAL

ADXS11-001 immunotherapy targeting HPV-E7: preliminary survival data from a phase 2 study in Indian women with recurrent/refractory cervical cancer

Petit R[1], Basu P[2]

Petit R., Basu, P., ASCO Annual Meeting, Chicago IL, 2013.

Source

[1]Advaxis, Inc. Princeton, NJ, [2]Chittaranjan National Cancer Institute, Kolkata, India

Abstract

Background: ADXS11-001 immunotherapy is a live attenuated *Listeria monocytogenes* (*Lm*) bioengineered to secrete a HPV-16-E7 fusion protein targeting HPV transformed cells. The *Lm* vector serves as its own adjuvant and infects APC where it cross presents, stimulating MHC class 1 and 2 pathways resulting in specific T-cell immunity to tumors. Here we describe preliminary survival data associated with ADXS11-001 administration in Lm-LLO-E7-015, a randomized P2 study conducted in India in 110 patients with recurrent/refractory cervical cancer; previously treated with chemotherapy, radiotherapy or both. **Methods:** Patients were randomized to either 3 doses of ADXS11-001 at 1 x 10^9 cfu or 4 doses of ADXS11-001 at 1 x 10^9 cfu with cisplatin chemotherapy. Naprosyn and oral promethazine were given as premedications and a course of ampicillin was given 72h after infusion. Patients received CT scans at baseline and 3, 6, 9, 12 and 18 months. The primary endpoint is overall survival. **Results:** As of February 2013, the trial has completed enrollment and 110 patients have received 264 doses of ADXS11-001. The percentage of patients alive at 6 months is 63% (67/107); at 9 months is 46% (49/106); at 12 months is 34% (30/87) and at 18 months is 15% (8/54). Tumor responses have been observed in both treatment arms with 6 CRs and 6 PRs; 36 additional patients had stable disease > 3 months, for a disease control rate of 44% (48/110). Activity against different high risk HPV strains has been observed. Three serious adverse events and 69 mild-moderate adverse events possibly related/related to ADXS11-001 treatment have been reported in 41% (45/110) of patients. The non-serious adverse events consisted predominately of transient, non-cumulative flu-like symptoms associated with infusion that either resolved on their own or responded to symptomatic treatment. **Conclusions:** ADXS11-001 can be safely administered to patients with advanced cancer alone and in combination with chemotherapy. ADXS11-001 is well tolerated and presents a predictable and manageable safety profile. Final 12-month overall survival, updated safety and translational analyses will be presented at the meeting.

The first clinical use of a live-attenuated Listeria monocytogenes vaccine: a Phase I safety study of Lm-LLO-E7 in patients with advanced carcinoma of the cervix.

Maciag PC, Radulovic S, Rothman J.

Vaccine. 2009 Jun 19;27(30):3975-83.

Source

Advaxis Inc., New Brunswick, NJ 08902, USA.

Abstract

Invasive carcinoma of the cervix (ICC) is the second most common cancer in women worldwide. Lm-LLO-E7 vaccine is a live-attenuated Listeria monocytogenes (Lm) that secretes the HPV-16 E7 antigen fused to a non-hemolytic fragment of the Lm protein listeriolysin O (LLO). In this Phase I trial, the safety of Lm-LLO-E7 was assessed in 15 patients with previously treated metastatic, refractory or recurrent ICC. Patients received 1 of 3 dose levels of Lm-LLO-E7 (1 x 10(9)CFU, 3.3 x 10(9)CFU or 1 x 10(10)CFU) as an intravenous infusion, followed by a second dose 3 weeks later. All patients experienced a flu-like syndrome which responded to non-prescription symptomatic treatment. Severe (grade 3) adverse events related to Lm-LLO-E7 were reported in 6 patients (40%), but no grade 4 adverse events were observed. At the highest dose some patients had severe fever and dose limiting hypotension. By the end of the study protocol, 2 patients had died, 5 had progressed, 7 had stable disease and 1 qualified as a partial responder. This study shows for the first time that a live-attenuated Lm is safe to be administered to late stage ICC patients.

PRECLINICAL

Anti-PD-1 antibody significantly increases therapeutic efficacy of *Listeria monocytogenes (Lm)*-LLO immunotherapy

Mikayel Mkrtichyan[1], Namju Chong[2], Rasha Abu Eid[1], Anu Wallecha[3], Reshma Singh[3],John Rothman[3] and Samir N Khleif[1*]
[1]Cancer Center, Georgia Regents University, 1120 15th Street, Augusta GA 30192, USA
[2]National Cancer Institute, NIH, Vaccine Branch, Bethesda, MD 20892, USA
[3]Advaxis Inc., Princeton, NJ 08540, USA

Journal for ImmunoTherapy of Cancer 2013, 1:15

Abstract

Background: One of the significant tumor immune escape mechanisms and substantial barrier for successful immunotherapy is tumor-mediated inhibition of immune response through cell-to-cell or receptor/ligand interactions. Programmed death receptor-1 (PD-1) interaction with its ligands, PD-L1 and PD-L2, is one of the important strategies that many tumors employ to escape immune surveillance. Upon PD-Ls binding to PD-1, T cell receptor (TCR) signaling is dampened, causing inhibition of proliferation, decreased cytokine production, anergy and/or apoptosis. Thus PD-Ls expression by tumor cells serves as a protective mechanism, leading to suppression of tumor-infiltrating lymphocytes in the tumor microenvironment. *Lm*-LLO immunotherapies have been shown to be therapeutically effective due to their ability to induce potent antigen-specific immune responses. However, it has been demonstrated that infection with *Lm* leads to up-regulation of PD-L1 on mouse immune cells that can inhibit effector T cells through PD-1/PD-L1 pathway. **Methods:** Therapeutic and immune efficacy of Listeria-based vaccine (Lm-LLO-E7) in combination with anti-PD-1 antibody was tested in E7 antigen expressing TC-1 mouse tumor model. Tumor growth, survival, as well as peripheral and tumor-infiltrating immune cell profiles after immunotherapy were assessed. **Results:** Here we demonstrate that the combination of an *Lm*-LLO immunotherapy with anti-PD-1 antibody that blocks PD-1/PD-L1 interaction, significantly improves immune and therapeutic efficacy of treatment in TC-1 mouse tumor model. Importantly, we show that in addition to significant reduction of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) in both spleen and tumor microenvironment that are mediated solely by the *Lm*-LLO immunotherapy, the addition of anti-PD-1 antibody to the treatment results in significant increase of antigen-specific immune responses in periphery and CD8 T cell infiltration into the tumor. As a result, this combinational treatment leads to significant inhibition of tumor growth and prolonged survival/complete regression of tumors in treated animals. We also demonstrate that *in vitro* infection with Lm results in significant upregulation of surface PD-L1 expression on human monocyte-derived dendritic cells suggesting the translational capacity of this finding. **Conclusions:**

Our findings demonstrate that combination of *Lm*-LLO-based vaccine with blocking of PD-1/PD-L1 interaction is a feasible approach with clinical translation potential that can lead to overall enhancement of the efficacy of anti-tumor immunotherapy.

Listeria-based HPV-16 E7 vaccines limit autochthonous tumor growth in a transgenic mouse model for HPV-16 transformed tumors.

Sewell DA, Pan ZK, Paterson Y.

Vaccine. 2008 Sep 26;26(41):5315-20.

Source

Department of Otorhinolaryngology - Head and Neck Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, United States.

Abstract

We have shown that Listeria-based cancer vaccines inhibit the growth of transplanted tumors in a transgenic mouse model of immune tolerance where HPV-16 E7 is expressed in the thyroid gland. In this study we determine whether these vaccines are able to inhibit autochthonous tumor growth in this animal model. Mice treated with Listeria vaccines expressing E7 had significantly smaller thyroid tumors than did mice treated with controls and possessed higher numbers of antigen-specific CD8(+) T cells within the spleens, tumors, and peripheral blood. This study shows that Listeria-based vaccines are able to slow autochthonous tumor growth and break immunological tolerance.

Two Listeria monocytogenes vaccine vectors that express different molecular forms of human papilloma virus-16 (HPV-16) E7 induce qualitatively different T cell immunity that correlates with their ability to induce regression of established tumors immortalized by HPV-16.

Gunn GR, Zubair A, Peters C, Pan ZK, Wu TC, Paterson Y.

J Immunol. 2001 Dec 1;167(11):6471-9.

Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA.

Abstract

Two recombinant Listeria monocytogenes (rLm) strains were produced that secrete the human papilloma virus-16 (HPV-16) E7 protein expressed in HPV-16-associated cervical cancer cells. One, Lm-E7, expresses and secretes E7 protein, whereas a second, Lm-LLO-E7, secretes E7 as a fusion protein joined to a nonhemolytic listeriolysin O (LLO). Lm-LLO-E7, but not Lm-E7, induces the regression of the E7-expressing tumor, TC-1, established in syngeneic C57BL/6 mice. Both recombinant E7-expressing rLm vaccines induce measurable anti-E7 CTL responses that stain positively for H-2D(b) E7 tetramers. Depletion of the CD8+ T cell subset before treatment abrogates the ability of Lm-LLO-E7 to impact on tumor growth. In addition, the rLm strains induce markedly different CD4+ T cell subsets. Depletion of the CD4+ T cell subset considerably reduces the ability of Lm-LLO-E7 to eliminate established TC-1 tumors. Surprisingly, the reverse is the case for Lm-E7, which becomes an effective anti-tumor immunotherapeutic in mice lacking this T cell subset. Ab-mediated depletion of TGF-beta and CD25+ cells improves the effectiveness of Lm-E7 treatment, suggesting that TGF-beta and CD25+ cells are in part responsible for this suppressive response. CD4+ T cells from mice immunized with Lm-E7 are capable of suppressing the ability of Lm-LLO-E7 to induce the regression of TC-1 when transferred to tumor-bearing mice. These studies demonstrate the complexity of L. monocytogenes-mediated tumor immunotherapy targeting the human tumor Ag, HPV-16 E7.

ADXS-cHER2 (ADXS31-164)

PRECLINICAL

Development of a live and highly attenuated Listeria monocytogenes-based vaccine for the treatment of Her2/neu-overexpressing cancers in human.

Shahabi V, Seavey MM, Maciag PC, Rivera S, Wallecha A.

Cancer Gene Ther. 2011 Jan;18(1):53-62.

Source

Advaxis Inc., New Brunswick, NJ 08902, USA.

Abstract

A chimeric human Her2/neu gene (ChHer2) harboring most of the known major histocompatibility complex class I epitopes of the HER2/neu oncogene was expressed as a fusion protein to a non-hemolytic fragment of listeriolysin O (LLO), by the highly attenuated Listeria vector LmddA, which lacks antibiotic selection markers and the ability to spread from cell-to-cell. This construct (ADXS31-164) was tested for immunogenicity and anti-tumor effects in mice. Despite being highly attenuated, ADXS31-164 proved to be efficacious in breaking immune tolerance toward the HER2/neu self-antigen. ADXS31-164 elicited strong T-cell immune responses in experimental animals. In tumors, ADXS31-164 caused a reduction in regulatory T cells (Treg) accompanied by an increase in the CD8(+)/Treg ratio. Comparison of this vaccine with the conventional antibiotic resistant Listeria vector (Lm-LLO-ChHer2) shows that ADXS31-164 is more efficacious in delaying tumor growth in Her2/neu transgenic animals. Because of its well-defined attenuation mechanism and independence from antibiotic selection markers, ADXS31-164 is potentially more suitable for human use. These results support the future clinical development of this vaccine for the treatment of HER2/neu-overexpressing malignancies, such as breast, colorectal and pancreatic cancers.

A novel human Her-2/neu chimeric molecule expressed by Listeria monocytogenes can elicit potent HLA-A2 restricted CD8-positive T cell responses and impact the growth and spread of Her-2/neu-positive breast tumors.

Seavey MM, Pan ZK, Maciag PC, Wallecha A, Rivera S, Paterson Y, Shahabi V.

Clin Cancer Res. 2009 Feb 1;15(3):924-32.

Department of Microbiology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania, USA.

Abstract

Purpose: The aim of this study was to efficiently design a novel vaccine for human Her-2/neu-positive (hHer-2/neu) breast cancer using the live, attenuated bacterial vector Listeria monocytogenes. **Experimental Design:** Three recombinant L. monocytogenes-based vaccines were generated that could express and secrete extracellular and intracellular fragments of the hHer-2/neu protein. In addition, we generated a fourth construct fusing selected portions of each individual fragment that contained most of the human leukocyte antigen (HLA) epitopes as a combination vaccine (L. monocytogenes-hHer-2/neu chimera). **Results:** Each individual vaccine was able to either fully regress or slow tumor growth in a mouse model for Her-2/neu-positive tumors. All three vaccines could elicit immune responses directed toward human leukocyte antigen-A2 epitopes of hHer-2/neu. The L. monocytogenes-hHer-2/neu chimera was able to mimic responses generated by the three separate vaccines and prevent spontaneous outgrowth of tumors in an autochthonous model for Her-2/neu-positive breast cancer, induce tumor regression in transplantable models, and prevent seeding of experimental lung metastases in a murine model for metastatic breast cancer. **Conclusion:** This novel L. monocytogenes-hHer-2/neu chimera vaccine proves to be just as effective as the individual vaccines but combines the strength of all three in a single vaccination. These encouraging results support future clinical trials using this chimera vaccine and may be applicable to other cancer types expressing the Her-2/neu molecule such as colorectal and pancreatic cancer.

ADXS-PSA (ADXS31-142)

PRECLINICAL

Combined immunotherapy with Listeria monocytogenes-based PSA vaccine and radiation therapy leads to a therapeutic response in a murine model of prostate cancer.

Hannan R, Zhang H, Wallecha A, Singh R, Liu L, Cohen P, Alfieri A, Rothman J, Guha C.

Cancer Immunol Immunother. 2012 Dec;61(12):2227-38.

Department of Radiation Oncology, UT Southwestern Medical Center, 5801 Forest Park Rd., Dallas, TX, 75390-9183, USA.

Abstract

Radiation therapy (RT) is an integral part of prostate cancer treatment across all stages and risk groups. Immunotherapy using a live, attenuated, Listeria monocytogenes-based vaccines have been shown previously to be highly efficient in stimulating anti-tumor responses to impact on the growth of established tumors in different tumor models. Here, we evaluated the combination of RT and immunotherapy using Listeria monocytogenes-based vaccine (ADXS31-142) in a mouse model of prostate cancer. Mice bearing PSA-expressing TPSA23 tumor were divided to 5 groups receiving no treatment, ADXS31-142, RT (10 Gy), control Listeria vector and combination of ADXS31-142 and RT. Tumor growth curve was generated by measuring the tumor volume biweekly. Tumor tissue, spleen, and sera were harvested from each group for IFN-γ ELISpot, intracellular cytokine assay, tetramer analysis, and immunofluorescence staining. There was a significant tumor growth delay in mice that received combined ADXS31-142 and RT treatment as compared with mice of other cohorts and this combined treatment causes complete regression of their established tumors in 60 % of the mice. ELISpot and immunohistochemistry of CD8+ cytotoxic T Lymphocytes (CTL) showed a significant increase in IFN-γ production in mice with combined treatment. Tetramer analysis showed a fourfold and a greater than 16-fold increase in PSA-specific CTLs in animals receiving ADXS31-142 alone and combination treatment, respectively. A similar increase in infiltration of CTLs was observed in the tumor tissues. Combination therapy with RT and Listeria PSA vaccine causes significant tumor regression by augmenting PSA-specific immune response and it could serve as a potential treatment regimen for prostate cancer.

Construction and characterization of an attenuated Listeria monocytogenes strain for clinical use in cancer immunotherapy.

Wallecha A, Maciag PC, Rivera S, Paterson Y, Shahabi V.

Clin Vaccine Immunol. 2009 Jan;16(1):96-103.

Research and Development, Advaxis Inc., 675 US Highway One, Suite 120, Technology Center of New Jersey, North Brunswick, NJ 08902, USA.

Abstract

Listeria monocytogenes has been exploited previously as a vaccine vector for the delivery of heterologous proteins such as tumor-specific antigens for active cancer immunotherapy. However, for effective use of live vector in clinics, safety is a major concern. In the present study, we describe an irreversibly attenuated and highly immunogenic L. monocytogenes platform, the L. monocytogenes dal-, dat-, and actA-deleted strain that expresses the human prostate-specific antigen (PSA) using an antibiotic resistance marker-free plasmid (the dal dat DeltaactA 142 strain expressing PSA). Despite limited in vivo survival, the dal dat DeltaactA 142 strain was able to elicit efficient immune responses required for tumor clearance. Our results showed that immunization of mice with the dal dat DeltaactA 142 strain caused the regression of the tumors established by the prostate adenocarcinoma cell line expressing PSA. An evaluation of immunologic potency indicated that the dal dat DeltaactA 142 strain elicits a high frequency of PSA-specific immune responses. Interestingly, immunization with the dal dat DeltaactA 142 strain induced significant infiltration of PSA-specific T cells in the intratumoral milieu. Collectively, our data suggest that the dal dat DeltaactA 142 strain is a safe and potent vector for clinical use and that this platform may be further exploited as a potential candidate to express other single or multiple antigens for cancer immunotherapy.

Development of a Listeria monocytogenes based vaccine against prostate cancer.

Shahabi V, Reyes-Reyes M, Wallecha A, Rivera S, Paterson Y, Maciag P.

Cancer Immunol Immunother. 2008 Sep;57(9):1301-13.

Source
Research and Development, Advaxis, Inc, North Brunswick, NJ, USA.

Abstract

Prostate specific antigen (PSA) is a likely immunotherapeutic target antigen for prostate cancer, the second leading cause of cancer-related death in American men. Previously, we demonstrated that attenuated strains of Listeria monocytogenes (Lm) can be used as effective vaccine vectors for delivery of tumor antigens causing regression of established tumors accompanied by strong immune responses toward these antigens in murine models of cancer. In the present study, we have developed and characterized a recombinant live attenuated L. monocytogenes/PSA (Lm-LLO-PSA) vaccine with potential use for the treatment of pCa. Human PSA gene was cloned into and expressed by an attenuated Lm strain. This recombinant bacterial vaccine, Lm-LLO-PSA was tested for stability, virulence, immunogenicity and anti-tumor effects in a murine model for pCa. Immunization with Lm-LLO-PSA was shown to lower the number of tumor infiltrating T regulatory cells and cause complete regression of over 80% of tumors formed by an implanted genetically modified mouse prostate adenocarcinoma cell line, which expressed human PSA. Lm-LLO-PSA was immunogenic in C57BL/6 mice and splenocytes from mice immunized with Lm-LLO-PSA showed significantly higher number of IFN-gamma secreting cells over that of the naïve animals in response to a PSA H2Db-specific peptide, as measured by both, ELISpot and intracellular cytokine staining. In addition, using a CTL assay we show that the T cells specific for PSA were able to recognize and lyse PSA-peptide pulsed target cells in vitro. In a comparison study with two other PSA-based vaccines (a pDNA and a vaccinia vaccine), Lm-LLO-PSA was shown to be more efficacious in regressing established tumors when used in a homologues prime/boost regimen. Together, these results indicate that Lm-LLO-PSA is a potential candidate for pCa immunotherapy and should be further developed.

Targeting Tumor Angiogenesis

An anti-vascular endothelial growth factor receptor 2/fetal liver kinase-1 Listeria monocytogenes anti-angiogenesis cancer vaccine for the treatment of primary and metastatic Her-2/neu+ breast tumors in a mouse model.

Seavey MM, Maciag PC, Al-Rawi N, Sewell D, Paterson Y.

J Immunol. 2009 May 1;182(9):5537-46.

Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA.

Abstract

Thirty years after angiogenesis was shown to play an enabling role in cancer, modern medicine is still trying to develop novel compounds and therapeutics to target the tumor vasculature. However, most therapeutics require multiple rounds of administration and can have toxic side effects. In this study, we use anti-angiogenesis immunotherapy to target cells actively involved in forming new blood vessels that support the growth and spread of breast cancer. Targeting a central cell type involved in angiogenesis, endothelial cells, we immunized against host vascular endothelial growth factor receptor 2 to fight the growth of Her-2/neu(+) breast tumors. Using the bacterial vector, Listeria monocytogenes (Lm), we fused polypeptides from the mouse vascular endothelial growth factor receptor 2 molecule (fetal liver kinase-1) to the microbial adjuvant, listeriolysin-O, and used Lm to deliver the Ags and elicit potent antitumor CTL responses. Lm-listeriolysin-O-fetal liver kinase-1 was able to eradicate some established breast tumors, reduce microvascular density in the remaining tumors, protect against tumor rechallenge and experimental metastases, and induce epitope spreading to various regions of the tumor-associated Ag Her-2/neu. Tumor eradication was found to be dependent on epitope spreading to HER-2/neu and was not solely due to the reduction of tumor vasculature. However, vaccine efficacy did not affect normal wound healing nor have toxic side effects on pregnancy. We show that an anti-angiogenesis vaccine can overcome tolerance to the host vasculature driving epitope spreading to an endogenous tumor protein and drive active tumor regression.

Cancer immunotherapy targeting the high molecular weight melanoma-associated antigen protein results in a broad antitumor response and reduction of pericytes in the tumor vasculature.

Maciag PC, Seavey MM, Pan ZK, Ferrone S, Paterson Y.

Cancer Res. 2008 Oct 1;68(19):8066-75

Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6076, USA.

Abstract

The high molecular weight melanoma-associated antigen (HMW-MAA), also known as melanoma chondroitin sulfate proteoglycan, has been used as a target for the immunotherapy of melanoma. This antigen is expressed on the cell surface and has a restricted distribution in normal tissues. Besides its expression in a broad range of transformed cells, this antigen is also found in pericytes, which are important for tumor angiogenesis. We generated a recombinant Listeria monocytogenes (Lm-LLO-HMW-MAA-C) that expresses and secretes a fragment of HMW-MAA (residues 2,160-2,258) fused to the first 441 residues of the listeriolysin O (LLO) protein. Immunization with Lm-LLO-HMW-MAA-C was able to impede the tumor growth of early established B16F10-HMW-MAA tumors in mice and both CD4(+) and CD8(+) T cells were required for therapeutic efficacy. Immune responses to a known HLA-A2 epitope present in the HMW-MAA(2160-2258) fragment was detected in the HLA-A2/K(b) transgenic mice immunized with Lm-LLO-HMW-MAA-C. Surprisingly, this vaccine also significantly impaired the in vivo growth of other tumorigenic cell lines, such as melanoma, renal carcinoma, and breast tumors, which were not engineered to express HMW-MAA. One hypothesis is that the vaccine could be targeting pericytes, which are important for tumor angiogenesis. In a breast tumor model, immunization with Lm-LLO-HMW-MAA-C caused CD8(+) T-cell infiltration in the tumor stroma and a significant decrease in the number of pericytes in the tumor blood vessels. In conclusion, a Lm-based vaccine against HMW-MAA can trigger cell-mediated immune responses to this antigen that can target not only tumor cells but also pericytes in the tumor vasculature.

Listeria monocytogenes-derived listeriolysin O has pathogen-associated molecular pattern-like properties independent of its hemolytic ability.

Wallecha A, Wood L, Pan ZK, Maciag PC, Shahabi V, Paterson Y.

Clin Vaccine Immunol. 2013 Jan;20(1):77-84.

Advaxis Inc., Princeton, NJ, USA.

Abstract

There is a constant need for improved adjuvants to augment the induction of immune responses against tumor-associated antigens (TAA) during immunotherapy. Previous studies have established that listeriolysin O (LLO), a cholesterol-dependent cytolysin derived from Listeria monocytogenes, exhibits multifaceted effects to boost the stimulation of immune responses to a variety of antigens. However, the direct ability of LLO as an adjuvant and whether it acts as a pathogen-associated molecular pattern (PAMP) have not been demonstrated. In this paper, we show that a detoxified, nonhemolytic form of LLO (dtLLO) is an effective adjuvant in tumor immunotherapy and may activate innate and cellular immune responses by acting as a PAMP. Our investigation of the adjuvant activity demonstrates that dtLLO, either fused to or administered as a mixture with a human papillomavirus type 16 (HPV-16) E7 recombinant protein, can augment antitumor immune responses and facilitate tumor eradication. Further mechanistic studies using bone marrow-derived dendritic cells suggest that dtLLO acts as a PAMP by stimulating production of proinflammatory cytokines and inducing maturation of antigen-presenting cells (APC). We propose that dtLLO is an effective adjuvant for tumor immunotherapy, and likely for other therapeutic settings.

Reviews

Multiple effector mechanisms induced by recombinant Listeria monocytogenes anticancer immunotherapeutics.

Wallecha A[1], Carroll KD[2], Maciag PC[1], Rivera S[1], Shahabi V[1], Paterson Y[3].

Adv Appl Microbiol. 2009;66:1-27.

[1]Advaxis Inc, 675 US Highway One, North Brunswick, NJ-08902
[2]Department of Antibody Technology ImClone Systems, a wholly-owned subsidiary of Eli Lilly & Co. New York, NY 10014, USA.
[3] Department of Microbiology, University of Pennsylvania School of Medicine, 323 Johnson Pavilion, 3610 Hamilton Walk, Philadelphia, PA, 19104-6076, USA.

Abstract

Listeria monocytogenes is a facultative intracellular gram-positive bacterium that naturally infects professional antigen presenting cells (APC) to target antigens to both class I and class II antigen processing pathways. This infection process results in the stimulation of strong innate and adaptive immune responses, which make it an ideal candidate for a vaccine vector to deliver heterologous antigens. This ability of L. monocytogenes has been exploited by several researchers over the past decade to specifically deliver tumor-associated antigens that are poorly immunogenic such as self-antigens. This review describes the preclinical studies that have elucidated the multiple immune responses elicited by this bacterium that direct its ability to influence tumor growth.

Cancer immunotherapy using Listeria monocytogenes and listerial virulence factors.

Wood LM, Guirnalda PD, Seavey MM, Paterson Y.

Immunol Res. 2008;42(1-3):233-45.

Source
Department of Microbiology, University of Pennsylvania School of Medicine, 323 Johnson Pavilion, 3610 Hamilton Walk, Philadelphia, PA, 19104-6076, USA.

Abstract

Our laboratory is interested in how immunogenicity may be modulated in vivo in order to better design more effective immunotherapeutics against cancer. Our main approach is to use a facultative intracellular bacterium, Listeria monocytogenes, which has the unusual ability to live and grow in the cytoplasm of the cell and is thus an excellent vector for targeting passenger antigens to the major histocompatibility complex (MHC) class I pathway of antigen processing with the generation of authentic CTL epitopes. We have used this approach to target tumor antigens expressed on breast, melanoma and cervical cancer. We are also exploring the role of Listerial virulence factors in potentiating adaptive immune responses by activating innate immunity. Specifically, we are using these proteins as adjuvants for B cell lymphomas.