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''USE OF BACTERIAL GHOSTS AS NOVEL DRUG DELIVERY SYSTEMS TO BOOST CANCER TREATMENT''

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ABSTRACT

Introduction:

The bacterial ghost (BG) system represents a completely unique and progressive approach within the development of bacterial-mediated cancer immunotherapy. The empty inner space of BGs are often crammed with drugs, proteins, DNA, enzymes, and other compounds. The induced lysis process doesn't harm the essential structural components of the bacteria, giving rise to immunologically active particles capable of stimulating the host system and delivering specific antigen (Ag) to professional antigen-presenting cells (APCs) or active substances to the target cells.

Production of bacterial ghosts: BGs are produced by expression of cloned gene E from bacteriophage ϕX174 leading to cell lysis in Gram-negative bacteria, like E. coli K12 strains, Klebsiella pneumonia, Mannheimia (Pasteurella) haemolytica, Neisseria meningitides, Salmonella typhimurium, Vibrio cholera, Helicobacter pylori, and others. Expression of gene E may be placed under transcriptional control of either the thermosensitive EpL/pR-cI857 promoter or chemical inducible promoter repressor systems, like lacPO or the tol expression system.

Gene E codes for 91 amino acids and exerts its lytic function by fusion of the inner and outer cell membranes, forming a particular transmembrane tunnel structure through which all the cytoplasmic content is expelled, thus leaving a bacterial envelope called a BG void of nucleic acids, ribosomes, and other intracellular constituents. The inner membrane (IM) and outer membrane (OM) structures of BGs remain intact during the lysis process. microscopy studies and enzymatic studies clearly showed a sealed periplasmic space at the border of the lysis tunnel. The efficiency of the E-mediated lysis process, and quantification of generated BGs and non lysed viable bacteria are de-

termined by flow cytometry assays employing a specific dye that's sensitive to the changes of discriminatory power of membrane potential and stains only cells that have lost membrane potential (BGs or dead bacteria).

Bacterial ghosts as advanced drug delivery systems: Many diseases including cancers require the systemic administration of highly aggressive drugs to already immunocompromised patients. Deleterious and sometimes severe side effects result from a scarcity of cellular and tissue selectivity. Another major issue is that the poor solubility of some drugs employed in cancer treatment. Considering these limitations, the event of a safer and more efficient drug delivery system (DDS) is that the priority for future advanced cancer treatments. Recently, bacterial ghosts made up of the colonic commensal Mannheimia haemolytica were used for in vitro delivery of doxorubicin (DOX) to human colorectal adenocarcinoma (Caco-2) cells.

Adherence studies showed that the M. haemolytica ghosts targeted the Caco-2 cells and released the loaded DOX within the cells. Cytotoxicity assays showed a two-fold enhancement in cytotoxic and anti-proliferative activity in cells incubated with DOX-loaded ghosts compared with cells that DOX was directly added to the culture media. This phenomenon could be caused by the degradation of DOX-loaded BGs within the endo-lysosome of target cells allowing DOX to bypass the multi-drug resistance (MDR) efflux pumps and leading to enhanced accumulation of DOX within the cytoplasm and so within the nuclear area of target cells. Current work with bacterial ghosts lies within the investigation of the carrying capacity of the cytoplasmic lumen. This intracellular space of BGs may be filled either with water-soluble substances or emulsions such the drug(s) of interest will be coupled to streptavidin anchored on the within of the cytoplasmic membrane. Moreover, bacterial ghosts may be filled and sealed for the delivery of fluid, non-anchored substances. during a recent study, E. coli ghosts were crammed with the reporter substance calcein and were sealed by fusion with membrane vesicles to take care of inner membrane integrity. Adherence and uptake studies showed that murine macrophages and human Caco-2 cells took up the bacterial ghosts, and

calcein was released within the cells.

Bacterial ghosts as immunologically active particles: due to the unique structure of the BG's envelope with preserved pathogen-associated molecular patterns (PAMPs), BGs are often utilized in biomedicine alone as an adjuvant or as a delivery vehicle for drugs or genes. The inner space of BG's empty envelope will be loaded with a mixture of peptides, drugs, or foreign DNA which allows us to style new sorts of polyvalent vaccines. BGs have excellent DNA loading capacity varying from 4000 to 6000 plasmid copies per BG betting on the concentrations of DNA solution used. BGs loaded with plasmid DNA are efficiently internalized and phagocytosed by both professional APCs and tumor cells. Cross-presentation of Ag delivered to dendritic cells (DCs) by BGs can activate both CD4+ and CD8+ T cells and stimulates the system to reinforce the response against Ag expressed by target cells. Inner and outer membrane structures of BGs including lipopolysaccharide (LPS) and other PAMPs remain intact after protein E-mediated lysis of Gram-negative bacteria. Thus, besides possessing a high loading capacity; BGs carry highly effective molecules for the stimulation of cross-presentation by DCs on their surface, especially, tumor-associated antigens (TAAs). BGs with their intact envelope structures don't seem to be only immune-stimulatory to professional phagocytes but also are capable of providing stimulatory signals to tumor cells. it's known that melanoma cells have the capacity to behave as non-professional APCs and may phagocyte both apoptotic and live cells, and it absolutely was recently shown that melanoma cells actively reply to exposure to BGs by increasing their rate of phagocytosis. Using BGs for gene delivery to the immune-competent cells, specifically, DCs yet as tumor cells, could initiate or restore the immunologic response against the delivered TAAs moreover as induce and increase the expression of target genes by APCs and tumor cells.

Conclusions:

These observations indicate the high capacity of BGs to focus on various histological forms of cancers. BGs are very useful non-living carriers, as they will carry foreign

antigens, nucleic acids, and medicines in one or more cellular locations simultaneously. Optimization and improvement of the chosen prospective model kind of BGs would help develop microbial-mediated disease treatment and drug delivery systems and their application in future clinical trials.

Keywords:
Bacterial ghost (BG), Drug delivery, Tumor therapy, Doxorubicin loaded BG.

Introduction

A brief review on the protective effect of camel milk in cancer Seyed Mousalreza Hosseini, Mahdi Yousefib, Said Zibaeec, Ali Taghipourd, Roshanak Salarie, Mohammadreza Norasf,*a Department of medication Internal, Faculty of drugs, Mashhad University of Medical Sciences, Mashhad, Iran b School of Persian and practice of medicine, Mashhad University of Medical Sciences, Mashhad, Iran cRazi Vaccine and Serum Research Institute of Mashhad, Irand Epidemiology & Research Methodology Faculty of Health, Mashhad University of medical sciences, Irane Department of Traditional Persian Pharmacy, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iranf School of Persian and practice of medicine, Mashhad University Medical Sciences, Mashhad,Cancer is one amongst the foremost major and prevalent health problems round the world that shows a high death rate.

There are much researches on the benefits of camel milk(CM) in cancers. Camel milk is extremely rich in nutrition and is employed within the treatment of various diseases. Traditionally, the employment of camel milk within the treatment and prevention of varied diseases existed in Iran, India, and Arabic countries. Recent research findings prove the effectiveness of camel milk within the treatment of diabetes, milk and food allergies, autism, liver toxicity, hepatitis, and cancers. Cell culture and animal studies introduce camel milk as a replacement option in cancer treatment.

Materials and method:

Electronic databases including PubMed, Scopus, and Cochrane Library were searched to access articles giving any in vitro, in vivo, and human evidence on the efficacy of CM within the treatment of cancer. Out of 80 records were found in7Abstracts - 1st International Nastaran Cancer Symposium-2015 / Journal of Cellular Immunotherapy 1 (2015) 1e45 Gene E codes for 91 amino acids and exerts its lytic function by fusion of the inner and outer cell membranes, forming a particular transmembrane tunnel structure through which all the cytoplasmic content is expelled, thus leaving a bacterial envelope called a BGdevoid of nucleic acids, ribosomes, and other intracellular constituents. The inner membrane (IM) and outer membrane (OM) structures of BGs remain intact during the lysis process. microscopy studies and enzymatic studies clearly showed a sealed periplasmic space at the border of the lysis tunnel. The efficiency of the E-mediated lysis process and quantification of generated BGs and nonlysedviable bacteria are determined by flow cytometry assays employing a specific dye that's sensitive to the changes of discriminatory power of membrane potential and stains only cells that have lost membrane potential (BGs or dead bacteria).Bacterial ghosts as advanced drug delivery systems: Many diseases including cancers require the systemic administration of highly aggressive drugs to already immunocompromised patients. Deleterious and infrequently severe side effects result from a scarcity of cellular and tissue selectivity. Another major issue is that the poor solubility of some drugs employed in cancer treatment. Considering these limitations, the event of a safer and more efficient drug delivery system(DDS) is that the priority for future advanced cancer treatments. Recently, bacterial ghosts made of the colonic commensalMannheimia haemolyticawere used for vitrodelivery of doxorubicin (DOX) to human colorectal adenocarcinoma (Caco-2) cells. Adherence studies showed that theM. hemolytic ghosts targeted the Caco-2 cells and released the loaded DOX within the cells. Cytotoxicity assays showed a two-fold enhancement in cytotoxic andanti-proliferative activity in cells incubated with DOX-loaded ghosts compared with cells that DOX was directly added to the culture media. This phenomenon could be caused by the degradation of DOX-loaded BGs within the endo-lysosome of target cells allowing DOX to bypass the multi-drug resistance (MDR) efflux pumps and leading to enhanced accumulation of DOX within

the cytoplasm so within the nuclear area of target cells. Current work with bacterial ghosts lies within the investigation of the carrying capacity of the cytoplasmic lumen. This intracellular space of BGs may be filled either with water-soluble substances or emulsions such the drug(s) of interest may be coupled to streptavidin anchored on the within of the cytoplasmic membrane. Moreover, bacterial ghosts is filled and sealed for the delivery of fluid, non-anchored substances. in a very recent study, E. colighosts were full of the reporter substance calcein and were sealed by fusion with membrane vesicles to take care of inner membrane integrity. Adherence and uptake studies showed that murine macrophages and human Caco-2 cells took up the bacterial ghosts, and cal-cein was released within the cells. Bacterial ghosts as immunologically active particles: due to the unique structure of the BG's envelope with preserved pathogen-associated molecular patterns (PAMPs), BGs is employed in bio-medicine alone as an adjuvant or as a delivery vehicle for drugs or genes. The inner space of BG's empty envelope may be loaded witha combination of peptides, drugs, or foreign DNA which allows us to style new sorts of polyvalent vaccines. BGs have excellent DNA loading capacity varying from 4000 to 6000 plasmid copies per BG counting on the concentrations of DNA solution used. BGs loaded with plasmid DNA are efficiently internalized and phagocytosed by both professional APCs and tumor cells. Cross-presentation of Ag delivered to dendritic cells (DCs) by BGscan activates both CD4+and CD8+T cells and stimulates the system to boost the reaction against Ag expressed by target cells. Inner and outer membrane structures of BGs including MicroRNAs and cancer: a perspective on the invention and functionBalal Sadeghia,*, Fereshteh Haghighib, Mandana Pishbinc,Mahdi Mirahmadic,department of Food Hygiene and Public Health, Faculty of veterinary Medicine, Shahid Bahonar University of Kerman,Kerman, IranbDepartment of Biology, Faculty of Science,Ferdowsi University of Mashhad, Mashhad, IrancNastaran Center for Cancer Prevention (NCCP), Mashhad, IrandStem Cell&Regenerative Medicine Research Group, Iranian Academic Center for Education, Culture and Research (ACECR), Khorasan RazaviBranch, Mashhad, Iran-mail address:sadeghi.balal@gmail.comExtended AbstractIntroduction:Since microRNAs (miRNAs) discovery, the knowledge on miRNAs and cancer has been increasing exponen-

tially (Figure 1). the primary miRNA was discovered in 1993 by Victor Ambros and colleagues. By the year 2000, the Ambros and Ruvkun laboratories had discovered the 2 founding members of a family of small non-coding RNAs, now called miRNAs.The detection of mature miRNA transcripts (21~22 not transcripts)originated from larger precursor transcripts. Two processes are necessary for the generation of mature miRNAs: (i) pre-miRNAs from pri-miRNAs within the nucleus by Drosha and (ii) processing of pre-miRNAs into mature miRNAs within the cytoplasm by Dicer. The biological role and in vivo functions of most mammalian miRNAs are very different. In invertebrates, miRNAs regulate developmental timing, neuronal differentiation, cell proliferation, growth control, and programmed necrobiosis. In mammals, miRNAs are found to play a task in embryogenesis and vegetative cell maintenance, hematopoietic cell differentiation, and brain development. Till now, microRNAs expression is deregulated during a wide selection of human diseases including cancer.MiRNAs in cancer: the primary report for miRNAs role in cancer, only two years after the invention of the primary human miRNA, byGeorge Calin and colleagues was published. Up today plenty of papers show miRNAs play a task in tumor invasion and metastasis. Many aspects of miRNAs roles like MicroRNA networks in cancer, MicroRNAs as predictors of prognosis, MicroRNAs for classification of disease, MicroRNA polymorphisms predisposing to cancer, MicroRNAs as non-invasive biomarkers MicroRNAsas predictors of drug efficacy, was studied. one amongst the foremost important challenges to beat cancer is early identification by biomarkers. plenty of studies highlight the potential of miRNAs as biomarkers for cancer, Furthermore the mutational status of miRNA binding sites in their protein-coding targets can even be thought to be adiagnostic tool. Also, exist to strategy for MiRNAs as therapeutic agents. MiRNA inhibition was the primary approach accustomed explores the potential of miRNAs in cancer therapy. The second strategy of miRNA therapeutics is to use miRNAs as a therapeutic agent as a replacement strategy. Conclusions: Over recent years, miRNAs have emerged as major players within the complex networks of gene regulation and are implicated in various aspects of human disease. These small RNAs have already significantly improved our understanding of carcinogenesis. microRNAs represent critical regulators of tumor cell differentiation, proliferation, cell cycle

progression, invasion and metastasis. Supported microRNA arrays various Abstracts - 1st International Nastaran Cancer Symposium-2015 / Journal of Cellular Immunotherapy 1 (2015) 1e45

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