Molecular Enzymology and Drug Targets

Extended Abstract
Vol. 6, Iss. 1
2020

Pharma– 2012 :Multifunctional locked nucleic acid modified chimeric survivin targeted nano-bullets against cancer stem cells -Jagat R. Kanwar -Deakin University

Jagat R. Kanwar

Deakin University, Australia

Theranostics, the combination of diagnostics and therapies is a new concept in cancer management. Our published work strongly suggests that orally administered multifunctional targeted "nano- bullets" (nanocarriers; NCs) with iron saturated bovine lactoferrin (Fe-bLf) were able to kill tumours. Here for the first time, we are developed multifunctional-targeted nanocapsules conjugated with stably modified aptamers to target and kill cancer as well as cancer stem cells. These nanocapsuleslabeled with biosensors, will deliver anti-cancer molecules to colon tumours and help to monitor the therapy in real-time imaging. A cell permeable dominant negative mutant form of survivin (dNSurR9C84A), dNSurR9C84A has shown promising anticancer properties by inhibition of survivin and reduces the chance of side effects since survivin is not expressed in normal cells in an adult. However due to short half-life of dNSurR9C84A a drug delivery system based on low molecular weight chitosan was used which could prolong the bioavailability of dNSurR9C84A. These chitosan nanoparticles were well characterized before examining effects on colon cancer cells (Caco-2). The nanoparticle transport studies were carried out both in vitro and ex vivo in order to understand the mechanism of low molecular weight chitosan nanoparticles with intestinal cells. The in vivo Biodistribution studies showed a highly selective and specific patter of uptake of the targeted nanocarriers or "nanobullets" (CHNP-dNSurR9C84A-LNA-Nu+Ep) in the tumour. The targeted nanocarriers were also able to significantly inhibit the tumour volume up to a period of 95 days. These nanobullets showed specific internalization in cancer stem cells and led to cancer stem cells specific apoptosis, thus proved to be appropriate for oral administration in colon cancer. Tumor-targeted delivery of anti-cancer drugs with controlled drug release function has been recognized as a promising strategy for pursuit of increased chemotherapeutic efficacy and reduced adverse effects. Development of magnetic nanoparticulates as delivery carriers to accommodate cytotoxic drugs for cancer of the liver treatment has evoked immense interest with reference to their convenience in biomedical application. Herein, we engineered multifunctional Janus nanocomposites, characterized by a head of magnetic Fe3O4 and a body of mesoporous SiO2 containing doxorubicin (DOX) as "nano-bullets" (M-MSNs-DOX). This nanodrug formulation possessed nanosize with controlled aspect-ratio, defined abundance in pore structures, and superior magnetic properties. M-MSN-DOX decided to induce selective growth inhibition to the neoplastic cell under magnetic flux instead of human normal cells thanks to its preferable endocytosis by the tumor cells and pH-promoted DOX release within the interior of cancer cells. Ultimately, both subcutaneous and orthotropic liver tumor models in mice have demonstrated that the proposed Janus nano-bullets imposed remarkable suppression of the tumor growth and significantly reduced systematic toxicity. Taken together, this study demonstrates an intriguing targeting strategy for cancer of the liver treatment supported a completely unique Janus nano-bullet, aiming for utilization of nanotechnology to get safe and efficient treatment of cancer of the liver. A nano-sized drug capsule designed to seek-and-destroy malignant cells shows signs of having the ability to significantly shrink ovarian cancer tumors. The researchers behind the novel drug, MansoorAmiji at Northeastern University and MIT's Robert Langer, say the key is within the packaging: a pH-sensitive nanoparticle that encapsulates the therapeutics, delivering them on to cancer sites in mice and suppressing tumor growth. The researchers reported their success within the journal Cancer Chemotherapy and Pharmacology. "The main challenge in ovarian cancer treatment is lack of selectivity for tumor cells versus normal cells," says Amiji, a pharmaceutical scientist and therefore the study's PI. "Many approaches have devastating side effects, attacking tons of normal cells like follicle and gastrointestinal cells." Ovarian cancer may be a tempting target for the technology because it's particularly difficult to treat and sometimes features a high relapse rate, Amiji says, but the nanoparticle system might be applicable to other sorts of cancer. To avoid such side effects and hone drug delivery, Amiji and his colleagues searched for ways to take advantage of key characteristics of tumor cells. The environment around most tumors is acidic, having lower pH levels than the remainder of the body. Levels are even more acidic inside tumors thanks to lack of blood and carboxylic acid buildup. They deduced that a pH-sensitive drug package could thus selectively target the tumor cells. The drug-carrying vessel must be sufficiently small to undergo a tumor's membrane and yet resilient enough to not be weakened by the body's immune cells before reaching the tumor site. Therefore the researchers engineered a nanoparticle out of pH-sensitive, biodegradable polymers. Very similar to a suitcase which could only be opened with a selected combination, this vessel could only be "unlocked" within the presence of low pH levels exhibited by tumor cells. Once unlocked, the vessel dissolves, releasing its drug contents specifically to cancer cells. Other existing cancer therapies employ similar nano vessels for drug delivery. The foremost common are liposomes: naturally-derived, spherical vesicles that package drugs, carrying them across tumor membranes into cancer cells. However, these drug carriers run the danger of getting haunted by macrophages before going to the tumor. Other potential drug carriers more immune to the body's natural defenses are shown to possess toxic side effects.

This work is partly presented at 2nd International Conference and Exhibition on Pharmaceutical Regulatory Affairs, November 23-24, 2012 held at Hyderabad International Convention Centre, India

Biography

Associate Professor Jagat R Kanwar is the Head of Nanomedicine-Laboratory of Immunology and Molecular Biomedical Research (LIMBR). Dr.Jagat R Kanwar has received his Master's degree in Medical Biochemistry and PhD in Molecular Immunology from PGIMER, Chandigarh, India in 1992. He has an international reputation and expertise in investigating fundamental and applied molecular signaling aspects of pathogenesis of cancer, chronic inflammation and neurodegenerative diseases, thereby, leading to the development of treatment strategies from bench to bedside. He has more than 100 publications in high impact factor and peer reviewed international journals, 27 book chapters and 3 edited books. Assoc Prof Kanwar's research has generated several patents/PCTs with more than five licensed patents for commercialization to BioPharma industry. His group is currently working on drug discovery and nanomedicine for oral and systemic drug delivery of a range of biomacromolecules (proteins/peptides, siRNAs and aptamers) for targeting survivin, HIF-1☐ and other apoptotic and inflammatory cell signaling molecules in cancer, chronic inflammation and neurodegenerative disorders.

jagat.kanwar@deakin.edu.au

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