

Copro-antiapoptotic protein survivin and lactoferrin biomarkers for improved detection and nanodelivery to colon cancer

Jagat R Kanwar, Ganesh Mahidhara, Rupinder K Kanwar and Chun Hei Antonio Cheung¹

Institute for technology research and innovation (ITRI), Deakin University, Australia

¹National Institute of Cancer Research, National Health Research Institutes (NHRI), Taiwan

We and others have found that survivin, a member of the family of inhibitor of apoptosis proteins that is overexpressed in several human tumours. Lactoferrin is also known to express in inflammatory diseases such as inflammatory bowel disease and Crohn's disease. We assessed the differential expression of survivin, other apoptotic biomarkers and lactoferrin in stool and serum samples of colorectal cancer (CRC) patients. We compared serum and stool samples from CRC patients and samples from healthy volunteers using an in vitro enzyme-linked immunosorbent assay to evaluate the survivin and lactoferrin response in patients. The sensitivity of the anti-survivin and lactoferrin response from patients with CRC was 65% and 70%, the specificity was 62% and 75% respectively with good predictive positivity and predictive negativity. Combined detection using survivin and lactoferrin produced better sensitivity (65%) and specificity (90%), respectively. In conclusion a positive association between survivin and lactoferrin concentrations in sera and stool samples of patients with CRCs was established. Our results suggest that analysis of both parameters would assist in screening patients with CRC. Our findings also suggest that the reduction in the serum survivin and copro-lactoferrin levels of advanced CRC patients after chemotherapy can be used as a predictor of response to the chemotherapy but not that of survival. In addition, we developed dominant negative mutant of survivin (SurR9-C84A) and loaded into Alginate enclosed chitosan- calcium phosphate nano carriers (ACSC-NCs), in order to improve the oral bioavailability and to protect the peptide from the locale of gastro intestinal tract. These CSC-NCs loaded with SurR9-C84A were tested in a xenograft mice model of colon cancer. We found all tumor bearing mice regressed tumors significantly. Anti-tumor activity was mediated by inducing apoptosis and necrosis in tumours. There was significant decrease in angiogenesis and vasculature in the CSC NCs-SurR9-C84A as compared to empty CSC-NCs ingested control tumor mice. In the present study we developed a safe, nontoxic, mucoadhesive, completely biodegradable, compatible and sustain released CSC-NCs as a proof of concept in colon cancer which can be used for other cancer types. Thus these CSC-NCs can be exploited for oral administration to protect from variable pH in intestinal track and resistance to gastric enzymes which otherwise digest proteins in gastrointestinal tract.

Biography

Associate Professor Jagat Kanwar is an immunologist and molecular biochemist. He is group leader of the Laboratory of Immunology and Molecular Biomedical Research has an international reputation in investigating fundamental and applied molecular aspects of cancer and chronic inflammation. He is an immunologist, molecular biologist and cell biologist. He has extensive training and expertise in studying the molecular mechanisms and devising treatments for human diseases like cancer and chronic inflammatory diseases such as asthma, atherosclerosis, inflammatory bowel disease (IBD), arthritis and multiple sclerosis in both in vivo and in vitro models. The research approach employed monotherapy (gene therapy, immunotherapy) or combinational therapy with commercially available chemotherapeutic agents including peptides. From 2002-2006, within Lactopharma his main research project involved the identification of milk bioactive molecules/ fractions for the treatment of cancer and employed monotherapy (gene therapy, immunotherapy or anti-angiogenic molecules) or combinational therapy with milk and natural plant bioactives and the results obtained have generated 3 patents and two provisionals are to be submitted. He is working on nanotechnology based peptide, siRNA and miRNA delivery for targeting survivin (currently most attractive cancer target), HIF-1 α and apoptotic cell signalling molecules expression in the cancers and inflammations. For commercial funded grants his research group carries out research in the areas of dairy/grain bioactives as immunomodulators, their role in bone and muscle development, osteoarthritis and wound healing. Presently his 7 PhD students are working on various cancer biomarkers and nanobiotechnological oral delivery systems for gene transfer technology and proteins in cancers. For commercial funded grants his research group carries out research in the areas of bioactives as immunomodulators, their role in bone, muscle development and osteoarthritis. His publications have added to the body of knowledge in the fields of nanobiotechnology, cancer gene therapy, cell biology and immunology. Kanwar's research work generated in total of 12 patent/PCTs with two provisionals in preparation. Five of these patents have been licensed for commercialization to biotech companies Antisoma, NeuronZ, Neuren Pharmaceuticals and Fonterra. He was invited as a speaker in more than 30 conferences and chaired sessions in Immunology, Nanotechnology, Nanomedicine and Biotechnology.