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MicroRNAs induce tamoxifen sensitivity by down-regulation of estrogen receptor alpha signaling in breast cancer

Gary Guishan Xiao
Creighton University School of Medicine, USA

MicroRNAs (miRNAs) have important regulatory functions in breast cancer tumorigenesis. We previously found that let-7 miRNAs were significantly downregulated in breast cancer tissues, and further demonstrated that these miRNAs target estrogen receptor alpha, resulting in cancer cell apoptosis in breast cancer cell lines. Tamoxifen resistance is a major clinical event in endocrine therapy of breast cancer. Recent studies suggest that overexpression of estrogen receptor (ER)-α36 may be associated with tamoxifen resistance. We hypothesize that let-7 miRNAs family may induce tamoxifen sensitivity by suppressing estrogen receptor (ER)-α36. In this study, we used qRT-PCR to examine expression of let-7 family miRNAs in resistant breast cancer cell lines to tamoxifen as well as expression of estrogen receptor (ER)-α36, a variant of ER-α66, after let-7 miRNA transfection. Immunoblot analysis was employed to check protein expression in FFPE tissue and breast cancer cell lines. Luciferase reporter assay was used to detect direct regulation of let-7 miRNA on ER-α expression. Cell proliferation assay was carried out after transfection of let-7 miRNAs. We found that there was an inverse correlation between the expression of ER-α36 and let-7 family miRNAs (b and i) in the FFPE tissue set. Let-7 miRNA sequences match sequence in the 3' untranslated region (3' UTR) of ER-α36, indicating ER-α36 may be a target of let-7. Co-transfection of let-7 mimics (b and i) with ER-α36 3' UTR luciferase construct decreased the activity of reporter gene. Conversely, let-7 inhibitors (b and i) enhanced the reporter gene activity. Transfection of let-7 mimics (b and i) inhibited both the mRNA and protein levels of ER-α36. On the contrary, transfection of let-7 inhibitors (b and i) enhanced the ER-α36 expression at both mRNA and protein levels in 184A1 cells. The high expression of ER-α36 in tamoxifen resistant MCF7 cells can be inhibited by transfection of let-7 mimics (b and i) and sensitivity toward tamoxifen is enhanced. We conclude that let-7 miRNAs enhance sensitivity of breast cancer cells to tamoxifen through suppression of the expression of ER-α36, suggesting that let-7 could be therapeutic target for breast cancer treatment.

Biography

Dr. Xiao is an Associate Professor and the Director of the Functional Genomics and Proteomics laboratories at the Creighton University School of Medicine, and an internationally recognized expert in the field of genomics and proteomics of cancer and bone disease. Dr. Xiao earns his Ph.D. in molecular computational biology at Chinese Academy of Sciences. He had his postdoctoral research trained in Baylor College of Medicine and UCLA, focusing on pharmacokinetics and biochemistry of non-steroid inflammatory drugs, and cell cycle regulation. He has been regular reviewer or ad hoc reviewer for several medial journals, different funding agency and several journal Editorial Board members.
Characterisation and impact of circulating tumor cell diversity on therapy response and metastasis formation

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Universitätsklinikum Jena, Germany

Shedding of cells from solid tumors can occur during growth, diagnostic manipulation (mammography, fine needle aspiration, punch biopsy) and surgery as the first step in the metastatic pathway. However, it requires additional steps for such cells to settle, grow and invade the host tissue in order to form overt metastasis. Most cells released from the primary tumor seem not to be capable to perform these additional steps.

We have shown, the cells released from solid tumors can recirculate in the body, they respond to therapy in a comparable way as the primary tumor, but in always all cases cells are left over after therapy which sooner or later can regrow and form metastases even after years. We now are investigating which properties allow the cells to survive therapy and which prerequisites are necessary to allow them to regrow. This will not only contribute to clarify the metastatic pathways but also help to find ways to target these cells as the origin of new metastases.
Bifidobacterium Infantis on Lewis lung cancer in mice

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Soluble fms-like tyrosine kinase receptor (sFlt-1) is soluble form of extramembrane part of VEGFR-1 that has antitumor effects. Bifidobacterium Infantis is a kind of nonpathogenic and anaerobic bacteria which may have specific targeting property of hypoxic environment inside of solid tumors. The aim of the present study was to construct Bifidobacterium Infantis-mediated sFlt-1 gene transferring system and investigate its anti-tumor effect on Lewis lung cancer (LLC) in mice. Our results demonstrated that the Bifidobacterium Infantis-mediated sFlt-1 gene transferring system was constructed successfully and the system could express sFlt-1 at the levels of gene and protein. This system could not only significantly inhibit growth of HUVECs induced by VEGF in vitro, but also inhibit the tumor growth and prolong survival time of LLC C57BL/6 mice safely. These data suggest that Bifidobacterium Infantis-mediated sFlt-1 gene transferring system presents a promising therapeutic approach for the treatment of cancer.
An investigation of PD-L1 expression and its association with tumor infiltrating T cells in human cervical carcinomas

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Purpose: To observe the expression of Programmed death receptor-ligand 1 (PD-L1) and the association between PD-L1 expression and T cell infiltration in human cervical carcinomas.

Methods: PD-L1 and PD-1 expression was respectively determined in five cases of normal cervical tissue, 7 cases of high-level cervical intraepithelial neoplasia (CIN II-III) and 67 cases of cervical carcinomas by immunohistochemistry staining; the tumor infiltrating CD4⁺T and CD8⁺T cells were determined by immunofluorescent staining, and the apoptosis of tumor infiltrating lymphocytes was examined by TUNEL assay in those cases.

Results: No PD-L1 expressed in normal cervical epithelium; PD-L1 negatively or weakly expressed in epithelia of high grade CIN, the average relative optical density was 0.82 ± 0.75; and PD-L1 expressed in 70% (47/67) cervical carcinomas, the average relative optical density in superficial infiltrating (<0.5 cm) and deep infiltrating cervical squamous cell carcinomas was 2.70 ± 1.68 and 2.90 ± 1.72. PD-1 expressed in partial tumor infiltrating lymphocytes in those cases. PD-L1 expression density of cervical carcinomas was significantly higher than that of CIN (P<0.01); PD-L1 expression density of superficial invasive cervical carcinomas was slightly lower than that of deep invasive cases, but there was no significant statistic difference between them; in addition, PD-L1 expression negatively associated with the number of tumor infiltrating CD8⁺T cells (r = -0.82, P<0.01), but not with the number of CD4⁺T cells (r = -0.05, P> 0.05). Apoptosis occurred in partial tumor infiltrating lymphocytes of cervical carcinomas.

Conclusion: Human cervical carcinoma cells express PD-L1, and it negatively associates with the number of tumor infiltrating CD8⁺T cells, but not with the number of CD4⁺T cells. PD-L1 expression of tumor cells may play role on apoptosis of tumor infiltrating lymphocytes.
To compare efficacy and cost effectiveness of different 5ht3 blockers in acute and delayed nausea and vomiting: a randomized study

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Aim: to compare efficacy and cost effectiveness of three different 5-HT3 blockers in controlling early and delayed nausea and vomiting following chemotherapy. MATERIALS AND METHOD: 30 patients in each group of advanced head and neck malignancy were given cisplatin based induction chemotherapy. All received anti emetics before and during chemo (group 1: condensation iv 16mg prechemotherapy and 8mg iv tds during infusion, group 2: granisetron 3mg iv prechemo and 3mg iv during chemo infusion, group 3: palonosetron 0.25mg iv prechemo). Nausea & vomiting were assessed according to common toxicity criteria for a period of 3 days baseline was matched for age group, stage and histology of tumor. RESULT: among the 78 patients who completed the study, group 2 had 2 & 4 cases respectively of acute and delayed emesis that was significantly lower than the other 2 groups (6 and 11 for group 1 and 2 & 10 for group 3), also overall cost in controlling delayed nausea & vomiting was much lower in group 2. CONCLUSION: the study reflects that granisetron group was the best 5HT3 blocker in terms of efficacy and cost effectiveness to control acute and delayed nausea and vomiting taking into account the Indian patient with respect to economic and health status.

Keywords: 5HT-3 blockers, chemotherapy, delayed nausea and vomiting.

Biography

Piyush Shukla has completed his MD in Radiation Oncology at the age of 28 from Barkatullah University Bhopal M.P. He is presently working as a Senior Resident in the department of Radiotherapy at All India Institute Of Medical Sciences N.Delhi. One of his paper has been selected in TRICITY H&N CANCER meet 2011 at Singapore.
Recent advances in genomics now make it possible to consider enumerating all of the genetic lesions in specific cancers. While these approaches will yield critical information regarding the identity, number, and types of alterations found in human tumors, a complementary approach to decipher the molecular basis of malignant transformation depends upon the application of genome scale tools to annotate the function of genes involved in cancer initiation and progression. Over the past several years, we have developed genome scale RNAi libraries and open reading frame expression libraries that permit a systematic evaluation of genes involved in cancer initiation and maintenance. Using these libraries, we have now performed screens in a panel of human cancer cell lines to systematically identify cancer vulnerabilities. By combining these functional approaches with information derived from mapping the structural abnormalities present in cancer genomes, we have identified several new oncogenes that contribute to cancer development. In addition, many commonly occurring and well-validated oncogenes and tumor suppressor genes remain refractory to molecularly targeted therapies. An alternative strategy for targeting such cancer drivers is to identify gene products that, when suppressed or inhibited, result in cell death only in the presence of an oncogenic allele. Through the use of systematic RNAi screens, we have identified several genes that act as synthetic lethal partners to known oncogenes. Taken together, these studies suggest that combining forward and reverse genetic approaches with information derived from the cancer genome characterization projects will yield a comprehensive list of cancer vulnerabilities and establish a general approach for the rational identification of oncogenic and co-dependent pathways in cancer.

Biography
Dr. Hahn is an Associate Professor at the Dana-Farber Cancer Institute and Harvard Medical School. He is the director of the Center for Cancer Genome Discovery and a Senior Associate Member of the Broad Institute. His laboratory focuses on using functional genomics to study cancer.
The anti-tumor role of gene UBTD1 and a positively regulatory loop between UBTD1 and p53

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Cellular senescence is a powerful barrier to oncogenesis and the mechanisms is unclear. P53 is one of the important genes in regulating cellular senescence. It was reported that p53 can bind to the promoter of UBTD1, which suggested that it may play an important role in the down stream of p53. Currently little is known about the role and mechanism of gene UBTD1 (Ubiquitin domain containing 1). Here we provide the evidence that UBTD1 is overexpressed in senescent fibroblast cells and normal gastric mucous tissues, and lowexpressed in gastric cancer cell lines and gastric cancer tissues transcriptionally and translationally, which suggests that it may play an important role in oncogenesis. We originally found the function of UBTD1 in inducing senescence, inhibiting oncogenesis and cell migration in both p53 mutant and p53 wild-type cancer cell lines by gene transfection, which suggested that UBTD1 does not depend on p53 absolutely. We also found that Ubiquitin domain is the active part of UBTD1. P53 can positively regulate the expression of UBTD1 mRNA by directly binding to the promoter of UBTD1 by ChIP assay, and UBTD1 can inversely increase the level of p53 protein possibly by enhancing the stability of p53 protein, which preliminarily elucidate there might be a new positive regulatory loop between UBTD1 and p53. Further research is still necessary to elucidate the exact mechanism, Which may provide useful prognosis factor and new method of therapy for clinical work.

Biography
Xiaowei Zhang is presently working on his PhD at the age of 28 years at Fudan University Shanghai Cancer Center China. He is also an physician in oncology department. At present, His works involve with the target therapy of cancer and the role of some important cancer related genes.
Inhibition of pancreatic cancer stem cell characteristics in human and \( \text{Kras}^{\text{G12D}} \) transgenic mice by resveratrol

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**Background:** Cancer stem cells (CSCs) can proliferate and self-renew extensively due to their ability to express anti-apoptotic and drug resistant proteins, thus sustaining tumor growth. Therefore, the strategy to eradicate CSCs might have significant clinical implications. The objectives of this study were to examine the molecular mechanisms by which resveratrol inhibits stem cell characteristics of pancreatic CSCs derived from human primary tumors and KrasG12D transgenic mice.

**Methodology/principal findings:** Human pancreatic CSCs (CD133\(^+\)CD44\(^+\)CD24\(^+\)ESA\(^+\)) are highly tumorigenic and form subcutaneous tumors in NOD/SCID mice. Human pancreatic CSCs expressing high levels of CD133, CD24, CD44, ESA, and aldehyde dehydrogenase also express significantly more Nanog, Oct-4, Notch1, MDR1 and ABCG2 than normal pancreatic tissues and primary pancreatic cancer cells. Similarly, CSCs from KrasG12D mice express significantly high levels of Nanog and Oct-4 than pancreatic tissues from Pdx-Cre mice. Resveratrol inhibits the growth (size and weight) and development (PanIN lesions) of pancreatic cancer in KrasG12D mice. Resveratrol inhibits the self-renewal capacity of pancreatic CSCs derived from human primary tumors and KrasG12D mice. Resveratrol induces apoptosis by activating caspase-3/7 and inhibiting the expression of Bcl-2 and XIAP in human CSCs. Resveratrol inhibits pluripotency maintaining factors (Nanog, Sox-2, c-Myc and Oct-4) and drug resistance gene ABCG2 in CSCs. Inhibition of Nanog by shRNA enhances the inhibitory effects of resveratrol on self-renewal capacity of CSCs. Finally, resveratrol inhibits CSC’s migration and invasion and markers of epithelial-mesenchymal transition (Zeb-1, Slug and Snail).

**Conclusions/significance:** These data suggest that resveratrol inhibits pancreatic cancer stem cell characteristics in human and KrasG12D transgenic mice by inhibiting pluripotency maintaining factors and epithelial-mesenchymal transition. In conclusion, resveratrol can be used for the management of pancreatic cancer.