105-04-29

The Associations of Genetic & Epigenetic Factors with Oral Cancer in Taiwan

李郁芬 教授
生物統計研究所

Abstract

Oral cancer (OC) is the 4th leading cause of death in men in Taiwan. Oral potentially malignant disorders (OPMDs) are associated with oral malignant transformation Both OC and OPMDs are complex that environmental factors, viral infections and genetic alterations most likely interact. As genetic alterations and epigenetic changes are equally important in the process, both streams of factors were investigated to understand the associations with OC and OPMDs, respectively.

It is well known that heavy tobacco smoking, high alcohol consumption, and betel nut chewing are the major risk factors for OC development. High-order non-linear interaction effects on OPMDs were evaluated by a Multifactor Dimensionality Reduction (MDR) method among 23 single nucleotide polymorphisms and 3 environmental risk factors. A 4-way interaction was identified for OPMDs which involving genes NAT2, MTHFR, and TNF-α as well as betel nut chewing ($p=0.013$).

Another case-control study was conducted to investigate the association between 1,505 CpG sites selected from 807 cancer-related genes (Illumina GoldenGate Methylation Array) and OC. Thirty-four CpG sites were identified with both sensitivity and specificity greater than 0.7, while the top two CpG sites were belong to genes FLT4 and TFPI2. The results of external validation using pyrosequencing assays for a new set of samples were in line with those obtained using the Illumina GoldenGate Methylation Array. Epigenetic-wide association studies (EWAS) will be conducted for further investigation by means of Infinium HumanMethylation450 BeadChip (including 485,577 methylation sites) and a new 853,307 CpG site platform (Illumina MethylationEPIC BeadChip).

105-05-06

Application of Herbal Medicines and Probiotics in Treating *Helicobacter Pylori* Infection

徐媛曼 教授
生物科技學系

Abstract

Helicobacter pylori is a highly contagious human pathogen. Almost half of the world's population is colonized with this bacterium. Most people have been infected with *H. pylori* in early childhood and infected patients might develop peptic ulcer diseases, mucosa associated lymphoid tissue lymphoma, or even gastric cancer. Treating *H. pylori* infection with antibiotics not only promotes the development of antibiotic-resistance in *H. pylori*, but also causes antibiotic-associated diarrhea and pseudomembranous colitis. In addition to antimicrobial agents, many studies have shown the efficiency of herbal medicals in curing infection. In our study, we showed the therapeutic activities of compounds isolated from *Fatsia polycarpa* Hayata, *Gardeniae fructus*, and *Scutellaria baicalensis* Georgi. Moreover, probiotics compete the nutrients and space with pathogens, and help to moderate the immunity of the host, therefore, it has shown its potential to treat and prevent infectious diseases. Therefore, we are trying to understand the interaction between probiotics, gastric epithelial cells, and *H. pylori* while infection. Based this study, we would like to clarify the efficacy and safety of probiotic applications.

105-05-13

How Do You Mend A Broken Heart?

謝清河 教授
中央研究院生物醫學科學研究所

Abstract

We have used a cardiac specific inducible Cre-*LoxP* transgenic mouse to delineate the underlying mechanism initiating stem cell-modulated cardiac repair and to investigate the regenerative efficiency in young and aged mice. Furthermore, we aimed to identify a tissue engineering or pharmacological intervention that improves the cardiac repair efficiency after myocardial infarction. We found that the critical period of stem cell-mediated cardiomyocyte replenishment is initiated within 7 days and saturates on day 10 post-infarction. Moreover, blocking the inflammatory reaction with COX-2 inhibitors may also reduce the capability of endogenous stem cells to repopulate lost cells. Injection of the COX-2 product PGE_2 enhances cardiomyocyte replenishment in young mice and recovers cell renewal through attenuating TGF-β1 signaling in aged mice. Further analyses suggest that cardiac stem cells are PGE_2-responsive and that PGE_2 may regulate stem cell activity directly through the EP2 receptor or indirectly by modulating its micro-environment *in vivo*. Consistently, an engineered vascular niche in the infarct further attracted stem cells to home to the injected sites, suggesting cardiomyocyte regeneration. More recently, by combining pulse-chase labeling and parabiosis model, we showed that circulating cells derived from the parabiont expressed cardiac-specific markers in the injured myocardium. Genetic fate-mapping also revealed that circulating hematopoietic cells acquired cardiac cell fate by means of cell fusion and transdifferentiation. These studies demonstrate a new strategy for cardiovascular repair with potential for future clinical translation.

References

- Hsieh PC, Segers VFM, Davis ME, MacGillivray C, Gannon J, Molkentin JD, Robbins F, Lee RT. “Evidence from a genetic fate-mapping study that stem cells refresh adult mammalian cardiomyocytes after injury”. *Nat Med.* 2007;13:970-974.
- Lin YD, Yeh ML, Yang YJ, Tsai DC, Zhu TY, Shih YY, Chang MY, Liu YW, Tang ACL, Chen TY, Luo CY, Chang KC, Chen JH, Wu HL, Hung TK, Hsieh PC. “Intramyocardial peptide nanofiber injection improves post-infarction ventricular remodeling and efficacy of bone marrow cell therapy in pigs.” *Circulation.* 2010;122:S132-S141.
- Lin YD, Luo CY, Hu YN, Yeh ML, Hsueh YC, Tang MJ, Springer ML, Hsieh PC. “Instructive nanofiber scaffolds with VEGF creates a microenvironment for arteriogenesis and cardiac repair.” *Sci Transl Med.* 2012; 4:146ra109.
- Hsueh YC, Wu JM, Yu CK, Wu KK, Hsieh PC. “Prostaglandin E2 promotes post-infarction cardiomyocyte replenishment by endogenous stem cells.” *EMBO Mol Med.* 2014;6:496-503.
- Wu JM, Hsueh YC, Ch’ang HU, Luo CY, Wu LW, Nakauchi H, Hsieh PC. “Circulating cells contribute to cardiomyocyte regeneration after injury.” *Circ Res.* 2015;116:633-641.

105-05-20

Development of Novel Drug Delivery Systems for Cancer Molecular Imaging and Therapy

吳漢忠 教授
中央研究院細胞與個體生物學研究所

Abstract

Lack of tumor specificity remains a major problem for chemotherapies in which side effects prevent the delivery of the drug dosages needed to eliminate the majority of cancer cells. Recently, we developed phage display methods to identify several novel peptides and human single chain variable fragment (scFv) antibodies that bind specifically to the plasma membrane of cancer cells. In an effort to develop targeting drug delivery systems, we used peptide-linked liposomes that carried doxorubicin to treat severe combined immunodeficiency (SCID) mice bearing human tumor xenografts. The peptide-functionalised liposomes were found to have an enhanced anti-tumor effect and reduced toxicity. Combined pHCT74-conjugated liposomal doxorubicin (pHCT74-LD) and pHCT74-conjugated liposomal vinorelbine (pHCT74-sLV) therapy exhibited an enhanced antitumor effect and markedly extended the survival of mice with human colorectal cancer in subcutaneous and orthotopic models. Targeting liposomes improved the therapeutic index by enhancing therapeutic efficacy, reducing side effects, and increasing the survival rate of tumor-bearing mice. The tumor site fluorescent intensity in the mice treated with targeting peptide-linked quantum dots showed higher tumor uptake and increased tumor-normal tissue ratios. In addition, *in vivo* imaging by scFv-conjugated quantum dots clearly demonstrated the potential clinical use of the scFv in tumor targeting and imaging. Ligand-conjugated liposomes enhance pharmacokinetic and pharmacodynamic properties, improve efficacy and safety profiles, and allows for controlled biodistribution and drug release. Our study indicates that peptide- or scFv-mediated drug delivery systems show great promise for their applications in tumor-targeted drug delivery and imaging.

105-05-27

New Drug Research, Translational Medicine, and Biotech Entrepreneurship – A Personal Experience

張子文 特聘研究員
中央研究院基因體研究中心

Abstract

Dr. Chang will share the background leading to the founding of Tanox, Inc. in 1986, the initial projects in the company, and the invention of anti-IgE therapy (which led to the development of omalizumab, trade name Xolair) for severe allergy and asthma. Xolair has now become a major drug in treating persistent severe asthma and approved for treating severe chronic spontaneous urticaria worldwide.

Dr. Chang will also share the experience in discovering CemX and the development of a new approach to target the IgE allergic pathway. Finally, he will talk about his drive in setting up a new company after official retirement and the programs to develop new drugs for the treatment of autoimmune diseases and cancer.

105-06-03

Capsid Biology of Hepatitis B Virus

施嘉和 特聘研究員
中央研究院生物醫學科學研究所

Abstract

Hepatitis B Virus (HBV) is an important human pathogen in Taiwan and worldwide. Chronic infection with HBV leads to the development of cirrhosis and hepatocellular carcinoma. While HBV vaccine is effective and available, chronic HBV infection is treatable, but most often not curable. As a DNA virus, HBV replicates via an RNA intermediate. HBV encodes a core protein (HBc), which can assemble into an icosahedral capsid particle. In HBV life cycle, capsid particles play multiple important functions, including RNA encapsidation, DNA synthesis, nuclear import of viral DNAs, and interactions with envelope proteins in virion secretion. In my seminar, I will focus on a so-called charge balance hypothesis, which emphasizes on the balanced electrostatic interactions between the positive charged amino acids and the negative charge content of the macromolecules in the capsid interior. This hypothesis has been experimentally tested in the context of capsid stability, assembly/ disassembly, RNA encapsidation, DNA synthesis, intracellular trafficking, and virion release. It would be interesting to extend the ground rule of balanced electrostatic interactions to other non-HBV viruses.