Medical Research Center for Gene Regulation(2002.09-2018.08)

Director
Prof. **Kyung Keun Kim,** M.D., Ph.D.

Major research goals

The deregulation of gene expression has been implicated in various chronic human disease. The main goal of the Medical Research Center for Gene Regulation is to develop new therapeutic approaches for cancer, Parkinson's disease, cardiovascular diseases and renal fibrosis, and bone metabolic diseases through manipulation of genes. Candidate genes involved in the pathogenesis of these disorders will be screened and cloned, though some genes are already acquired in previous period. We will determine the mechanisms by which these genes contribute to development and progression of the diseases. Altering the specific gene expression by candidate compounds will be tested in cellular systems. To evaluate therapeutic effectiveness, we will test these therapeutic candidates in animal disease models. Finally, we will try preclinical trials for application to humans. Identification and characterization of novel disease-related genes, and development of therapeutic candidate compounds and enhanced gene delivery system should lead to new strategies to control gastric, colorectal and prostate cancers, cardiac hypertrophy, and bone metabolic disorders.

Major research topics

For this research, experiments will be performed with the following plans: 1) Screening the chemical libraries to obtain candidate substances that block the function of KITENIN and p73 in colorectal cancer, HOXB13 in prostate cancer and evaluation of Near Infrared Dye IR-783 to predict prostate cancer prognosis. 2) Evaluation of the molecular mechanism of tumorigenesis by deubiquitinating enzyme USP1 and KAI1 transcriptional regulation through TAp73. 3) Synthesis and biological evaluation of small molecules probe for cancer metastasis & diagnosis 4) Characterization of post-translational modification of transcriptional factors involved in cardiovascular diseases. 5) Investigate the effects of altering master gene expression on regulating osteoblast and osteoclast functions. 6) Development of animal disease model for cancer, cardiovascular diseases, and bone metabolic diseases to evaluate the therapeutic potential of specific gene regulation in animal model system. 7) Designing of preclinical application

and clinical human protocol for proliferative, cardiovascular, bone metabolic disorders.

Major achievements

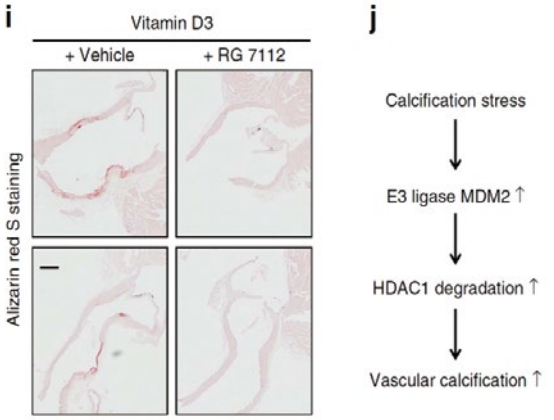
1) Identification of candidate small molecules inhibiting the KITENIN/AP-1 signaling function via in vivo experiments and confirm the effect of identified inhibitors by performing in vivo mouse cancer metastasis model system; 2) Identification of HOXB13-mediated suppression of p21waf1/cip1 regulates JNK/c-jun signaling in prostate cancer cells and evaluated the efficacy of CD46-targeting chimeric Ad5/35 adenoviral gene therapy for colorectal cancers; 3) Identification of eplication Protein A(RPA) deficiency to activate the Fanconi anemia DNA repair pathway, and characterized a novel role for the deubiquitinase USP1 in the control of centrosome duplication and the role of USP1 auto-cleavage in DNA interstrand crosslink repair; 4) Overexpressed p73 deduces cell motility of colorectal cancer cell lines and characterization of 5'-OH-5-nitro-Indirubin oxime(AGM130) via mouse colorectal cancer model; 5) Synthesis of small molecular inhibitor of KITENIN signalling for blocking cancer metastasis; 6) Uncover a previously unappreciated ubiquitination pathway and identification of MDM2-mediated HDAC1 ubiquitination as a new therapeutic target in vascular calcification; 7) Characterized the role of CrkII signaling in RANKL-induced osteoclast differentiation and function and elucidated that Mst2 controls bone homeostasis by regulating osteoclast and osteoblast differentiation.

Major relevant publications(in 2016)

1. Kwon DH, Eom GH, Ko JH, Shin S, Joung H, Choe N, Nam YS, Min HK, Kook T, Yoon S, Kang W, Kim YS, Kim HS, Choi H, Koh JT, Kim N, Ahn Y, Cho HJ, Lee IK, Park DH, Suk K, Seo SB, Wissing ER, Mendrysa SM, Nam KI, Kook H. MDM2 E3 ligase-mediated ubiquitination and degradation of HDAC1 in vascular calcification. Nat Commun. 2016;7:10492.
2. Bae JA, Kho DH, Sun EG, Ko YS, Yoon S, Lee KH, Ahn KY, Lee JH, Joo YE, Chung IJ, Lee SH, Kim H, Kim KK. Elevated Coexpression of KITENIN and the ErbB4 CYT-2 Isoform Promotes the Transition from Colon Adenoma to Carcinoma Following APC loss. Clin Cancer Res. 2016;22(5):1284-94.
3. Kim JH, Kim K, Kim I, Seong S, Jeong BC, Nam KI, Kim KK, Molkentin JD, Kim N. RCANs regulate the convergent roles of NFATc1 in bone homeostasis. Sci Rep. 2016;6:38526.
4. Cho YS, Do MH, Kwon SY, Moon C, Kim K, Lee K, Lee SJ, Hemmi S, Joo YE, Kim MS, Jung C. Efficacy of CD46-targeting chimeric Ad5/35 adenoviral gene therapy for colorectal cancers. Oncotarget. 2016;7(25):38210-38223.
5. Jang SW, Jung JK, Kim JM. Replication Protein A(RPA) deficiency activates the Fanconi anemia DNA repair pathway. Cell Cycle. 2016;15(17):2336-45.
6. Cho SH, Hong CS, Kim HN, Shin MH, Kim KR, Shim HJ, Hwang JE, Bae WK, Chung IJ. FGFR4 Arg388 is Correlated with Poor Survival in Resected Colon Cancer Promoting Epithelial to Mesenchymal Transition. Cancer Res Treat. 2016 Nov;Epub ahead of print.

Representative figures of major achievements

1. Diagram of MDM2/HDAC1 signal cascade in vascular calcificatio(Nat Commun. 2016;7:10492)



2. Schematic diagram summarizing the molecular pathways altered during the formation of colorectal adenoma and progression to adenocarcinoma(Clin Cancer Res. 2016;22(5):1284-94)