Poster Number

53 **N16, a nacreous protein, inhibits osteoclast differentiation and enhances osteogenesis**

Zhen-Yan Xu[1], Ka-Yee Au[2], Jia-Yi Ma[1], Pei-Bo Li[1], Wei-Wei Su[1], and Pang-Chui Shaw[1, 2, 3]
1. Guangzhou Quality R&D Center of Traditional Chinese Medicine, Guangdong Key Laboratory of Plant Resources, School of Life Science, Sun Yat-Sen University, Guangzhou, 510275, China
2. School of Life Sciences, The Chinese University of Hong Kong, Hong Kong S.A.R., China
3. State Key Laboratory of Phytochemistry and Plant Resources in West China, Institute of Chinese Medicine,The Chinese University of Hong Kong, Hong Kong S.A.R., China

Osteoporosis is a disease characterized by a significant loss of bone mass which leads to higher bone fragility and is attributed to the imbalance between bone resorption and formation. Organic matrix of nacre has been shown to regulate calcification during shell formation and the water-soluble components facilitate bone repair by inducing osteoblast differentiation and bone formation in vitro and in vivo. In this study, the effects of N16, a nacreous protein, on osteoclast differentiation and osteogenesis were investigated using the pre-osteoclast cell line RAW264.7 and pre-osteoblast cell line MC3T3-E1, respectively. Here we showed that N16 potently suppressed the proliferation, RANKL-induced formation of multinucleated osteoclasts and TRAP activity in pre-osteoclasts in a dose-dependent way. The nacre protein also inhibited actin ring formation and RANKL-induced mRNA expression of transcription factor NFATc1 and osteoclast-associated genes, including TRAP, c-Src, cathepsin K. Besides, the results on pre-osteoblast found that N16 increased ALP activity as well as mineralized nodule formation with concomitant increases in the mRNA expression of osteoblast marker genes, namely osteopotin, osteocalcin and Runx2. Our findings demonstrate this nacreous protein exerts both anabolic and anti-resorptive effects on bone and is a promising anti-osteoporosis agent.

54 **Interplay between ER stress and hypoxia pathways in chondrocytes**

Angela Q Yao, Wilson CW Chan, Vivian CW Ng, Tan Zhijia, Kwok Y Tsang, Kathryn SE Cheah and Danny Chan
Department of Biochemistry, Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong

Interplay between stress signals can regulate cell fate. Potential connections are emerging between hypoxia and ER homeostasis. It is well established that presence of mis-folded protein in the endoplasmic reticulum (ER) triggers the unfolded protein response (UPR) as part of the ER-stress signal for cell survival. Under low oxygen tension or hypoxia, the cell activates the hypoxic stress signal via the activation of Hif genes, and utilize components of the ER-stress pathways for cell survival and adaptation to the stress condition. However, whether activation of ER stress by accumulation of mis-folded protein has a direct relationship with activation of hypoxia and components of the hypoxia stress pathways is unknown. Collagen X is an ECM specifically expressed by hypertrophic chondrocytes. We previously generated transgenic and gene-targeted mouse models for metaphyseal chondrodysplasia type Schmid (MCDS), expressing mutant Collagen X (13del) that cannot folded correctly, and are retained within the ER, activating ER-stress. Interestingly, we showed that components of the hypoxic stress were also activated concomitantly. This is evidenced by the activated expression of two key transcription factors of hypoxia stress, HIF-1and HIF-2expressed and localized within hypertrophic chondrocytes of MCDS mice compared to WT mice. In addition, the oxygen tension of hypertrophic chondrocytes in MCDS mice is significantly decreased when assayed using EF5, a bio-reductive marker of hypoxia. This study suggested, for the first time in vivo, that ectopic expression of mis-folded protein in chondrocytes which induces ER stress can also trigger hypoxia and hypoxia pathways. Understanding the mechanism of this newly discovered relationship between hypoxia and ER stress, and how do they control cell fates, will have important implications to development and many human diseases.