Thermal stress promote tumorigenesis in ESCC via TRPV2-dependent pathway

Rongqi Huang[1,2], Shuai Li[1,2], Chao Tian[1], Huifang Zhao[1], Yuchen Yang[1], Zuoxian Lin[1], Na Cheng[1,3] & Zhiyuan Li[1,2,3,4 *]

Key Laboratory of Regenerative Biology, Guangdong Provincial Key Laboratory of Stem Cell and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

University of Chinese Academy of Sciences, Beijing, China

Department of Anatomy and Neurobiology, Xiangya School of Medicine, Central South University, Changsha, China

GZMU-GIBH Joint School of Life Sciences, Guangzhou Medical University, Guangzhou, China

Esophageal squamous cell carcinoma (ESCC) is a leading cause for cancer death worldwide. The etiology of the disease has been suggested to be multifactorial. Expose the esophageal mucosa to heat stimuli has been recognized as a risk for the initiation and development of ESCC, while the underlying mechanism remains uncharacterized. Here, we show that TRPV2 acts as a key sensor of noxious thermal stress via examination the responses of ESCC cells (Eca-109 and TE-1) to heat stimulation at the range of 37 ℃—65 ℃, we found that recurrently acute thermal stress (> 54 ℃) could promoted cancerous behaviors (proliferation, migration and invasion) of ESCC cells, prolonged exposure to heat stimuli could induce cell death at the early stage, while subsequently the cancerous behaviors of the 'survived' ESCC cells were enhanced considerably; The pro-angiogenesis capacity of the ESCC cells were also found to be increased profoundly in a 3D culture assay; and both tumor formation and metastasis of the cells were promoted substantially in a nude mice model. Expression of the transient receptor potential vanilloid receptor 2 (TRPV2), one of the non-specific cation channel receptor family members, were found to be upregulated in either ESCC cells compared with the non-tumor esophageal squamous cells (NE2) or in clinical ESCC samples compared with adjacent non-tumor tissues. The ESCC cancerous behaviors were augmented markedly upon the activation of TRPV2, and these effects were inhibited significantly by the TRPV2 inhibitor tranilast or abolished by TRPV2 knock-out by using Crispr-Cas9. The cellular cancerous behaviors have been linked to activation of TRPV2 in these cells. Mechanistically, the role of TRPV2 playing in progression of ESCC were mainly regulated by PI3K and Hsp signaling pathways. Our findings suggest that TRPV2 play an important role in the tumorigenesis in ESCC. TRPV2-PI3K pathway holds promise for the prevention and treatment of ESCC.