Molecular targeting of ERKs-RSK2 signaling axis in human cancer

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Receptor tyrosine kinases (RTKs) which are activated by diverse stimuli, such as growth factors, cytokines and environmental stresses, play a key role in cell proliferation, transformation and cancer development in humans. Since constitutive active mutations in Ras and Raf are frequently observed with high percentage in many solid tumors, including colon, pancreas, ovarian, melanoma, non-small cell lung and other cancers, Ras-mediated Rafs/MEK/ERKs/RSK2 signaling axis plays a key role in the regulation of cell proliferation, transformation and cancer development. Thus, Ras/Rafs/MEKs/ERKs/RSKs signaling pathway has become an important target to develop/identify chemopreventive and therapeutic agents. Recently, our results demonstrated that RSK2, a downstream kinase of ERKs, is an important proof-of-concept on the human cancer development. Ectopic expression of RSK2 induced anchorage-independent cell transformation without stimulation of tumor promoters such as epidermal growth factor. Moreover, human skin cancer tissue array demonstrated that total- and phospho-RSK2 protein levels were higher in skin cancer tissues compared with normal skin tissues. Utilizing cutting edge molecular and computational research tools, we provided evidences that kaempferol and eriodictyol were natural compounds which target and inhibit RSK2 activity. Moreover, we found that magnolin, a natural compound abundantly found in magnolia flos, targeted ERK1 and ERK2 and inhibited ERK1 and ERK2's activities with 68 nM and 16.5 nM of IC_{50} values. Moreover, magnolin suppressed cell migration and invasion in cancer cells by inhibition of epithelial-to-mesenchymal transition of cancer cells. Taken together, our results provide strong evidences that ERKs and RSK2 are key kinases regulating cell proliferation and transformation, and are important targets to develop/identify small molecules as chemopreventive and/or therapeutic agents.

Speaker Biography

Yong-Yeon Cho, PhD, is an Associate Professor and Director for Integrated Research Institute of Pharmacutical Sciences at the College of Pharmacy, The Catholic University of Korea. He earned his PhD degree at the Tohoku University (Applied Genetic Engineering) under the supervision of Professor Tokuo T Yamamoto in Sendai, Japan in 2000. He then joined Zigang Dong as a Post-Doc at the Hormel Institute, University of Minnesota, in Dec-2001. He brought with him his expertise in Molecular Biology and Genetic Engineering, which was integral to the research of protein-protein interactions, signaling networks and molecular targeting of small molecules. Based on his scientific achievements, he became Research Assistant Professor at the Hormel Institute, University of Minnesota in 2005. His efforts resulted in the breakthrough that the post-translational modification of stem cell factors plays an important role to regulate stemness of ES cells and reprogramming efficiency. He came back and started a new endeavor in Korea in 2011. Currently, he continues his research on molecular mechanisms of novel signaling pathways regulating protein stability regulation in cancer development and chemoresistance.

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