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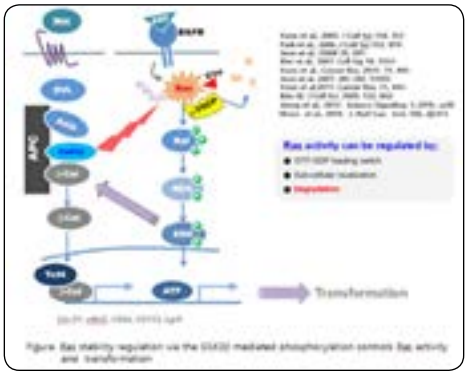
Kang-Yell Choi

Yonsei University, South Korea

Degradation of both β-catenin and RAS via targeting the Wnt/β-catenin pathway is an ideal approach for colorectal cancer treatment

Interaction between the Wnt/beta-catenin and the Ras-ERK pathways, two major transforming pathways, have been posited. However, molecular mechanisms and cooperative roles of these two pathways are poorly understood. Both *APC* and *KRAS* mutations synergistically promote cellular transformation and tumor growth, attributed to activation of the RAS-ERK pathway via activation of the Wnt/ β-catenin signaling. One key event in this crosstalk is the stabilization of RAS, especially mutant KRAS, by APC loss. Stabilization of both β-catenin and RAS plays a critical role in the synergistic transformation, and both β-catenin and RAS levels are highly increased in CRC patient tissues. Epidermal growth factor receptor (EGFR), a direct transcriptional target of the Wnt/β-catenin signaling pathway, is also overexpressed in human CRC, and plays a role in the synergistic tumorigenesis. Therefore, inhibition of both the Wnt/β-catenin and EGFR-RAS-ERK pathways, especially by reducing levels of the proteins elevated in CRC, could be an ideal approach for the treatment of human CRC. This concept for an ideal therapeutic approach has been proved by small molecules destabilizing both β-catenin and RAS by activation of GSK3β via targeting the Wnt/β-catenin pathway. GSK3β activated by the small molecules induce phosphorylation and subsequent polyubiquitin-dependent proteasomal degradations of both β-catenin and Ras and subsequent transcriptional suppression of EGFR overcome current limitation of the insensitiveness of the EGFR targeting therapies such as cetuximab attributed by a K-Ras mutation of patients. Moreover, these small molecules effectively suppress activaiton of cancer stem cell activated through aberrancies of the Wnt/ β-catenin and Ras-ERK pathways.



Recent Publications:

1. Cha P H, Cho Y H, Lee S K, Lee J H, Jeong W-J, et al. (2016) Small molecule binding of the axin-RGS domain promotes β-catenin and Ras degradation. Nature Chemical Biology 12: 593–600.
2. Kim H Y, Choi S, Yoon J H, Lim H J, Lee H, et al. (2016) Small molecule inhibitors of Dishevelled-CXXC5 interaction are new drug candidates for bone anabolic osteoporosis therapy. EMBO Molecular Medicine 8:375–387.
3. Lee S H, Kim M Y, Kim H Y, Lee Y M, Kim H S, et al. (2015) The dishevelled-binding protein cxxc5 negatively regulates cutaneous wound healing. Journal of Experimental Medicine 212(7):1061–80.

4. Kim H Y, Yoon J Y, Yoon J H, Cho K W, Lee S H, et al. (2015) CXXC5 is a negative-feedback regulator of the Wnt/β-catenin pathway involved in osteoblast differentiation. Cell Death and Differentiation. 22(6):912–20.
5. Moon B S, Jeong W J, Park J, Kim T I, Min D S, et al. (2014) Oncogenic K-Ras accelerates cancer stem cell activation via aberrant Wnt/beta-catenin signaling. JNCI-Journal of the National Cancer Institute 106(2):373.

Biography

Kang-Yell Choi finished his doctorate in Biochemistry at the Purdue University in 1993, and performed research related with cell signaling with the yeast pheromone signaling pathway as a model system at Harvard Medical School as a postdoctoral fellow. There, he characterized Saccharomyces Ste5 functioning at the MAP kinase pathway as a 1st protein introduced concept for the "Scaffold Protein" in the community. In 1995, he returned back to Korea as a professor of Yonsei University. Since then, he has been working on mammalian cell signaling related with several different pathophysiologies such as growth control of cells and human cancer. He is serving as the chief of the National Research Laboratory of the Molecular Complex Control for recent 5 years, and currently positioned as the Director of the Translational Research Center for Protein Function Control supported by Ministry of Science, ICT and Future Panning of Korea.

kychoi@yonsei.ac.kr

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