Journal Club No. 749 **November 29th, 2016**

Kruthi Suvarna

Introduction

CRC is one of the most frequent cancers and the second leading cause of cancer related deaths in Western countries. CRC arises through the occurrence of multiple and sequential genetic abnormalities including APC and KRAS mutations. These mutations lead to aberrant activation of Wnt/beta-Catenin and Ras/Erk pathways. Accumulating evidence shows that the Ras/Erk pathway strongly interacts with the Wnt/beta-Catenin pathway during the formation and growth of CRC. Thus therapies targeting both the pathways are suggested to be ideal treatments for human CRC; however, therapeutics targeting both of these pathways has not been developed because mechanism regulating these pathways is not well understood.

Small-molecule binding of the axin RGS domain promotes beta-Catenin and Ras degradation

Pu-Hyeon Cha, Yong-Hee Cho, Sang-kyu Lee, JaeHeon Lee and Kang-Yell Choi (Yonsei University, Seoul, Korea.)

Nature Chemical Biology, Vol 12, August 2016.

Abstract

Both the Wnt/b-catenin and Ras pathways are aberrantly activated in most human colorectal cancers (CRCs) and interact cooperatively in tumor promotion. Inhibition of these signaling may therefore be an ideal strategy for treating CRC. We identified KY1220, a compound that destabilizes both beta-catenin and Ras, via targeting the Wnt/beta-catenin pathway, and synthesized its derivative KYA1797K. KYA1797K bound directly to the regulators of G-protein signaling domain of axin, initiating b-catenin and Ras degradation through enhancement of the b-catenin destruction complex activating GSK3b. KYA1797K effectively suppressed the growth of CRCs harboring APC and KRAS mutations, as shown by various in vitro studies and by in vivo studies using xenograft and transgenic mouse models of tumors induced by APC and KRAS mutations. Destabilization of both b-catenin and Ras via targeting axin is a potential therapeutic strategy for treatment of CRC and other type cancers activated Wnt/b-catenin and Ras pathways.