From discovering the noncanonical roles of ribose-5-phosphate Isomerase A in colorectal tumorigenesis and hepatocarcinogenesis toward precision medicine using zebrafish model

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Ribose-5-phosphate isomerase A (RPIA), the key enzyme in non-oxidative phase of pentose phosphate pathway (PPP) generates ribose-5-phosphate for nucleotide synthesis. Deregulation of RPIA is known to promote cancer formation, however, the underlying mechanism of RPIA-mediated tumorigenesis was unclear. In this study, we discovered a non-canonical function of RPIA in colorectal tumorigenesis. In colorectal cancer (CRC) patients, RPIA is significantly elevated. Overexpression of RPIA increased cell proliferation and oncogenicity via activation of β-catenin, and RPIA enters the nucleus to form a complex with APC and β-catenin. Further investigation suggested that RPIA protects β-catenin by preventing its phosphorylation, ubiquitination, and subsequent degradation. Different from the catalytic role in PPP, RPIA-mediated tumorigenesis via the C-terminus of RPIA (AAs 290 to 311) which were not previously identified. Gut specific RPIA transgenic zebrafish developed tumorigenesis as early as 3 months by activation of β-catenin and its target genes. Our findings suggest RPIA, an enzyme in pentose phosphate pathway, can enter nucleus and associate with APC/β-catenin, and shed a light for precise therapy by targeting the non-enzymatic domain for human CRC with overexpression of RPIA.

Previously, we had demonstrated that RPIA increased hepatoma cell proliferation and colony formation through activation of extracellular signal-regulated kinase (ERK) signaling pathway using cell line and xenograft mouse model. To further investigate RPIA-mediated hepatocarcinogenesis, two independent lines of transgenic zebrafish expressing human RPIA in the liver were generated. These studies reveal that RPIA overexpression triggers lipogenic factor/enzyme expression, steatosis, fibrosis and proliferation of the liver. In addition, the severity of fibrosis and the extent of proliferation are positively correlated with RPIA expression levels. Furthermore, RPIA-mediated induction of hepatocellular carcinoma (HCC) requires the ERK and β-catenin signaling pathway but is not dependent upon transaldolase levels. Our study presents a mechanism for RPIA-mediated hepatocarcinogenesis and suggests that RPIA represents a valuable therapeutic target for the treatment of HCC.

Our study provide in vivo animal model and possible mechanism for RPIA-mediated tumorigenesis in colon and liver, and imply RPIA could be a superior target for therapeutic agents intended to treat CRC and HCC.