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p38γ MAPK signaling and pancreatic tumorigenesis

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Pancreatic ductal cancer (Pda) lacks established therapeutic targets and is consequently among the deadliest malignancies with near-universal K-Ras mutations. Here, we report that a K-Ras effector p38γ (MAPK12) is required for pancreatic tumorigenesis through stimulating metabolic reprogramming. Both conditional p38γ-knockout and pharmacological inhibition decrease pancreatic tumorigenesis and inhibit Pda growth. Mechanistically p38γ binds PFKFB3 dependent of mutated K-Ras and phosphorylates this glycolytic activator at S467, which is required for aerobic glycolysis and Pda growth. Activation of the p38γ/p-PFKFB3 pathway in clinic specimens further correlates with decreased patient survival. Thus, p38γ MAPK is essential for Pda tumorigenesis by linking K-Ras oncogene activity and metabolic reprogramming and may be targeted for therapeutic intervention. Ras is the most established oncogene in human cancer, with its mutation (K-Ras) occurring in about 50% human colon cancer and its hyperexpression (H-Ras) in more than 50% of human breast cancer. Ras oncogene activity, however, is determined by downstream effectors and elucidation of this regulation is essential to understand why not all Ras mutations can lead to human malignancies. MAPKs (Mitogen-Activated Protein Kinases), including ERK, JNK and p38, signal downstream of Ras by converting extracellular and Ras signals into specific cellular response through a group of transcription factors. Our previous work established that Ras-induced p38 alpha phosphorylation/activation inhibits the oncogene activity by negative feedback. Results from our recent studies further showed that p38 gamma, a p38 family protein, is induced by Ras and in turn required for Ras transformation in rat intestinal epithelial cells and for Ras-invasive activity in human breast cancer. These results together indicate that signaling integrations among p38 family members determine Ras oncogene activity in a given tissues and p38 proteins regulate Ras activity by isoform-dependent mechanisms. Currently, we are investigating mechanisms by which Ras induces p38γ expression and by which p38γ is required for Ras-induced transformation/invasion. Nuclear receptors are group of transcription factors that play an important role in reproduction, homeostasis and cancer development through regulating gene expression in response to their ligand. Our second research interest is to study signal cross-talks between Ras/MAPK pathways and nuclear receptors. Studies from our lab have established a c-Jun/AP-1 dependent trans-activation for stress-induced Vitamin D Receptor (VDR) expression and an anti-apoptotic activity of VDR by a K-Ras dependent mechanism. Our results further showed that another nuclear receptor ER (Estrogen Receptor) inhibits stress MAPK-mediated cell death independent of its transcriptional activity by converting pro-apoptotic c-Jun activity into a c-Jun-dependent AP1 transcription. These results together suggest that nuclear receptors may cooperate with Ras/MAPKs to regulate stress-response independent of their transcription activity. We are currently investigating whether regulation of nuclear receptors represents a novel strategy for human cancer treatment.

Biography

Guan Chen is a professor at Medical College of Wisconsin. He has completed his MD from Bengbu Medical College, Anhui, P.R. China in the year 1982 and did his MS at Sun Yat-Sen Univeristy, Guangzhou P.R. China in the year 1985. He has completed his PhD in Pharmacology, University of Heidelberg, Germany in 1990.

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