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Sam68 regulates colon tumorigenesis by genotoxic stress-induced NF-κB activation

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Nuclear factor kappa B (NF-κB) is a transcription factor that controls genes for cell survival and NF-κB signaling has emerged as one of the most important mediators of the cellular response to genotoxic stresses. Genotoxic agents trigger a 'nuclear-to-cytoplasmic' NF-κB activation signaling pathway; however, the early events controlling the initiation of the signaling pathway is poorly understood. Our data demonstrate that Src-associated-substrate-during-mitosis-of-68 kDa/KH domain containing, RNA binding, signal transduction associated 1 (Sam68/ KHDRBS1) plays a key role in genotoxic stress-initiated NF-κB signaling pathway. Sam68 directly binds to Poly (ADP-ribose) polymerase 1 (PARP1) and regulates PARP1 enzymatic activity *in vitro*. Sam68 deficiency abolishes DNA damage-stimulated polymers of ADP-ribose (PAR) production and the PAR-dependent NF-κB transactivation of anti-apoptotic genes. Sam68 null cells are hypersensitive to genotoxicity caused by genotoxic agents. Up-regulated Sam68 coincides with elevated PAR production and NF-κB activation in human and mouse colon cancer. Interference with Sam68 protein sensitizes human colon cancer cells to genotoxic stress-induced apoptosis and the hypersensitivity is abolished by ectopic expression of constitutively activated NF-κB. Further, genetic deletion of Sam68 substantially alleviates colon tumor burden in mice model. Taken together, our findings reveal a novel function of Sam68 in the genotoxic stress-initiated nuclear signaling, which is critical for colon tumorigenesis.

Biography

Kai Fu has completed his PhD from the University of Science and Technology of China. He started his Post-doctoral training in the Department of Biochemistry and Molecular Biology at Johns Hopkins Bloomberg School of Public Health since 2012.

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