

Role of Chk2 on tumorigenesis

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In response to ionizing radiation (IR), the tumor suppressor p53 is stabilized and promotes either cell cycle arrest or apoptosis. Chk2 activated by IR contributes to this stabilization, possibly by direct phosphorylation. Like p53, Chk2 is mutated in patients with Li-Fraumeni syndrome. Since the ATM gene is required for IR-induced activation of Chk2, it has been assumed that ATM and Chk2 act in a linear pathway leading to p53 activation. To clarify the role of Chk2 in tumorigenesis, we generated gene-targeted Chk2-deficient mice. Unlike ATM^{-/-} and p53^{-/-} mice, Chk2^{-/-} mice do not spontaneously develop tumors, although Chk2 does suppress DMBA-induced skin tumors. Tissues from Chk2^{-/-} mice, including thymus, CNS, fibroblasts, epidermis and hair follicles, show significant defects in IR-induced apoptosis or impaired G1/S arrest. Quantitative comparison of the G1/S checkpoint, apoptosis, and expression of p53 proteins in Chk2^{-/-} versus ATM^{-/-} thymocytes suggested that Chk2 regulates p53-dependent apoptosis in an ATM-independent manner. These data indicate that distinct pathways regulate the activation of p53 leading to cell cycle arrest or apoptosis.

Disruption of Brca1 results in cellular demise or tumorigenesis depending on cellular context. Inactivation of p53 contributes to Brca1-associated tumor susceptibility. We show that Chk2 inactivation is partially equivalent to p53 inactivation, in that Chk2 deficiency facilitates the development, survival, and proliferation of Brca1-deficient T cells at the expense of genomic integrity. Brca1 deficiency was found to result in Chk2 phosphorylation and the Chk2-dependent accumulation and activation of p53. Furthermore, inactivation of Chk2 and Brca1 was cooperative in breast cancer. Our findings identify a critical role for Chk2 as a component of the DNA damage-signaling pathway activated in response to Brca1 deficiency.