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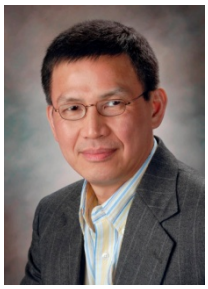

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The cellular response to DNA damage includes cell cycle arrest, activation of DNA repair and induction of apoptosis. Our research is focused on elucidation of the signaling mechanisms that regulate the response to genotoxic stress. Specifically, our work is directed at determining how DNA damage is converted into intracellular signals that control cell behavior.

One project of our current studies involves investigating the role of c-Abl tyrosine kinase in DNA damage-induced cellular responses. Our work has shown that activation of c-Abl is associated with interaction of c-Abl and the p53 tumor suppressor (*Nature* 38:272-274, 1996). We have also demonstrated that activation of c-Abl by DNA damage is associated with phosphorylation and activation of p73 (*Nature* 399(6738):814-817, 1999). We are currently in the process of establishing systems by which the functional role of c-Abl can be assessed in a more biological relevant context from molecular, cellular to whole animal levels.

Our other project focuses on functional regulation of tumor suppressor p53, which is a transcription factor that is activated in response to genotoxic stress, leading to the induction of a number of genes whose products mediate cell cycle arrest, apoptosis and DNA repair. Because of its growth inhibitory function, maintaining p53 at low level, under non-stress condition, is essential for cell survival. This is achieved primarily by the action of Mdm2, which is an ubiquitin E3 ligase that targets p53 for ubiquitination-dependent proteolysis. We have been involved in the investigation of signals and pathways important for regulation of MDM2-mediated p53 control. We have recently obtained compelling evidence that allow us to propose a novel model of p53 regulation, and contributed to the advance of the p53 field (*Mol Cell Biol* 20(4):1243-1253, 2000. *Cancer Res* 61:1741-1746, 2001. *Cancer Res*. 61: 6703-6707, 2001. *Mol Cell Biol* 21(24):8533-46, 2001. *Mol Cell Biol.* 2003 23(14):4939-47. *Mol Cell Biol*. 2003 23(12):4230-46. *Oncogene* .26(29):4209-15, 2007. *Cancer Res.* 67(13):6026-30, 2007. *J Biol Chem*. 2008 Mar 20. *Cancer Research* 2008;68(22):9131-6). Our understanding of p53 regulation is now at a point where we can design approaches to modulate the activity of p53, which may have application potential in modifying cellular radiation responses. In addition, we have developed a cell-based assay to screen for synthetic small molecules able to activate p53. Such molecules, if identified, may hold great promises not only in research but also in therapeutics.

Another project focuses on gaining a better understanding of how the tissue microenvironment can influence cell behavior and stress response. In this regards, we have established three-dimensional coculture systems to model cell-cell and cell-extracellular matrix interactions so we can assess cell stress response in a tissue-like context. This system has not only enabled us to investigate intricate interactions of different cell types with their neighbors and with the extra cellular surroundings but also to dissect biochemically the mechanisms. We are currently testing the hypothesis that oxidative stress induced senescent stromal cells persist and accumulate, which could create a permissive microenvironment to promote proliferation of epithelial cells that harbor mutations, contributing to the progression of carcinogenesis (*Cancer Res*, 65(15): 6734-44, 2005). We are currently expanding the 3D coculture system by including adipocytes or immune cells to study the correlation of obesity and increased risk of cancer as well as the association of inflammatory response and human cancer, two very important areas of cancer research.