

Mouse Models of Radiosensitivity

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Ionizing radiation (IR) is a known environmental, medical, and military hazard that can produce dreadful health impairments. At the molecular and cellular level, radiation toxicity paradigm defines DNA damage as the most critical biological effect inferred by IR [1,2]. Specifically, IR produces clustered DNA damage, particularly double-strand DNA breaks (DSBs). Signal transduction pathways and DNA repair systems are activated in response to IR to protect cells from injury. Discovery of radiosensitive human diseases has revealed two disease classes consistent with the distinct biological responses to IR: recognition of DSBs and repair of DSBs.

After tumor irradiation, the patients with one class of radiosensitive diseases developed severe dermatitis and deep tissue necrosis. This disease class includes ataxia-telangiectasia (AT) [3], the Nijmegen breakage syndrome (NBS) [4], ataxia-telangiectasia-like disorder (ATLD) [5] and Nijmegen breakage syndrome-like disorder (NBSLD) [6]. Genes responsible for these disorders have been identified as *ATM* for AT, *NBS1* for NBS, *MRE11A* for ATLD and *RAD50* for NBSLD [7]. Proteins encoded by these genes are all required for checkpoint response, a signal transduction pathway that recognizes DSBs [8].

Another class of radiosensitive diseases exhibits severe combined immunodeficiency (SCID), and the responsible genes are *DNA-PKcs*, *Artemis* and *LIG4* (DNA ligase IV) [9]. Proteins encoded by these genes are involved in the repair of DSBs via a process called non-homologous end-joining (NHEJ) [10].

Identification of genes responsible for radiosensitive diseases allowed for development of radiosensitive mouse models. Mice deficient in *Atm* were created for targeting the checkpoint response [11]. However, inactivation of *Mre11*, *Rad50*, or *Nbs1* led to early embryonic lethality, allowing only for models with conditional knockout of these genes. In addition to MRN complex (*Mre11*, *Rad50* and *Nbs1*) which recognizes DSB end and recruits *ATM*, other proteins are essential for IR-induced checkpoint and cell cycle arrest including *H2AX* and *p53* [12]. Mice deficient in these proteins also demonstrate increased radiosensitivity [13]. SCID mouse models represent genes involved in IR-induced DSB repair through NHEJ [14].

Studies of mouse models of radiosensitive diseases demonstrated that immunodeficiency and elevated risk of leukemia/lymphoma associated with radiosensitivity is attributed to defects in DNA damage response and repair mechanisms acquired during development of the immune system. In the absence of checkpoint response, the risk of abnormal end joining of broken DNA is increased. Without NHEJ, the DSBs must be repaired by other less specific mechanisms to insure cell survival thus increasing probability of errors. Consequently, accumulation of cells with the abnormal DNA rearrangements may increase the risk of developing lymphoma/leukemia.

The most recent studies of molecular mechanisms underlying IR-induced cell death emphasize multiple pathways regulating cellular response to IR beyond DNA damage and repair. These pathways include membrane-dependent signaling pathways and by stander effect, a process of cellular response to irradiation of the neighboring cells rather

than to direct IR exposure [15]. Targeting proteins regulating these pathways opens new avenues for development of new animal models of radiosensitivity. One recent example is a knockout of mitochondrial tumor suppressor *Fus1* in mice. This model demonstrated novel radioprotective function for *Fus1* which modulates radiosensitivity of normal tissues via regulation of anti-oxidant response pathways [16]. Interestingly, *Fus1*-deficient mice had increased frequency of spontaneous tumors and immunologic disorders [17,18], consistent with the mechanistic link of radiosensitivity to abnormal immune functions and increased risk of cancer.

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