

**THE TUMOR SUPPRESSOR P53 ACTS DURING TOTAL-BODY IRRADIATION TO DECREASE HEMATOPOIETIC STEM/PROGENITOR CELL FITNESS AND TO PROMOTE LYMPHOMA DEVELOPMENT**

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Exposure to ionizing radiation can cause acute toxicity and long-term side effects, such as radiation-induced cancer. While inhibition of the tumor suppressor p53 ameliorates acute hematological radiation toxicity in mice, this approach may increase the risk of radiation-induced cancer because radiation accelerates tumor development in mice with germline knockout of p53. Recent studies indicate that activation of p53 by the DNA damage response is dispensable for p53-mediated tumor suppression, suggesting that preventing acute toxicity by blocking p53 during irradiation will not increase the risk of radiation-induced cancer. To test this hypothesis, we investigated the effects of temporarily blocking p53 during total-body irradiation (TBI) with 320 kVp X-rays on tumor formation using transgenic mice harboring a doxycycline (Dox)-inducible short hairpin RNA (shRNA) against p53. Unexpectedly, we observed that temporary knockdown of p53 during TBI not only ameliorated acute toxicity of the hematopoietic system, but also improved long-term survival of mice by preventing the development of thymic T-cell lymphoma. Lymphoma formation was preceded by clonal expansion of CD4<sup>hi</sup>CD8<sup>+</sup> thymocytes with dysregulated Notch signaling. In addition to suppressing clonal expansion in the irradiated thymus, temporary knockdown of p53 during TBI improved fitness of hematopoietic stem/progenitor cells (HSPCs) in the bone marrow. These findings suggest that reversibly blocking p53 during irradiation is a promising approach to ameliorate acute toxicity without exacerbating radiation-induced cancer.