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A Beclin1 knockout mouse model mimicking acute radiation syndrome

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ABSTRACT

Objective: To determine the role of the Beclin-1 (Becn1) protein in radiation-exposed mice.
Methods: A gene targeting strategy was employed to generate Becn1-floxed mice, which were then crossed with Ubc-iCre mice to create preconditional gene knockout mice (also referred to as Becn1$^{f/f}$;Ubc-iCre mice). Then, tamoxifen (TMXF) induction was used to generate Becn1 knockout mice. Both Becn1 knockout and lethally irradiated mice were euthanized a day before their respective median survival time. Their organs and tissues including the heart, liver, spleen, lung, kidney, and intestine were collected for examination. Furthermore, the Becn1 knockout and lethally irradiated mice were compared through genetic, histological, and functional analyses.
Results: Mice subjected to systemic Becn1 gene knockout and those exposed to a lethal dose of γ-ray irradiation exhibited similar phenotypes, including reduced survival time (median survival: 8–9 d for KO *vs.* 8–11 d for irradiated), morphological and pathological changes in various tissues and organs, hematopoietic system disruptions, and DNA damage. Hematoxylin and eosin (H&E)-stained sections showed analogous pathological changes in both the Becn1 knockout and lethally irradiated mice, such as the disrupted splenic architecture with decreased white pulp, degenerating thymic follicles, significantly reduced nucleated cells within the femur, and extensively denuding intestinal villi. These mice demonstrated impaired proliferation and differentiation capacities of hematopoietic stem and progenitor cells (HSPCs), presenting similar DNA damage indicators, such as heightened reactive oxygen species (ROS) levels and increased γ-H2AX expression in the bone marrow, heart, spleen, and thymus. Notably, the Becn1 protein in the mice underwent rapid degradation within 6 h after radiation exposure.
Conclusion: Whole-body biallelic deletion of Becn1 in adult mice mimics the effects of lethal radiation, indicating that Becn1 is a hyperradiosensitive protein.

1. Introduction

The expansion of nuclear technology has increased human exposure to radiation. Radiation can harm cells, tissues, and organs by causing biomolecular damage such as the generation of oxygen free radicals, DNA strand breaks, and protein degradation.[1,2] Studies on radiation protection primarily focus on repairing radiation-induced tissue damage and reducing the adverse effects of radiotherapy on normal tissues. However, practical implementation remains a challenge.[3,4] Chaves-Pérez et al.[5] identified the radiation-sensitive URI protein as crucial for intestinal integrity post-irradiation. Beclin1 (Becn1), a key autophagy-related protein within the Vps34 complex, functions as a tumor suppressor.[6–12] In MCF7 breast cancer cells, Becn1 transfection can enhance autophagy, inhibit tumor proliferation, and reduce tumorigenesis.[13] Besides, mice with heterozygous deletion of Becn1 show an increased incidence of spontaneous tumor formation.[14,15] Clinically, *Becn1* loss is commonly observed in prostate, breast, and ovarian cancers, with a particularly high prevalence in ovarian cancer.[16–18] These findings underscore the role of Becn1 in tumor suppression and its potential as a therapeutic target.

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