RADIATION DAMAGE

The DNA-sensing AIM2 inflammasome controls radiation-induced cell death and tissue injury

Bo Hu,[1]* Chengcheng Jin,[1]* Hua-Bing Li,[1]* Jiyu Tong,[1,2] Xinshou Ouyang,[3] Naniye Malli Cetinbas,[4] Shu Zhu,[1] Till Strowig,[1]† Fred C. Lam,[4] Chen Zhao,[5] Jorge Henao-Mejia,[1]‡ Omer Yilmaz,[4] Katherine A. Fitzgerald,[6] Stephanie C. Eisenbarth,[1,7] Eran Elinav,[1]§ Richard A. Flavell[1,8]||

Acute exposure to ionizing radiation induces massive cell death and severe damage to tissues containing actively proliferating cells, including bone marrow and the gastrointestinal tract. However, the cellular and molecular mechanisms underlying this pathology remain controversial. Here, we show that mice deficient in the double-stranded DNA sensor AIM2 are protected from both subtotal body irradiation–induced gastrointestinal syndrome and total body irradiation–induced hematopoietic failure. AIM2 mediates the caspase-1–dependent death of intestinal epithelial cells and bone marrow cells in response to double-strand DNA breaks caused by ionizing radiation and chemotherapeutic agents. Mechanistically, we found that AIM2 senses radiation-induced DNA damage in the nucleus to mediate inflammasome activation and cell death. Our results suggest that AIM2 may be a new therapeutic target for ionizing radiation exposure.

Whole-body exposure to 2 Gy or higher radiation can induce hematopoietic syndrome, which might lead to death from infection or hemorrhage within 30 days (*1*). Higher doses of radiation cause severe damage to the gastrointestinal (GI) tract, resulting in diarrhea, malabsorption, and lethality within 10 days (*1*). However the cellular targets of GI syndrome and the mechanism of radiation-induced cell death remain controversial. Different forms of cell death have been implicated in radiation-induced GI syndrome, including apoptosis (*2*) or mitotic catastrophe (*3*) of intestinal epithelial cells (IECs), and apoptosis of endothelial cells in the intestinal vasculature (*4*). Although GI toxicity is a common complication in cancer patients undergoing radiotherapy or chemotherapy with DNA-damaging agents, there are currently no effective medical treatments to prevent or ameliorate GI syndrome. It is therefore important to gain a better understanding of the underlying mechanisms of cell death and tissue injury in response to double-strand DNA damage.

Several innate pattern recognition receptors (PRRs), including NLRP1, NLRP3, NLRC4, NLRP6, and Absent in melanoma 2 (AIM2), can drive the assembly of multiprotein complexes named inflammasomes to govern caspase-1 activation (*5*). Inflammasomes are critical regulators of intestinal tissue homeostasis through modulating intestinal microbial ecology, inflammation, and tissue repair (*6*). However, the role of inflammasomes in radiation-induced intestinal damage is unknown.

To investigate this, we used an established mouse model of radiation-induced small intestine syndrome in which mice are exposed to a lethal dose of subtotal body irradiation (SBI) with their limbs and head shielded to avoid hematopoietic damage (*3*). In this model, most wild-type (WT) mice died from severe intestinal damage within 10 days of radiation exposure. Notably, mice lacking caspase-1 were resistant to SBI-induced lethality (Fig. 1A), suggesting that inflammasome pathways play a critical role in controlling intestinal radiosensitivity. This commonly used caspase-1 knockout strain (*7*) was recently also found to be deficient in caspase-11 [here referred to as *Casp1(11)*$^{-/-}$]. Caspase-11 mediates noncanonical inflammasome activation in response to various Gram-negative bacterial infections, whereas caspase-1 is critical for the canonical inflammasome pathway downstream of several intracellular PRRs including NLRP3 and AIM2 (*8*). We therefore repeated the experiment and found that mice lacking only caspase-1 or the adapter protein ASC were also protected from SBI-induced lethality, indicating that a caspase-1–dependent, ASC-dependent canonical inflammasome pathway regulates intestinal radiosensitivity (Fig. 1, B and C).

AIM2 is an innate immune sensor that mediates assembly and activation of inflammasome in response to double-stranded DNA (dsDNA) (*9*, *10*). We found that AIM2-deficient mice were protected from SBI-induced lethality and intestinal damage (Fig. 1D). In accordance with previous observations (*11*–*13*), WT mice exhibited severe loss of crypts 3.5 days after SBI, whereas crypts of AIM2-deficient mice largely maintained their integrity (Fig. 1E). By contrast, no difference in survival from the GI syndrome was observed for mice lacking other inflammasome sensors including NLRP3 or NLRC4, indicating the specific role of the AIM2 inflammasome in controlling SBI-induced intestinal damage (fig. S1, A and B).

Upon binding to dsDNA via its HIN200 domain, AIM2 recruits the adapter protein ASC through its pyrin domain and assembles into an inflammasome to activate caspase-1, and thus maturation and secretion of proinflammatory cytokines interleukin-1β (IL-1β) and IL-18. In addition, activation of the AIM2 inflammasome in macrophages can induce caspase-1–dependent cell death known as pyroptosis (*5*, *9*). To elucidate the pathway downstream of the AIM2 inflammasome that might mediate intestinal radiosensitivity, we studied *Il1b*$^{-/-}$, *Il1r1*$^{-/-}$, and *Il18*$^{-/-}$ mice and found them to be equally susceptible to SBI-induced GI syndrome as WT controls (fig. S1, C to E). Therefore, AIM2 does not act through cytokine production to regulate intestinal damage in response to radiation. As IEC death plays a critical role in SBI-induced GI syndrome (*3*), we next examined the contribution of caspase-1–mediated cell death in this model. We selectively deleted caspase-1 in IECs by crossing mice carrying floxed caspase-1 alleles with mice expressing Cre under the control of Villin promoter (Villin-Cre). IEC-specific caspase-1 deletion protected mice from SBI-induced GI syndrome (Fig. 2A), suggesting that caspase-1–mediated pyroptosis of IECs is critical in controlling SBI sensitivity downstream of the AIM2 inflammasome. Consistently, fewer cells that stained positive for terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick end labeling (TUNEL^{+}) were observed in the crypts of the jejunum of *Casp1(11)*$^{-/-}$ and *Aim2*$^{-/-}$ mice 24 hours after SBI (Fig. 2, B and C). In addition, the amounts of cleaved caspase-3 and caspase-7 were not decreased in intestines of *Aim2*$^{-/-}$ mice compared to WT (fig. S2, A and B), indicating that the reduction in the number of TUNEL^{+} cells in *Aim2*$^{-/-}$ mice was caused by abrogation of caspase-1–mediated pyroptosis (fig. S2C), not caspase-3/7–dependent apoptosis. AIM2 was suggested to inhibit AKT activation to suppress colorectal tumorigenesis (*14*, *15*). However, we did not observe any increase of AKT activity in *Aim2*$^{-/-}$ mice after radiation, implying that AKT might not be involved in AIM2 inflammasome signaling in response to radiation (fig. S2D). Mechanistically, loss of clonogenic (stem or progenitor) cells in the crypts has been suggested to be responsible for radiation-induced intestinal damage (*16*).

[1]Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520, USA. [2]Biomedical Translational Research Institute, Jinan University, Guangzhou 510632, China. [3]Section of Digestive Diseases, Yale University, New Haven, CT 06520, USA. [4]Koch Institute for Integrative Cancer Biology, Massachusetts Institute of Technology, 500 Main Street, Cambridge, MA 02139, USA. [5]Hematology Oncology Fellowship Program, National Institutes of Health, Bethesda, MD 20892, USA. [6]Division of Infectious Diseases and Immunology, Program in Innate Immunity, University of Massachusetts Medical School, Worcester, MA 01605, USA. [7]Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT 06520, USA. [8]Howard Hughes Medical Institute, Chevy Chase, MD 20815-6789, USA.

*These authors contributed equally to this work. †Present address: Helmholtz Centre for Infection Research, Inhoffenstrasse 7, 38124 Braunschweig, Germany. ‡Present address: Institute for Immunology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA. §Present address: Immunology Department, Weizmann Institute of Science, Rehovot, Israel.
||Corresponding author. Email: richard.flavell@yale.edu

We performed the microcolony formation assay in vivo and found that AIM2 deficiency significantly enhanced crypt survival and regeneration in response to a range of radiation doses as assessed by histological analysis of hematoxylin and eosin (H&E) staining (fig. S3, A and B), as well as 5-bromo-2′-deoxyuridine (BrdU) incorporation (fig. S3C). Furthermore, intestinal organoids derived from AIM2-deficient crypts were more resistant to radiation (fig. S3, D and E). Taken together, our data suggest that the AIM2 inflammasome–mediated pyroptosis of clonogenic cells in the intestinal crypts plays a critical role in radiation-induced GI syndrome.

Mice deficient in inflammasome components, including ASC, caspase-1(11) (*17*), and AIM2 (*15*, *18*), can develop altered intestinal microbiota composition. Therefore, we cohoused WT controls used in these studies with the individual knockout strains at least 2 weeks before radiation in all of our experiments to equilibrate their gut microbiota (Figs. 1 and 2 and fig. S1), and thereby ruled out the contribution of dysbiosis in the AIM2 inflammasome–mediated regulation of radiation-induced intestinal injury. Taken together, our data demonstrated that the AIM2 inflammasome acts intrinsically in IECs to control intestinal radiosensitivity through caspase-1–mediated pyroptosis.

In addition to gastrointestinal toxicity (GI syndrome), acute irradiation can also induce bone marrow damage (hematopoietic syndrome), depending on the dose and route of radiation exposure (*1*, *19*, *20*). To further investigate whether the AIM2 inflammasome also contributes to radiosensitivity in the bone marrow compartment, we subjected mice to a lower dose (7 Gy) of total body irradiation (TBI). In this model, about 50% of WT mice died from hematopoietic syndrome starting around 2 weeks after irradiation; notably, *Aim2*$^{-/-}$ and *Casp1*$^{-/-}$ mice were resistant to TBI and survived beyond a month (Fig. 3, A and B, and fig. S4A).

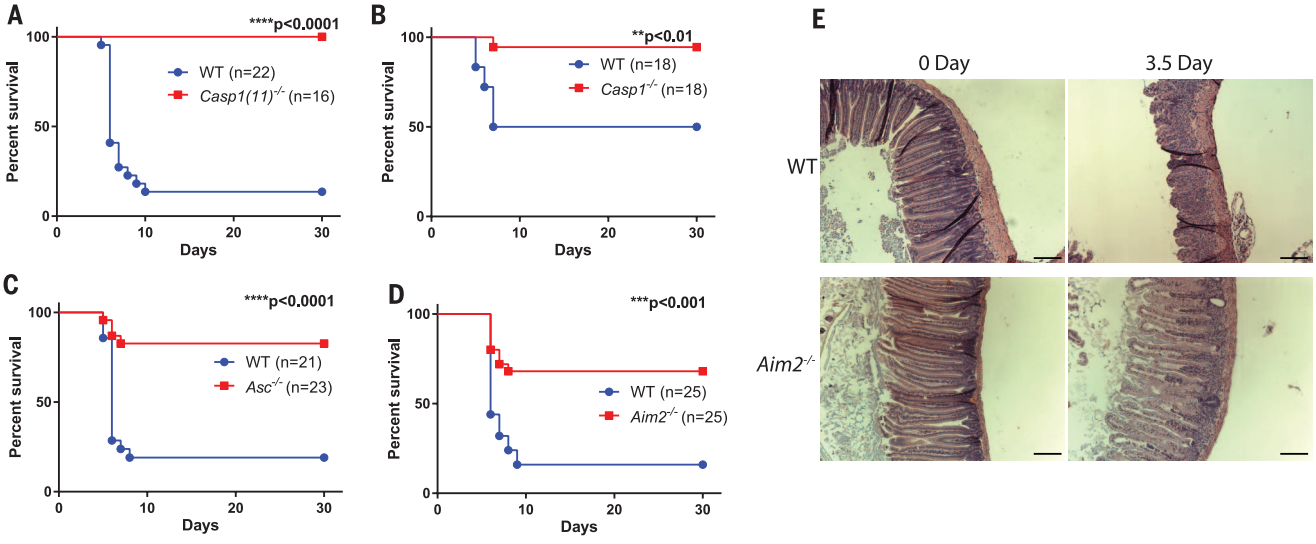

Fig. 1. AIM2 inflammasome deficiency protects mice from SBI-induced small intestine syndrome. (**A** to **D**) WT mice were cohoused with *Casp1(11)*$^{-/-}$, *Casp1*$^{-/-}$, *Asc*$^{-/-}$, or *Aim2*$^{-/-}$ mice for at least 2 weeks and then exposed to 14.2 Gy of subtotal-body irradiation (SBI). Kaplan-Meier survival analysis of *Casp1(11)*$^{-/-}$ mice (A), *Casp1*$^{-/-}$ mice (B), *Asc*$^{-/-}$, mice (C), *Aim2*$^{-/-}$ (D) mice and their cohabitated WT mice was performed. Each figure represents the pooled data from two to three independent experiments. The total number of mice in each group and the *P* value by log-rank comparison are indicated on the plots. (**E**) Representative pictures of H&E staining of the jejunum from *Aim2*$^{-/-}$ mice and their cohabitated WT mice at day 0 and day 3.5 after 14.2 Gy of SBI. Scale bars, 100 μm.

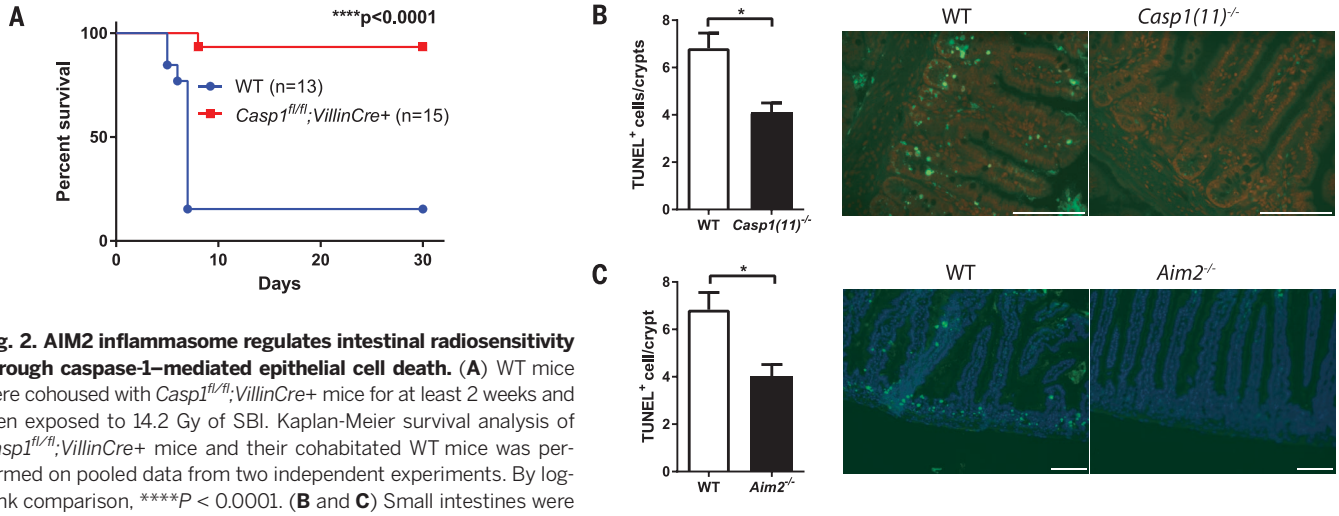

Fig. 2. AIM2 inflammasome regulates intestinal radiosensitivity through caspase-1–mediated epithelial cell death. (**A**) WT mice were cohoused with *Casp1*$^{fl/fl}$*;VillinCre*+ mice for at least 2 weeks and then exposed to 14.2 Gy of SBI. Kaplan-Meier survival analysis of *Casp1*$^{fl/fl}$*;VillinCre*+ mice and their cohabitated WT mice was performed on pooled data from two independent experiments. By log-rank comparison, ****$P < 0.0001$. (**B** and **C**) Small intestines were harvested from *Casp1(11)*$^{-/-}$, *Aim2*$^{-/-}$, and their cohabitated WT mice 24 hours after 14.2 Gy of SBI, and cell death was analyzed by TUNEL staining. Epithelial cells stained positively for TUNEL showed green fluorescence. Nuclei were stained with PI (propidium iodide, red) or DAPI (4′,6-diamidino-2-phenylindole, blue). Scale bars, 100 μm. Numbers of TUNEL-positive cells per crypts were quantified (n = 3 to 5 mice per group, at least 20 crypts of each mouse were counted), and representative images are shown. Results are expressed as mean ± SEM, *$P < 0.05$ by Student's t test.

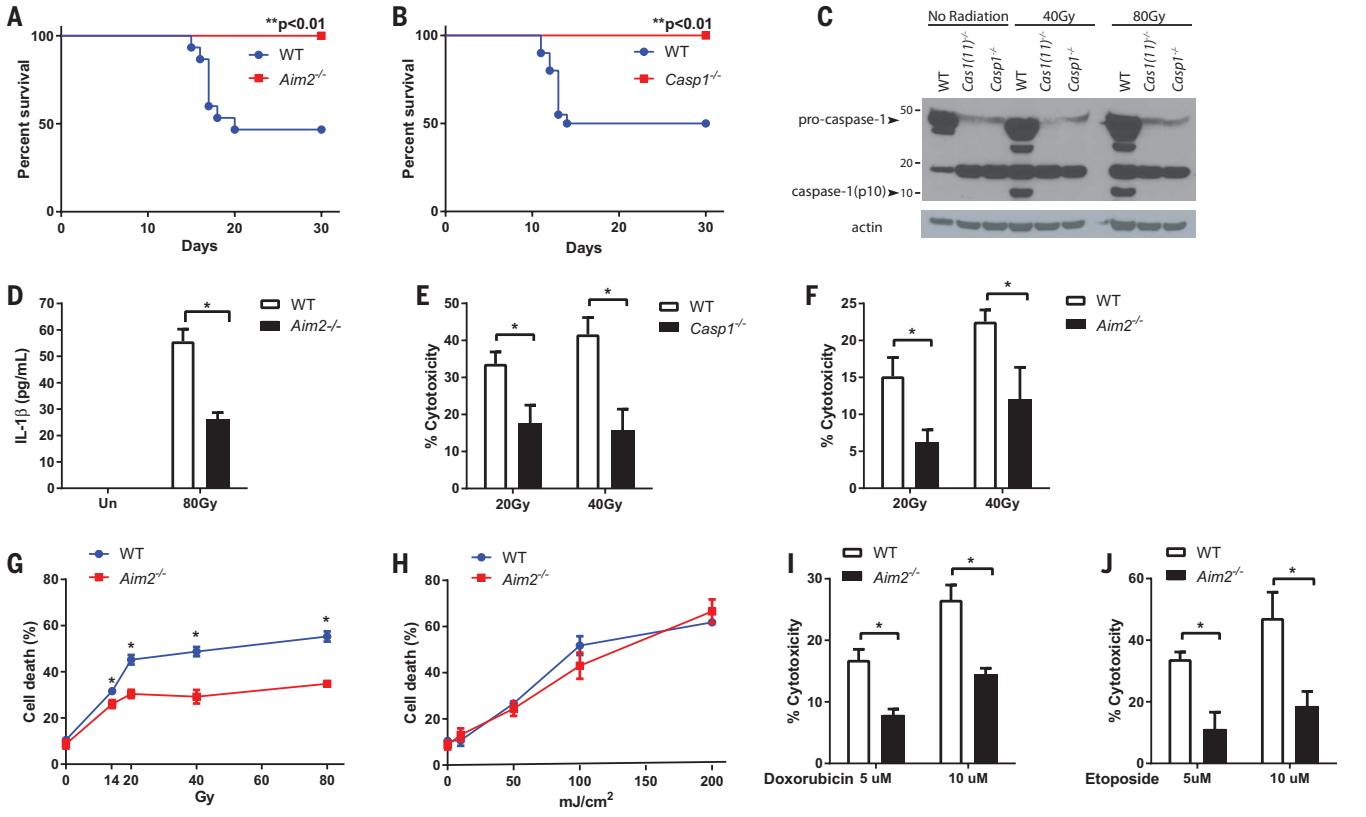

Fig. 3. AIM2 inflammasome mediates radiosensitivity of hematopoietic cells in response to dsDNA damage. (**A** and **B**) Kaplan-Meier survival analysis was performed on *Aim2*$^{-/-}$ mice (A), *Casp1*$^{-/-}$ mice (B), and their WT controls exposed to 7 Gy of total-body irradiation (TBI). Each figure represents the pooled data from two independent experiments (n = 10 to 20 mice per group). (**C**) Caspase-1 activation in WT and *Casp1*$^{-/-}$ BMDMs 4 hours after exposure to the indicated doses of radiation was assayed by immunoblotting of the cleaved form of caspase-1 (p10 subunit). (**D**) Supernatant was collected from unirradiated or 80 Gy–irradiated lipopolysaccharide (LPS)–primed WT and *Aim2*$^{-/-}$ BMDMs, and IL-1β concentration was measured by enzyme-linked immunosorbent assay. (**E**, **F**, **I**, and **J**) WT, *Casp1*$^{-/-}$, or *Aim2*$^{-/-}$ BMDMs were treated with different doses of ionizing radiation or drugs inducing dsDNA breaks, and cell death was measured by the amount of lactate dehydrogenase (LDH) released into the supernatant. (**G** and **H**) WT and *Aim2*$^{-/-}$ BMDMs were treated with different doses of ionizing radiation or UV radiation, and cell death was quantified by trypan blue staining. Determinations were performed in triplicate and expressed as the mean ± SEM. * $P < 0.05$ by Student's t test.

To investigate the cellular mechanism of AIM2-mediated radiosensitivity, we used primary bone marrow–derived macrophages (BMDMs). In WT cells, ionizing radiation activated the AIM2 inflammasome, as directly evidenced by the cleavage of caspase-1 to yield the p10 subunit and secretion of mature IL-1β, which were absent from *Casp1*$^{-/-}$ and *Aim2*$^{-/-}$ BMDMs (Fig. 3, C and D, and fig. S4B). Consistent with our in vivo findings, we observed a dose-dependent increase of cell death in response to ionizing radiation in WT BMDMs, which was significantly reduced in AIM2-deficient or caspase-1–deficient BMDMs (Fig. 3, E to G). As radiation-induced uric acid release from dead or damaged cells was previously suggested to activate caspase-1 in spleen cells (*21*), we harvested conditioned medium from irradiated bone marrow cells and found that it did not affect survival of either unirradiated WT or *Aim2*$^{-/-}$ bone marrow cells (fig. S4C). Our data suggest that the AIM2 inflammasome acts in a cell-autonomous manner in response to radiation, independently of soluble factors released from dead or injured cells. WT and *Aim2*$^{-/-}$ BMDMs were equally sensitive to ultraviolet (UV) radiation, which causes single-strand DNA breaks (Fig. 3H); however, *Aim2*$^{-/-}$ BMDMs showed significantly higher resistance to the commonly used chemotherapeutic agents doxorubicin and etoposide, which kill malignant cells by introducing DNA double-strand breaks (DSBs) (Fig. 3, I and J). In line with the in vitro data, *Aim2*$^{-/-}$ mice were also less sensitive to intestinal damage and lethality induced by high-dose doxorubicin treatment (fig. S4, D and E). Altogether, these findings suggested that the AIM2 inflammasome is specifically involved in mediating cell death in response to DSBs such as those caused by ionizing radiation and chemotherapeutic agents.

To further explore the molecular mechanism by which the AIM2 inflammasome responds to ionizing radiation, we reconstituted the AIM2 inflammasome in human embryonic kidney (HEK) 293T cells by overexpressing Flag-tagged AIM2, caspase-1, and ASC. Radiation induced the formation of AIM2-positive specks, a classical marker for inflammasome assembly, and resulted in cell death (fig. S5, A and B). In addition, we generated a Flag-tagged AIM2 mouse in which a Flag tag was knocked into the C terminus of AIM2 protein using the clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9–based genome-editing system (here referred to as AIM2-Flag mice, fig. S5C), because highly specific antibodies against endogenous murine AIM2 are not available (*14*). As we found an important role of AIM2 in regulating cell death and tissue injury in immune cells and the small intestine, we first verified the steady-state expression of endogenous AIM2 protein in the spleen and small intestine using the AIM2-Flag mice (fig. S5D). Next, we analyzed irradiated primary macrophages from AIM2-Flag mice by immunofluorescence (IF) microscopy. Endogenous AIM2 showed very diffuse and weak staining before radiation exposure but formed puncta in the nucleus upon radiation exposure (Fig. 4, A and B, and fig. S5E). Moreover, considerable colocalization of AIM2-containing specks and gamma-H2AX–positive foci was observed in the nucleus, suggesting that AIM2 is recruited to sites of dsDNA breaks (Fig. 4C and fig. S5F). In support of our IF experimental observations, a strong interaction between Flag-tagged AIM2 and gamma-H2AX

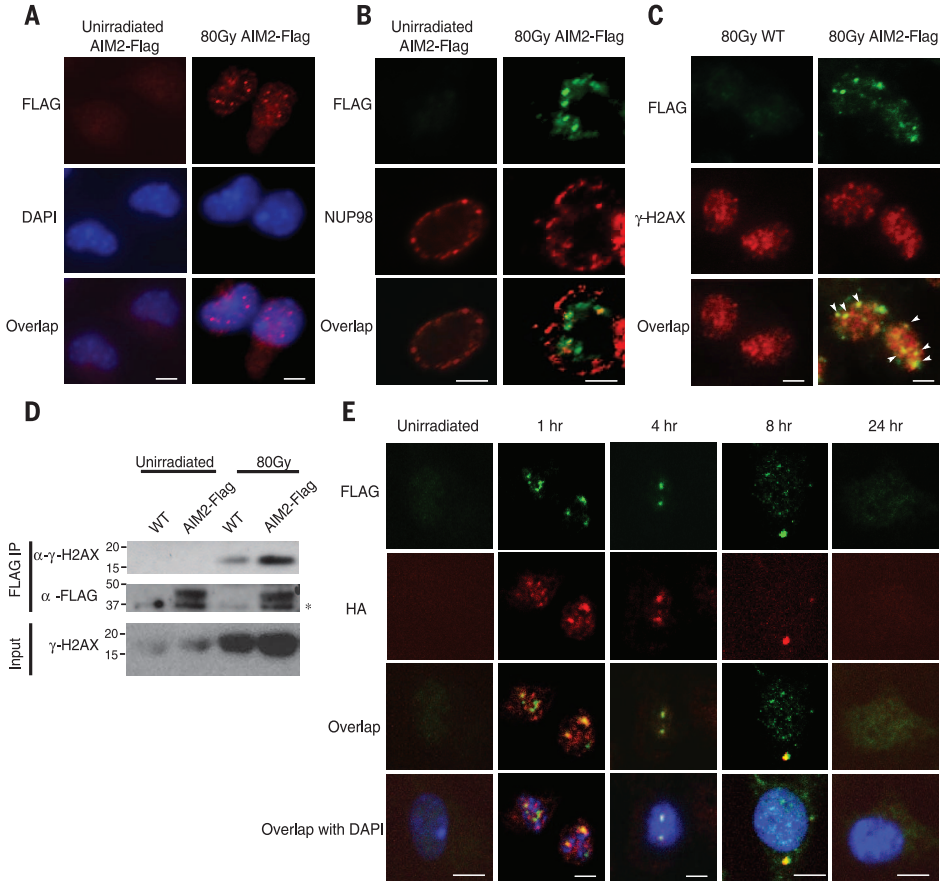

Fig. 4. Ionizing radiation induces the formation AIM2 specks in the nucleus. Primary macrophages from AIM2-Flag mice (**A** to **D**) or AIM2-Flag/ASC-HA double knockin mice (**E**) were left unirradiated or exposed to 80 Gy of ionizing radiation. For IF microscopy, cells were fixed at 4 hours [(A), (B), and (C)] or at indicated time points (E) after radiation. AIM2 was stained with antibody against Flag (anti-Flag) [red in (A); green in (B), (C), and (E)] and costained with nuclear envelope protein NUP98 [red, (B)] or gamma-H2AX [red, (C)] or ASC [using anti-HA, red, (E)]. Cell nuclei were visualized by DAPI (blue) in (A) and (E). Colocalization of AIM2-Flag specks and gamma-H2AX foci was indicated by white arrowheads in (C). Scale bars, 5 μm. Figures represent results from three independent experiments, and at least 100 cells were analyzed for each condition. (D) Coimmunoprecipitation (co-IP) of gamma-H2AX with AIM2-Flag in irradiated macrophages using anti-Flag M2 agarose beads. The immunoprecipitates (Flag IP) or the total lysates were analyzed by immunoblotting with antibodies against gamma-H2AX (Ser139) or the Flag tag. Samples from untagged WT mice were used as controls to determine the specificity of immunoblots. Nonspecific band is indicated with an asterisk. Data represent two independent experiments.

was detected by coimmunoprecipitation in irradiated cells (Fig. 4D). To further investigate the molecular mechanism of AIM2 inflammasome assembly, we also generated an ASC-HA knockin mouse to tag endogenous ASC protein with the human influenza hemagglutinin (HA) epitope using a similar strategy (fig. S5, G and H), and we crossed it to the AIM2-Flag mice to study the interaction between AIM2 and ASC. Notably, using AIM2-Flag/ASC-HA double knockin mice, we found that radiation induced AIM2 and ASC colocalization and speck formation in the nuclei after radiation exposure, and the speckles containing both AIM2 and ASC later accumulated in the perinuclear region (Fig. 4E). Together with the data showing robust caspase-1 processing in irradiated macrophages (Fig. 3C), these results provide strong evidence for the assembly and activation of an inflammasome in response to radiation. AIM2 was previously known as a cytoplasmic DNA sensor (*9*, *10*). Although its nuclear localization has been implicated in certain cell lines, the biological importance of nuclear AIM2 was not understood, and the subcellular distribution of endogenous AIM2 is unclear (*22*–*24*). Our results suggest that the recruitment of AIM2 to chromatin sites of radiation-induced DNA damage may be involved in mediating inflammasome activation and cell death.

Our present study demonstrates an unexpected role for AIM2 in sensing ionizing radiation–induced DNA damage in the nucleus. AIM2 acts thereby through the inflammasome pathway to trigger caspase-1–mediated cell death in intestinal epithelial cells and bone marrow cells. We show here that deficiency in the AIM2 inflammasome protects mice from radiation-induced small intestine syndrome as well as hematopoietic failure. Although the relative contribution of pyroptosis and other forms of cell death such as apoptosis to radiation-induced tissue damage merits further investigation, our findings may have important implications for development of therapy against radiation induced GI or hematopoietic toxicity. Drugs that block the activity of the AIM2 inflammasome may be effective in treating patients exposed to ionizing radiation, such as in radiation exposure via nuclear reactors or cancer patients suffering from hematopoietic or GI toxicity as a consequence of radiotherapy or chemotherapy.

REFERENCES AND NOTES

1. F. A. Mettler Jr., G. L. Voelz, *N. Engl. J. Med.* **346**, 1554–1561 (2002).
2. W. Qiu *et al.*, *Cell Stem Cell* **2**, 576–583 (2008).
3. D. G. Kirsch *et al.*, *Science* **327**, 593–596 (2010).
4. F. Paris *et al.*, *Science* **293**, 293–297 (2001).
5. M. Lamkanfi, V. M. Dixit, *Cell* **157**, 1013–1022 (2014).
6. T. Strowig, J. Henao-Mejia, E. Elinav, R. Flavell, *Nature* **481**, 278–286 (2012).
7. K. Kuida *et al.*, *Science* **267**, 2000–2003 (1995).
8. N. Kayagaki *et al.*, *Nature* **479**, 117–121 (2011).
9. T. Fernandes-Alnemri, J. W. Yu, P. Datta, J. Wu, E. S. Alnemri, *Nature* **458**, 509–513 (2009).
10. V. Hornung *et al.*, *Nature* **458**, 514–518 (2009).
11. E. A. Komarova, K. Christov, A. I. Faerman, A. V. Gudkov, *Oncogene* **19**, 3791–3798 (2000).
12. A. J. Merritt, T. D. Allen, C. S. Potten, J. A. Hickman, *Oncogene* **14**, 2759–2766 (1997).
13. A. J. Merritt *et al.*, *Cancer Res.* **54**, 614–617 (1994).
14. J. E. Wilson *et al.*, *Nat. Med.* **21**, 906–913 (2015).
15. S. M. Man *et al.*, *Cell* **162**, 45–58 (2015).
16. C. Booth, G. Tudor, J. Tudor, B. P. Katz, T. J. MacVittie, *Health Phys.* **103**, 383–399 (2012).
17. E. Elinav *et al.*, *Cell* **145**, 745–757 (2011).
18. S. Hu *et al.*, *Cell Reports* **13**, 1922–1936 (2015).
19. M. E. Berger, D. M. Christensen, P. C. Lowry, O. W. Jones, A. L. Wiley, *Occup. Med. (Lond.)* **56**, 162–172 (2006).
20. J. K. Waselenko *et al.*, *Ann. Intern. Med.* **140**, 1037–1051 (2004).
21. V. M. Stoecklein *et al.*, *J. Immunol.* **194**, 1178–1189 (2015).
22. K. S. Cresswell *et al.*, *Biochem. Biophys. Res. Commun.* **326**, 417–424 (2005).
23. B. A. Diner *et al.*, *Mol. Syst. Biol.* **11**, 787 (2015).
24. N. Kerur *et al.*, *Cell Host Microbe* **9**, 363–375 (2011).

ACKNOWLEDGMENTS

We thank V. M. Dixit, N. Kayagaki, and E. S. Alnemri for sharing materials and reagents, and V. A. Rathinam for technical advice. We thank P. Bongiorni for assistance with radiation experiments. The data presented in this manuscript are tabulated in the main paper and in the supplementary materials. H.-B.L. is supported by NIH T32 2T32DK007356. This work was supported by the Howard Hughes Medical Institute (R.A.F.).

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/354/6313/765/suppl/DC1
Materials and Methods
Figs. S1 to S5
References (*25*–*35*)

28 March 2016; accepted 16 September 2016
10.1126/science.aaf7532

Science
AAAS

The DNA-sensing AIM2 inflammasome controls radiation-induced cell death and tissue injury

Bo Hu, Chengcheng Jin, Hua-Bing Li, Jiyu Tong, Xinshou Ouyang, Naniye Malli Cetinbas, Shu Zhu, Till Strowig, Fred C. Lam, Chen Zhao, Jorge Henao-Mejia, Omer Yilmaz, Katherine A. Fitzgerald, Stephanie C. Eisenbarth, Eran Elinav and Richard A. Flavell

(November 10, 2016)
Science **354** (6313), 765-768. [doi: 10.1126/science.aaf7532]

Editor's Summary

AIMing to block tissue damage

Ionizing radiation kills actively dividing cells such as those in the gut and in the bone marrow. Hu *et al.* found a pathological role for the protein AIM2 in irradiation-induced tissue damage. AIM2 is best known for its role in sensing double-stranded DNA in the cytoplasm and alerting the body to infections. It seems that AIM2 also senses DNA damage caused by radiation and then triggers intestinal epithelial cells and bone marrow cells to die. Deficiency in AIM2 protected mice from irradiation-induced gastrointestinal syndrome and hematopoietic failure.

Science, this issue p. 765

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.