X-rays trigger a calcium signaling cascade in cells of the immune system: A potential weapon against tumors

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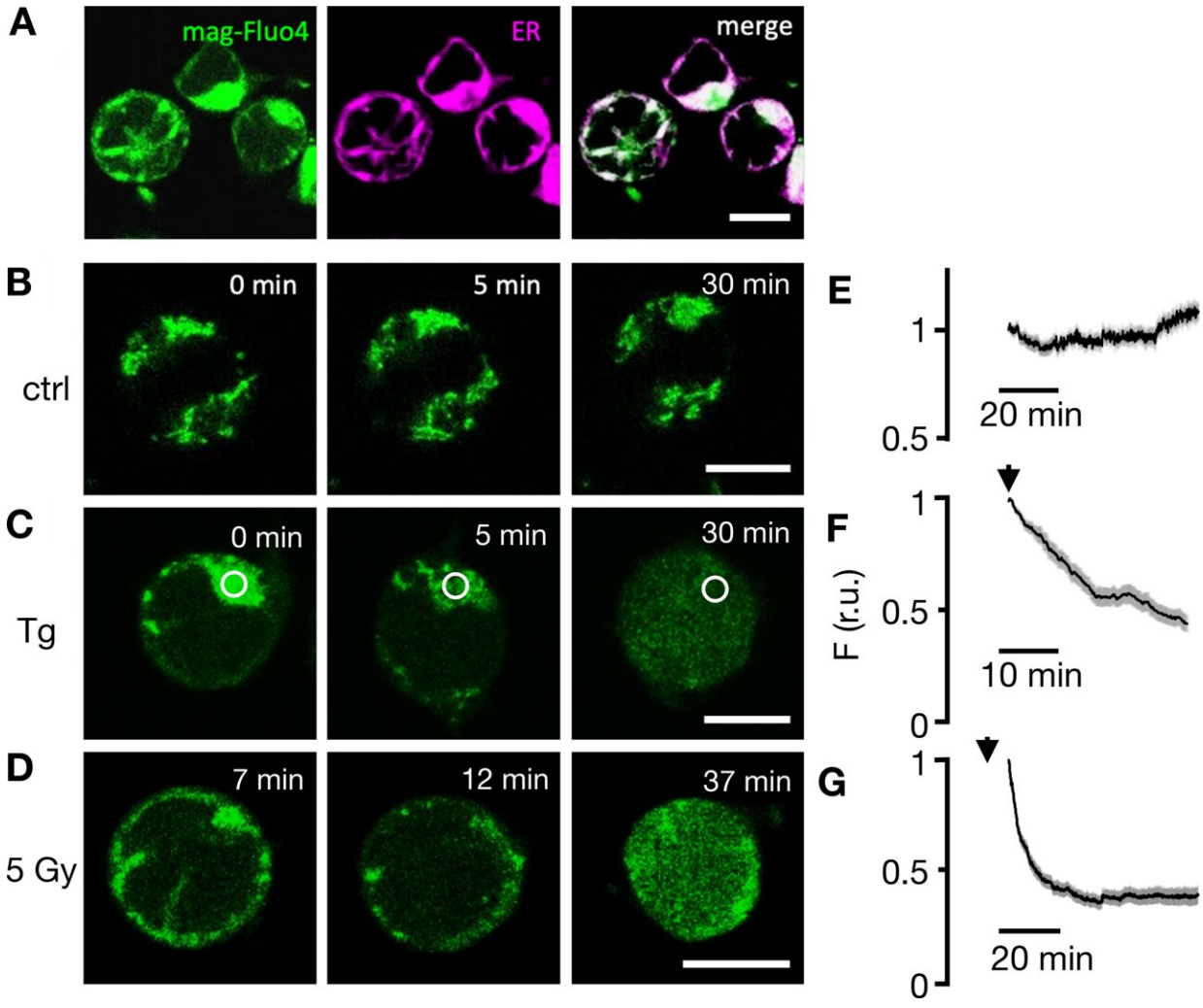

Fluorescent sensor Mag-Fluo-4 reports depletion of ER Ca^{2+} in Jurkat cells as a response to irradiation. (A) Fluorescent images of representative Jurkat cells

loaded with Mag-Fluo-4 (green, first column) and stained with ER tracker red (magenta, second column) exhibit colocalization of both fluorescent signals in merged image (third column). (B) In untreated control cells, the Mag-Fluo-4 fluorescence in the ER remains constant. (C) Challenging cells with 2 µM Tg (D) or irradiating cells with 5 Gy x rays elicits progressive decrease in Mag-Fluo-4 fluorescence in ER with concomitant increase in cytosol. Times in images denote time point of imaging after respective treatment. Corresponding mean values of relative Mag-Fluo-4 fluorescence (± SD) in ROI (white circle in C) over ER in untreated control cells (E), cells exposed to 2 µM Tg (F), and cells irradiated with 5 Gy x rays (G). Start of imaging after treatments are indicated by an arrow. Data in E–G were normalized to fluorescence values at start of analysis from ≥35 cells per treatment in ≥7 experiments. Scale bars, 10 µm. Credit: *Journal of General Physiology* (2022). DOI: 10.1085/jgp.202112865

Radiation therapy is a proven approach to destroying tumors. However, it is possible that it might be able to do even more in the future—namely stimulate the immune system at the same time and so fight cancer even more intensively. The foundations for this have been laid by researchers led by TU Darmstadt. They have found that X-rays trigger a calcium signaling cascade in cells of the immune system. The results have now been published in the *Journal of General Physiology*.

Ionizing radiation is successfully used in cancer treatment to kill tumor cells. Over the past two decades, it has become clear that treatment success can be increased even further if the radiation treatment is combined with measures to stimulate the immune system. In this context, a new study being carried out with biologists from TU Darmstadt and the GSI Helmholtz Center for Heavy Ion Research plus researchers from the clinics of the Frankfurt and Homburg universities is attracting attention. The researchers report in the *Journal of General Physiology* that the desired stimulating effect on the immune system is triggered directly when T-cells are also irradiated by X-rays. Dominique

Tandl, researcher at the Department of Biology at TU Darmstadt, and her co-authors demonstrate in the recently published study that clinically relevant doses of X-rays in T lymphocytes trigger a signaling cascade that is typical of the immune reaction that begins with the release of the messenger substance calcium (Ca^{2+}) from internal stores.

Activated by what is known as store operated Ca^{2+} entry (SOCE), the concentration of Ca^{2+} in the cells begins to oscillate at a critical frequency, which in turn leads to the displacement (translocation) of a transcription factor from the cytoplasm into the cell nucleus. Once there, this transcription factor initiates gene expression, and the cell begins to make molecules that are important for the immune response, such as cytokines. Since the irradiation of tumors invariably always affects the blood cells in the target tissue, medicine could utilize the stimulating effect of X-rays on T lymphocytes. The researchers hope that their studies will contribute to improving cancer treatment in the long term, as Professor Gerhard Thiel, head of the Membrane Biophysics Group at the Department of Biology at TU Darmstadt and co-author of the study, says. "It could be possible to enhance the killing effect of ionizing radiation on tumor cells and at the same time to stimulate the immune system with the help of this radiation."

More information: Dominique Tandl et al, X-ray irradiation triggers immune response in human T-lymphocytes via store-operated Ca2+ entry and NFAT activation, *Journal of General Physiology* (2022). DOI: 10.1085/jgp.202112865

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