JGP Journal of General Physiology

RESEARCH NEWS

X rays activate T cell calcium signaling

Ben Short

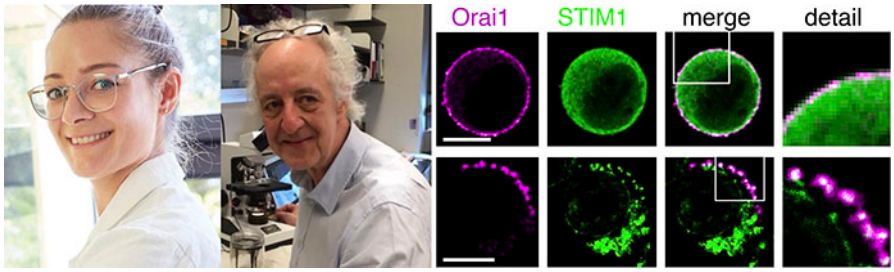
***JGP* study reveals that clinically relevant doses of ionizing radiation induce an immune response in T cells by triggering the store-operated Ca^{2+} entry pathway.**

Ionizing radiation (IR) is a key anti-cancer treatment due to its ability to induce DNA damage and cell death. But the effects of IR on other cellular pathways, in both tumors and neighboring healthy tissues, is much less understood. In this issue of *JGP*, Tandl et al. show that x rays trigger an immune response in T cells by activating the store-operated Ca^{2+} entry (SOCE) pathway, a finding that could have important implications for both the toxic and therapeutic effects of radiotherapy (1).

Irradiation of patient tumors inevitably impacts blood cells circulating through the targeted tissue. While some studies have reported immunosuppressive effects of irradiation, others have shown that IR can stimulate the immune system. Indeed, combining radiotherapy with immune checkpoint inhibitors has synergistic impacts on tumor growth (2, 3).

Gerhard Thiel and colleagues at Technische Univesität Darmstadt recently found that clinically relevant x-ray doses activate T lymphocytes (4). "We found that irradiated T cells become bigger and start to adhere, which are indicators of an active immune response, and that this was likely associated with changes in Ca^{2+} signaling," Thiel says.

To investigate these changes, Thiel and colleagues, including graduate student Dominique Tandl, loaded Jurkat cells (a leukemic T-cell line) with a Ca^{2+}-sensitive dye and imaged them in real time with a fluorescent microscope directly coupled to an x-ray source (1). Clinically relevant x-ray doses had no immediate impact on the cytosolic Ca^{2+} concentration of T cells. After a delay of ∼10–70 min, however, the majority of irradiated T cells began to show rapid oscillations in their cytosolic Ca^{2+} levels. These oscillations were suppressed by the removal of extracellular Ca^{2+} or the addition of a broad spectrum Ca^{2+} channel blocker, indicating that they depend on the influx of Ca^{2+} into the cell.



Dominique Tandl (left), Gerhard Thiel (center), and colleagues reveal that x-ray irradiation activates T cells by stimulating the SOCE pathway. Compared to unirradiated control cells (top row), clinically relevant x-ray doses (bottom row) cause Orai1 (magenta) and STIM1 (green) to cluster at ER–plasma membrane contact sites where they mediate Ca^{2+} influx. This leads to cytosolic Ca^{2+} oscillations and nuclear translocation of the key T cell transcription factor NFAT.

The major mechanism of Ca^{2+} entry into T cells is the SOCE pathway (5), in which the depletion of Ca^{2+} stores in the ER triggers the clustering of STIM1 and Orai1 proteins at ER–plasma membrane contact sites, where they form calcium release–activated calcium (CRAC) channels that mediate Ca^{2+} influx. Tandl et al. found that x-ray irradiation triggers STIM1/Orai1 clustering in T cells. Crucially, treating T cells with a CRAC channel inhibitor, or knocking out the Orai1 protein, reduced x-ray–induced Ca^{2+} oscillations.

The researchers also found that irradiation initiates the SOCE pathway by depleting Ca^{2+} levels in the ER. The delayed onset of Ca^{2+} oscillations suggests that this isn't because x rays disrupt the integrity of the ER membrane. Instead, the researchers speculate, the reactive oxygen species generated by irradiation may modulate the activity of ER Ca^{2+} channels or pumps.

In response to T cell receptor activation, SOCE-mediated Ca^{2+} oscillations stimulate translocation of the transcription factor NFAT into the nucleus, where it induces the expression of numerous genes crucial for T cell immune function. Tandl et al. found that x-ray irradiation also induces NFAT's movement into the nucleus, and that blocking Ca^{2+} oscillations with a CRAC channel inhibitor prevents this translocation, as well as the subsequent increase in cell size associated with T cell activation.

Taken together, Tandl et al.'s findings reveal how x-rays can stimulate the immune function of T cells. In the short term, Thiel plans to investigate how IR depletes ER Ca^{2+} stores. In the longer term, however, he hopes that their studies will lead to improvements in cancer therapy. "It may be possible to optimize the killing effect of radiation on tumor cells, while also inducing the positive effect of immune stimulation," Thiel says.

References

1. Tandl, D., et al. 2022. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.202112865
2. Sharabi, A.B., et al. 2015. *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(15)00007-8
3. Frey, B., et al. 2017. *Immunol. Rev.* https://doi.org/10.1111/imr.12572
4. Voos, P., et al. 2018. *Front. Immunol.* https://doi.org/10.3389/fimmu.2018.00922
5. Trebak, M., and J.P. Kinet. 2019. *Nat. Rev. Immunol.* https://doi.org/10.1038/s41577-018-0110-7

bshort@rockefeller.edu.