



John Heath, PhD

Former postdoctoral fellow in Experimental Medicine, McGill University
Current position: Postdoctoral fellow at Prince Margaret Cancer Centre



Josie Ursini-Siegel, PhD

Scientific Director, Molecular Oncology Group, and Principal Investigator, Lady Davis Institute for Medical Research
Professor, Departments of Oncology and Biochemistry, McGill

Science Advances

Complex I Inhibition combined with TLR Activation in the Breast Tumor Microenvironment Educates Cytotoxic Neutrophils

John Heath, Ryuhjin Ahn, Valerie Sabourin, Young Kyuen Im, Sabrina Rezzara Richard, Alva Annett, Caitlynn Mirabelli, Samantha Worme, Sarah M Maritan, Caitlyn Mourcos, Anna Maria Lazaratos, Elias Maldonado, Yun Yun Shen, Forest M White, Claudia L Kleinman, Peter M Siegel, and Josie Ursini-Siegel.

Traditional immunotherapies primarily focus on reactivating tumour-specific T cells, which have limited effectiveness in breast cancers classified as immune cold—tumours that lack significant T cell infiltration. Our study presents an alternative approach that harnesses the innate immune system by educating neutrophils to acquire tumoricidal properties.

We discovered that combining systemic Toll-like receptor (TLR) agonists with mitochondrial complex I inhibitors stimulates neutrophils to produce reactive oxygen species (ROS) and cytotoxic granules, thereby directly attacking breast cancer cells independently of cytotoxic T cell activity.

This study highlights that TLR agonists elevate NF- κ B signaling in neutrophils, increasing the production of secretory granules and components of the NADPH oxidase complex, necessary for a respiratory burst that elicits cytotoxic responses. Meanwhile, complex I inhibitors amplify this effect by potentiating the capacity of neutrophils to undergo a respiratory burst, leading to oxidative damage of breast cancer cells. Importantly, neutrophil depletion in experimental models abolished the anti-tumour effects, underscoring the critical role of these immune cells in the therapy's success. This dual treatment approach not only mobilizes neutrophils into the tumour microenvironment but also enhances their cytotoxic functions, offering a promising new therapeutic strategy for immune cold breast tumours that have so far eluded effective immune-based treatments.

The study also brings to light the importance of understanding the complex interactions between the tumour microenvironment and the immune system. By targeting key biological processes required for the survival of heterogeneous cancer cell populations, researchers can develop more effective therapies that abrogate the activation of a pro-tumorigenic immune microenvironment and instead engage novel modes of tumour immune surveillance.

In conclusion, this research builds on the understanding that breast cancers often evade immune destruction through complex metabolic and inflammatory mechanisms, and it shifts the focus toward targeting innate immune cells rather than relying solely on adaptive immunity. While further research is needed to fully elucidate the mechanisms by which complex I inhibitors enhance neutrophil function, this study marks a significant step forward in precision oncology.