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John Heath

PhD student, Experimental Medicine
McGill University

Alexandre Orthwein, PhD

Assistant Professor, Gerald Bronfman
Department of Oncology, McGill University

Principal Investigator, Lady Davis Institute

EMBO reports

POGZ promotes homology-directed DNA repair in an HP1-dependent manner

John Heath, Estelle Simo Cheyou, Steven Findlay, Vincent M Luo, Edgar Pinedo Carpio, Jeesan Lee, Billel Djerir, Xiaoru Chen, Théo Morin, Benjamin Lebeau, Martin Karam, Halil Bagci, Damien Grapton, Josie Ursini-Siegel, Jean-Francois Côté, Michael Witcher, Stéphane Richard, Alexandre Maréchal, and Alexandre Orthwein

In humans, 1/700 cases of autism spectrum disorders or intellectual disabilities are classified as White Sutton Syndrome (WHSUS) and are caused by mutations in a gene called POGZ. Functionally, little is known about the role of POGZ. We are one of the first groups to study the contribution of POGZ in vivo by designing a murine model targeting this gene. Using this system, we showed that Pogz is necessary for embryonic development. Furthermore, the genetic loss of a single copy of Pogz yields behavioral and growth defects, such as reduced brain mass and improper B cell development. Interestingly, in both of these tissues, Pogz haplo-insufficiency was associated with increased DNA damage, indicative of a potential role for Pogz in DNA repair.

At the molecular level, we identified a key role for POGZ in the repair of the most lethal genomic lesion, DNA double-strand break (DSB). POGZ works in tandem, and in requirement, with heterochromatin protein 1 (HP1) to promote the presence of the BRCA1/BARD1 complex at DSB in order to fulfill successful DNA repair by homologous recombination (HR). While it remains unclear, whether a DNA repair deficiency drives WHSUS, we believe that our work serves as a foundation for further characterizing this human syndrome.

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