



Agata Smogorzewska, M.D., Ph.D.

SKOLER HORNBACH FAMILY PROFESSOR, LABORATORY OF GENOME MAINTENANCE

Throughout its lifetime, a cell's DNA is under constant metabolic and environmental assault that can lead to damage. If left unchecked, the resulting genome instability can initiate cancer and a variety of other human disorders. Using Fanconi anemia and other genetic diseases as a backdrop, Smogorzewska's research aims to elucidate the pathways that protect organ function and prevent cancer, with a focus on those that replicate and repair DNA.

Research in the Laboratory of Genome Maintenance is focused on DNA repair, with special emphasis on repair that takes place during replication. The group's interests are broad, ranging from the molecular function of proteins involved in the DNA damage response to the cellular and in vivo consequences of deficiencies in proper DNA replication and repair.

The DNA interstrand crosslink (ICL) is the prototype DNA lesion repaired during replication. ICLs covalently link the Watson and Crick strands of the DNA, and the repair of these lethal lesions requires a dual excision of the crosslinked bases as well as repair of the resulting double-strand breaks. This feat is accomplished in a multi-step process mediated by the Fanconi anemia (FA) pathway and factors that promote homologous recombination (HR), including BRCA1 and BRCA2. FA patients lack components of this pathway and suffer from bone marrow failure and infertility due to failures in the maintenance of hematopoietic and germline stem cells. FA is also associated with a very high incidence of cancer due to the mutagenic nature of incorrectly repaired ICLs.

In recent years, the lab has identified *SLX4*, *RAD51*, and *UBE2T* as genes mutated in Fanconi anemia patients. By identifying these and other novel genes in patients with FA and related disorders, the group is able to use insights and patient-derived tools in the quest to understand the mechanism of DNA repair at the cellular level. Currently, the prevention and treatment of tumors are the major clinical challenges for the disease. The lab found that cancers from Fanconi anemia patients are characterized by extreme genomic instability, marked by complex structural variants and dramatic copy number changes of tumor-driving genes. Based on the examination of sporadic cancers, they propose that the functional overload of a genetically unaltered FA pathway by aldehydes from tobacco and alcohol contributes to genomic changes, fueling the development of sporadic head and neck cancer.

Current work in the lab focuses on identification of sources of endogenous DNA damage and understanding cellular DNA damage responses in keratinocytes. The lab is building patient-derived and mouse models to study the fundamental biology of head and neck cancers with the goal of identifying preventive and treatment strategies for these cancers.

ICL repair deficiency is also associated with kidney and liver dysfunction. A rare human disease called karyomegalic interstitial nephritis (KIN) develops when FAN1, a nuclease that functions in ICL repair, is deficient. FAN1 has also been identified as a genetic modifier of Huntington's disease (HD). The lab uses a mouse model of FAN1 deficiency to gain insights about the pathogenesis of KIN and HD, as well as to obtain global understanding of how genome maintenance pathways protect organ function.

EDUCATION

B.S. in molecular biology and biochemistry, 1995
University of Southern California

Ph.D., 2002
The Rockefeller University

M.D., 2003
Weill Cornell Medical College

MEDICAL TRAINING

Residency in clinical pathology, 2003–2006
Massachusetts General Hospital

POSTDOC

Harvard Medical School, 2005–2009

POSITIONS

Assistant Professor, 2009–2015

Associate Professor, 2015–2023

Professor, 2023–

Director, Marlene Hess Center for Research on Women's Health and Biomedicine, 2023–
The Rockefeller University

AWARDS

Burroughs Wellcome Fund Award, 2008

Irma T. Hirschl/Monique Weill-Caulier Trust Research Award, 2010

Rita Allen Foundation Scholar, 2010

Doris Duke Charitable Foundation Clinical Scientist Development Award, 2011

Pershing Square Sohn Prize, 2014

The Rockefeller University Distinguished Teaching Award, 2014

David B. Frohnmayer Early Investigator Award, 2015

Howard Hughes Medical Institute Faculty Scholar, 2016

Gabrielle H. Reem and Herbert J. Kayden Early-Career Innovation Award, 2017

SELECTED PUBLICATIONS

Webster, A.L.H., Sanders, M.A. et al. Genomic signature of Fanconi anaemia DNA repair pathway deficiency in cancer. *Nature* 612, 495–502 (2022).

Rickman, K.A. et al. Distinct roles of BRCA2 in replication fork protection in response to hydroxyurea and DNA interstrand crosslinks. *Genes Dev.* 34, 832–846 (2020).

Kottemann, M.C. et al. Removal of RTF2 from stalled replisomes promotes maintenance of genome integrity. *Mol. Cell* 69, 24–35 (2018).

Thongthip, S. et al. *Fan1* deficiency results in DNA interstrand cross-link repair defects, enhanced tissue karyomegaly, and organ dysfunction. *Genes Dev.* 30, 645–659 (2016).

Wang, A.T. et al. A dominant mutation in human *RAD51* reveals its function in DNA interstrand crosslink repair independent of homologous recombination. *Mol. Cell* 59, 478–490 (2015).