Title: Special Section: Replication Stress, a threat to the nuclear and mitochondrial genome

Author: Lisa Wiesmüller

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Editorial
Special Section: Replication Stress, a threat to the nuclear and mitochondrial genome.

Lisa Wiesmüller[1], Karin Scharffetter-Kochanek[2], and Hartmut Geiger[3].

[1] Department of Obstetrics and Gynecology, Ulm University, Germany, lisa.wiesmueller@uni-ulm.de
[2] Department of Dermatology and Allergic Diseases, Ulm University, Germany, karin.scharffetter-kochanek@uniklinik-ulm.de
[3] Institute of Molecular Medicine, Ulm University, Germany, hartmut.geiger@uni-ulm.de

Corresponding author:
Lisa Wiesmüller
Department of Obstetrics and Gynaecology, Ulm University
Prittwitzstrasse 43
89077 Ulm, Germany
Phone: +49 731 500 58800
Fax: +49 731 500 58804
email: lisa.wiesmueller@uni-ulm.de

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Dysfunction of chromosomal DNA repair was recognized as disease mechanism in the sixties, when nucleotide excision repair defects were identified as the cause of *Xeroderma pigmentosum* [1]. In the seventies the key mechanisms to ensure discontinued DNA replication past a lesion were discovered: (i) switching between the parental strands involving the Bloom syndrome and Fanconi anemia (Fanc) complementation group proteins to bypass an interstrand DNA crosslink [2] and (ii) direct DNA synthesis across DNA lesions via specialized translesion synthesis (TLS) polymerases. In the nineties polymerase η defects were connected with *Xeroderma pigmentosum variant* [3]. Since then the list of Fanc proteins, TLS polymerases, RecQ helicases and other disease-associated factors involved in replication fork recovery has been growing. Even for breast cancer susceptibility genes like *BRCA2* pathogenic mutations causing replication fork protection without affecting classical disease-related functions in homologous recombination were described [4].

As outlined in this Special Section by Jean-Sebastien Hoffmann´s team, replication stress can be dissected into distinct stages starting with slowing, stalling all the way to collapsing of replication forks [5]. It arises as a consequence of either exogenous or endogenous challenges ultimately creating an obstacle for replication progression or compromising the replicative machinery by an imbalance of the enzymes or nucleotide pools. Each stage of replication stress can introduce genomic alterations, ranging from point mutations generated by TLS, to sister chromatid exchanges at stalled forks and non-allelic homologous recombination between repeats upon fork collapse. For many years the impact of replication-associated DNA damage signaling on the development of diseases was underestimated, because mechanistic knowledge was lagging behind. As an example, chromosome aberrations involving short homologous sequences at break junctions were exclusively attributed to DNA double-strand break (DSB) repair by non-homologous end joining before break-induced replication