Accepted Manuscript

Title: Replication stress in hematopoietic stem cells in mouse and man

Authors: Johanna Flach, Michael Milyavsky

PII: S0027-5107(17)30033-7
DOI: https://doi.org/10.1016/j.mrfmmm.2017.10.001
Reference: MUT 11624

To appear in: *Mutation Research*

Received date: 24-2-2017
Revised date: 31-8-2017
Accepted date: 12-10-2017

Please cite this article as: Johanna Flach, Michael Milyavsky, Replication stress in hematopoietic stem cells in mouse and man, Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis https://doi.org/10.1016/j.mrfmmm.2017.10.001

Replication stress in hematopoietic stem cells in mouse and man

Johanna Flach[1,#], Michael Milyavsky[2,#]

[1]Department of Hematology and Medical Oncology & Institute of Molecular Oncology, University Medical Center Goettingen, Germany

[2]Department of Pathology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

#correspondence: mmilyavsky@post.tau.ac.il or Johanna.Flach@med.uni-goettingen.de

Abstract

Life-long blood regeneration relies on a rare population of self-renewing hematopoietic stem cells (HSCs). These cells' nearly unlimited self-renewal potential and lifetime persistence in the body signifies the need for tight control of their genome integrity. Their quiescent state, tightly linked with low metabolic activity, is one of the main strategies employed by HSCs to preserve an intact genome. On the other hand, HSCs need to be able to quickly respond to increased blood demands and rapidly increase their cellular output in order to fight infection-associated inflammation or extensive blood loss. This increase in proliferation rate, however, comes at the price of exposing HSCs to DNA damage inevitably associated with the process of DNA replication. Any interference with normal replication fork progression leads to a specialized molecular response termed replication stress (RS). Importantly, increased levels of RS are a hallmark feature of aged HSCs, where an accumulating body of evidence points to causative relationships between RS and the aging-associated impairment of the blood system's functional capacity. In this review, we present an overview of RS in HSCs focusing on its causes and consequences for the blood system of mice and men.

RS - definition and pathways

Broadly, the term replication stress (RS) defines all obstacles that occur during DNA replication causing the replication fork to stall [1, 2] (Figure 1). Accurate genome duplication is by its nature a very complex and challenging process. It requires the action of many molecular players that need to exert their functions in a perfectly concerted manner. In order to preserve the integrity of the DNA and to replicate DNA with high accuracy and efficiency, sophisticated mechanisms have evolved. As detailed below, these are mainly mediated by checkpoint kinases with the overall goal to stabilize stalled replication forks and to block origin firing [3]. Their actions help the cell to survive and faithfully complete replication under conditions of stress. When the replication machinery encounters "simple" problems, such as barriers caused by DNA lesions, insufficient nucleotides, or unusual DNA structures, its activity is temporarily ceased with the overall structure of the replisome remaining intact. This process is called fork stalling. Once the problem responsible for stalling is resolved, DNA replication can resume [4]. Alternatively, if the forks are unable to overcome the damage, they collapse. Fork collapse is characterized by a disruption of replisome integrity with dissociation of involved proteins from the template. It is important to note that although stalled and collapsed forks are formally distinct entities, forks that have stalled for more than a few hours tend to collapse [5]. Collapsed forks often undergo