

DIVERGING ROLES OF THE WRN HELICASE AND THE MUS81 ENDONUCLEASE IN THE MAINTENANCE OF CHROMOSOME INTEGRITY FOLLOWING REPLICATION STRESS

Pietro Pichierri

Istituto Superiore di Sanità - Dipartimento Ambiente e Connessa Prevenzione Primaria, Viale Regina Elena 299 - 00161 Roma, Italy

The integrity of eukaryotic chromosomes relies on a sophisticated mechanism that allows DNA lesion repair, faithful replication and chromosome segregation. An accurate duplication of chromosomes is crucial to the maintenance of genome stability, since any replication error has the potential to introduce harmful DNA lesions, such as DNA double-strand breaks or gaps, giving rise to gross chromosomal rearrangements. However, to counteract this eventuality, eukaryotic cells have evolved multiple pathways that permit completion of chromosome replication even in the presence of replication stress. Despite the redundancy in these mechanisms, some of them are preferred over others because less prone to formation of chromosome rearrangements.

Over the years, many factors participating to one or multiple replication recovery mechanisms have been identified, and most of them have been found mutated in human chromosome instability syndromes or have been associated to cancer predisposition, such as ATR, RecQ helicases, BRCA1/2 or Fanconi anemia proteins. Only in the last few years, several groups started to investigate in human cells how these multiple factors are regulated and inter-related, as well as to appreciate the cellular hierarchy in their usage at perturbed forks. Recently, these studies have become increasingly important, not only for basic science, but also for cancer biology as it is now well acknowledged that genome instability, which is a hallmark of cancer cells, is primarily acquired because of chronic replication stress.

Our results suggest that a correct response to perturbed replication relies on the Werner syndrome helicase (WRN), which is a tightly-regulated protein that interfaces with multiple checkpoint factors. Absence of WRN determines excessive replication fork collapse and chromosome instability, mostly through activation of more error-prone pathways. Moreover, we identified the predominant of these pathways, which grants survival of WS cells at cost of genome instability, and we observed that it relies on the MUS81/EME1 endonuclease.

Novel findings showing how MUS81/EME1 may replace WRN during replication fork recovery, will be reported, and how activation of back-up pathways during replication stress may correlate to chromosome instability, and may be exploited in a target therapy of cancer will be discussed.