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Introduction

Telomere biology and DNA repair: Enemies with benefits

This special issue features in-depth reviews of telomere biology and DNA repair. Understanding how telomeres function requires insights into the nature and regulation of the cellular pathways that detect and repair DNA lesions. As telomeres block unwarranted DNA repair reactions and avoid detection by the DNA damage signaling pathways, detailed knowledge of the earliest steps in the relevant DNA damage response pathways can point to the possible regulatory nodes where telomeres interfere with these processes. Furthermore, telomeres have co-opted some of the complexes involved in the DNA damage response, presumably to serve specific protective roles or facilitate the maintenance of the telomeric DNA. Conversely, studies of dysfunctional telomeres have shed new light on the regulation and nature of the cellular DNA damage response, illuminating specific attributes of the pathways that are not readily apparent from the analysis of genome-wide DNA damage. This cross-fertilization between the two fields is reminiscent of how immunologists have furthered the understanding of pathogens and, vice versa, how virologists and microbiologists have provided insights into the host defense system. It is anticipated that efforts like this special issue will foster a continued interdisciplinary synergy between the DNA repair and telomere biology fields.

Know your enemy

The telomere field initially focused on the end-replication problem and its solutions, leading to the discovery of telomerase, its regulation, and its relevance to human disease. Little attention was paid to the rapid advances in the area of DNA damage signaling and repair. Early views of how telomeres might block DNA repair reactions invoked specialized terminal DNA structures (hairpins, G4 DNA) or tenacious protein caps that effectively served as the oft-quoted aglets on shoelaces. Not only were these models inadequate, they ignored the very nature of the enemy telomeres must defend against.

The DNA damage response is not a single enemy with just one weapon that can harm chromosome ends. First, there are two distinct DNA damage detection pathways that could potentially be activated by the natural ends of chromosomes. The ATM kinase pathway (often equated with Tel1 in budding and fission yeast) responds to double-stranded breaks (DSBs) through a poorly understood process in which the Mre11/Rad50/Nbs1 (Xrs2 in yeast) complex (also referred to as MRN or MRX depending on the organism) binds to DNA ends and activates the ATM kinase in conjunction with the Tip60 HAT [1,2]. In addition, telomeres in some organisms, notably vertebrates, contain sufficient single-stranded (ss) DNA to activate the ATR kinase (equated with Mec1 in budding yeast and Rad3 in fission yeast). The ATR kinase pathway relies on the abundant ss DNA binding protein RPA to recognize and associate with ss DNA [1,3]. The activation of ATR signaling involves additional contributions of the Rad9-Rad1-Hus1 clamp (9-1-1) and its clamp loader Rad17 as well as ATRIP and TopBP1. Thus, the silencing of the ATM and ATR kinase pathways is unlikely to rely on a single telomere trick. It has been proposed that shelterin, the vertebrate telomeric protein complex, hides the chromosome end from the ATM kinase pathway by remodeling telomeres into a closed structure, the t-loop [4,5]. In the t-loop, MRN is unlikely to recognize the telomere terminus as a DNA end, thus preventing the activation of the ATM kinase. On the other hand, ATR signaling is blocked by the POT1 component of shelterin. POT1 binds to single-stranded telomeric DNA and was proposed to exclude RPA from gaining access to the telomere [5,6].

Second, the DNA repair reactions that threaten telomeres are varied in nature. DSBs are processed by either homology-directed repair (HDR) or non-homologous end-joining (NHEJ) [7–12]. These two pathways engage DNA ends in a mutually exclusive fashion and, like the ATM and ATR signaling pathways, are initiated in crucially distinct ways. NHEJ employs the ring-shaped Ku70/80 heterodimer, which loads onto DNA ends and facilitates their synapsis and ligation by DNA ligase IV. The vertebrate t-loop structure was invoked as a protective measure against ATM signaling is probably also an effective way to block Ku70/80 and thus could thwart NHEJ in its earliest steps [5]. However, in budding yeast, Rap1 is the main protector against NHEJ [13] and while the mechanism by which Rap1 acts is not understood, it is unlikely to involve a t-loop structure. Even in mammals, additional mechanisms, not involving the t-loop, are required to protect telomeres from NHEJ right after DNA replication.

HDR is initiated when Rad51 replaces RPA on single-stranded DNA and it might be sufficient to repress RPA binding to avoid inappropriate HDR at telomeres. However, it is likely that additional mechanisms are employed by telomeres. Although some of the players in the repression of HDR are now known (at least for mammalian telomeres, e.g. the Rap1 and POT1 components of shelterin [14,15]), the mechanism of their intervention has not been elucidated.

Keep your friends close and keep your enemies closer

All eukaryotes employ telomere specific proteins to repress the DNA damage response at their natural chromosome ends. In vertebrates and in fission yeast, these proteins form the shelterin complex [5,16] whereas plants, budding yeast, ciliates, and worms have a different armament for their defense. Initially surprising was the discovery of well-established DNA damage response proteins as residents in the telomeric chromatin. This was first demonstrated in yeast where the NHEJ factor Ku is required for the maintenance of telomeres [17–22]. It is now clear that telomeres in several

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organisms are associated with proteins that are well known to act in DNA repair reactions, DNA damage signaling, and other DNA transactions.

In mammals, these factors are often recruited to telomeres by shelterin and are therefore referred to as shelterin accessory factors [16]. Although the shelterin accessory factors are not as abundant as shelterin and are often only transiently present at telomeres, their role in telomere biology is crucial. The challenge ahead is to understand how telomeres have managed to tame these potentially threatening protein complexes to only undertake actions that are advantageous to telomeres. It is in this analysis that the true synergy between the fields of telomere biology and DNA repair is most eagerly anticipated.

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