Telomeres and DNA double-strand breaks: ever the twain shall meet?

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Dedication. In appreciation of his heart-felt commitment to research and education, and the life-long influence he has had on the lives of students and colleagues, the authors wish to dedicate this paper to Professor Joel S. Bedford.

Abstract. Telomeres were first recognized as a bona fide constituent of the chromosome based on their inability to rejoin with broken chromosome ends produced by radiation. Today, we recognize two essential and interrelated properties of telomeres. They circumvent the so-called end-replication problem faced by genomes composed of linear chromosomes, which erode from their termini with each successive cell division. Equally vital is the end-capping function that telomeres provide, which is necessary to deter chromosome ends from illicit recombination. This latter property is critical in facilitating the distinction between the naturally occurring DNA double-strand breaks (DSBs) found at chromosome ends (i.e., telomeres) and DSBs produced by exogenous agents. Here we discuss, in a brief historical narrative, key discoveries that led investigators to appreciate the unique properties of telomeres in protecting chromosome ends, and the consequences of telomere dysfunction, particularly as related to recombination involving radiation-induced DSBs.

Keywords. Telomeres, double-strand breaks, ionizing radiation, DNA repair.

Scope of discussion

As a general topic, telomeres and their relationship to DNA double-strand breaks (DSBs) is too broad to be contained within the pages of a brief review. We have, therefore, chosen to limit our discussion to DSBs that are produced exogenously, principally by ionizing radiation (IR). In addition, while occasional mention is made of studies involving lower eukaryotes, our intended emphasis is on the telomeres of higher eukaryotes, particularly mammals. It is instructive to address this topic from a brief historical perspective.

In the beginning...

The turn of the 20th century witnessed the fields of genetics and cytology merge, as researchers sought to understand the relationship between genes and chromosomes. During that time, there was lively, even bitter, debate as to the rudimentary mechanics of homologous chromosome pairing during meiosis. Many subscribed to the theory of 'telosynapsis',...
Dealing with DNA ends

It would be decades before the structure of DNA was elucidated [8] and the implications that this discovery entailed were realized, a time during which the fledgling telomere field seemed to languish. By the 1970s much progress had been made toward understanding the deposition of energy in matter by IR, and its effect on cells and molecules. By the 1980s it had become dogma that the principle target for chromosome aberration formation was the DNA DSB [9]. From a biophysical standpoint, however, controversy existed as to how IR interacted with DNA to form DSBs. In hindsight, the controversy was due, in no small part, to the fact that methods to quantify DSBs in mammalian cells were either insensitive, fraught with potential artifact, or both. In early studies, radiation chemists observed that the yield of DSBs in DNA irradiated with X-rays in aqueous solution showed an upward quadratic curvature with dose [10, 11]. This suggested to Chadwick and Leenhouts [12] that a principle component of DSB formation required cooperative damage of two closely spaced charged particle tracks (i.e., fast electrons set in motion by separate photo absorptive events). More specifically, each of the two independent tracks was envisioned to produce a DNA ‘single-strand break’ (SSB) situated within a few base pairs of one another, the net result being a DSB. This conclusion and its ramifications have since been vigorously challenged on the basis of both biophysical considerations and by direct experimental measurements [13–15]. In the mean time, adopters of this theory were faced with a dilemma whose proposed solution, as discussed below, involved telomere-DSB interactions. Classical cytogenetic theory dictates that an exchange aberration occurring between two different chromosomes (e.g., a dicentric or reciprocal translocation) requires the illegitimate rejoining of broken ends produced by a pair of breaks, one on each of the participating chromosomes [16]. Modernized versions of this theory merely substitute “DSB” for “chromosome break” in this context. If a DSB does, in fact, require the coincident passage of two independent particle tracks, then DSBs formed by this mechanism should be produced with dose-squared kinetics. It follows that if two such DSBs are needed for an exchange, then dicentrics should increase with the fourth power of dose. Of course, they do not, being formed instead with kinetics described by the venerable linear-quadratic equation $\alpha D + \beta D^2$, where $D$ is the dose, $\alpha$ and $\beta$ being proportionality constants [9, 16–18]. In attempting to provide an explanation for this discrepancy, Chadwick and Leenhouts proposed an altogether different mechanism for the origin of radiation-induced chromosome aberrations. In discordance with the notions set forth by Muller and McClintock, they proposed that most IR-induced interchanges involved a DSB from a broken chromosome rejoining with a telomere of another chromosome [19]. Limited experimental evidence, in the flowering plant Haplopappus, was offered in support of this mechanism [20].

With the revelation of the anxiously sought-after sequence of the human telomere [21], came molecular probes that enabled a direct re-examination of the above assertion in mammalian cells. Fluorescence in...