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Palindromes and genomic stress fractures: Bracing and repairing the damage

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ARTICLE INFO

Article history:
Published on line 30 June 2006

Keywords:
Cruciform
Palindrome
DNA hairpin
MRX and MRN
Center-Break palindrome revision
Resolvase

ABSTRACT

DNA palindromes are a source of instability in eukaryotic genomes but remain under-investigated because they are difficult to study. Nonetheless, progress in the last year or so has begun to form a coherent picture of how DNA palindromes cause damage in eukaryotes and how this damage is opposed by cellular mechanisms. In yeast, the features of double strand DNA interruptions that appear at palindromic sites *in vivo* suggest that a resolvase-type activity creates the fractures by attacking a palindrome after it extrudes into a cruciform structure. Induction of DNA breaks in this fashion could be deterred through a Center-Break palindrome revision process as investigated in detail in mice. The MRX/MRN likely plays a pivotal role in prevention of palindrome-induced genome damage in eukaryotes.
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1. Introduction

The last several years has seen an increased frequency of publications that implicate palindromes in diverse pathological contexts. Natural palindromes or near-palindromes of about 200–800 bp have been discovered to exist at sites of sporadic and recurrent chromosomal rearrangements in humans [1–6]. There is evidence that large palindromes arise *de novo* in tumor cells in disease-specific chromosomal positions [7]. The possibility that palindromes initiate gene amplification has been discussed for a number of years [8] and is closer to being dissected in detail now that different steps have been reproduced in model systems ([9] and cited therein; [10]). An interesting observation made in yeast is that strains compromised for telomere maintenance escape from senescence by replacing their telomeres with long palindromes [11]. Possibly, this “PAL” mechanism of chromosome maintenance has a mammalian correlate in that mouse ES cells in which a telomere is removed infrequently acquire a long apparent palindrome at the site [12]. A provocative link between palindromes in mitochondrial DNA and senescence in fungi also exists [13]. This review will discuss how DNA palindromes are endowed with an ability to disrupt genome integrity, and what we know to date about mechanisms that curtail the potential for damage.

1.1. *What is a palindrome?*

The word “palindrome” is in common use but has been inconsistently applied to a spectrum of DNA repeat arrangements. Motifs termed palindromes range from small, perfectly or imperfectly matched inverted repeats to extensive stretches of inverted identity separated by kilobase-pair long spacers (diagrammed in Fig. 1). Because these various sequence configurations can have quite different biophysical and biological properties, it is important to stipulate how we define “palin-

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doi:10.1016/j.dnarep.2006.05.014

drome" here. "Palindrome" will denote a DNA sequence that is immediately juxtaposed to an exact inverted (that is, reverse complementary) copy of itself. A palindrome has no central spacer and no mismatches between component repeats (Fig. 1).

There are sequences that deviate subtly from our strict definition of a palindrome, and that fall into a gray area, i.e. they are inverted repeats with very small spacers and/or small discrepancies between the two arms (Fig. 1). The biophysical behavior of these "near palindromes" can be similar to real DNA palindromes [14], but this is not easily predicted by sequence gazing. We will use the term "near-palindrome" as a convenient way to refer to these sequences and set them apart from other categories of inverted repeats. Thus (recognizing that this is something of a tautology) near-palindromes are functionally defined as sequences that are like palindromes in terms of biological and biophysical character, with some quantitative differences only.

The reason to take care with semantic distinctions is illustrated in Fig. 1. While there is overlap in the structural and biological possibilities presented by different classes of inverted repeats, non-palindromic and palindromic inverted repeats differ in one major respect. Spaced inverted repeats, though intrinsically self-complementary, are not able to self-pair unless an extensive stretch of single stranded DNA is first exposed. An example of this is diagrammed in Fig. 2, where strand separation is forced by replication. In contrast, palindromes and near-palindromes can buckle under stress into a self-paired "cruciform" structure while still essentially double-stranded. The helix opening that initiates the process can be caused by torsional strain and, in the case of a palindrome, only a limited number of base pairs have to melt before both "Watson" and "Crick" can form hairpins by self-annealing (reviewed in [15]). The extrusion process untwists the two strands, further extending the length of the hairpin arms so that overall, conversion to a four-way branch structure, or cruciform, relieves negative superhelical stress [16]. Hypernegative supercoiling provides both the push needed to initiate cruciform extrusion, and the force necessary to stabilize the four-way branch.

1.2. *How do palindromes undermine genome stability?*

The ability of a DNA palindrome to convert from the lineform to a cruciform structure is a critical link between palindromy and DNA damage. It is known that palindromes can serve positive roles in transcription, replication and specialized developmental processes, and the jobs they do exploit their ability to attain an anomalous DNA structure. Domesticated palindromes are usually (though with exceptions) fairly short, and often work in conjunction with structure- and sequence-specific proteins [17–22]. However palindromes can also appear at random sites as a result of replication errors, a chance integration event, or some type of illegitimate recombination. Where a palindrome of roughly 100 bp or more occurs, it creates a weak spot in the DNA that, quite literally, cannot take the strain. If a lineform DNA molecule with a palindromic sequence experiences torque, at some threshold level of hypernegative supercoiling, it will extrude into a cruciform structure.

Creation of a cruciform will not itself actually fracture DNA. When a cruciform appears, conditions could change so as to allow it to be resorbed without causing damage. However there is a consistent and growing body of evidence that with cruciform extrusion, there is an increased likelihood of DNA breakage at the site.

Some examples of this are provided by experiments in which palindromes or near-palindromes have been artificially inserted into a yeast genome. One indication of break induction was the creation of a recombination "hotspot" upon introduction a 160 bp palindrome into *S. pombe* genome [23]. In another study, site-specific DNA breaks were associated with two different 140 bp palindromes introduced at the His4 locus of *S. cerevisiae*. The breaks could be physically detected on Southern blots [24]. A key observation forged the link between palindromes, cruciforms, DNA breaks and a candidate enzymatic activity with the demonstration that a near-palindrome in yeast chromosome II became the site of a specific chromosomal break in which the resulting DNA ends were *hairpin-capped*. Accordingly, Lobachev et al. suggested that the breaks were produced by a resolvase acting on the four-way branch of a cruciform [25]. Further, hairpin terminated breaks were suggested to promote chromosomal translocation. It remains to be shown that such palindrome-directed breaks are resolvase-dependent, however this missing piece is understandable, given that identification of resolvase enzyme(s) in eukaryotes is still a work in progress (for a recent discussion see [26]).

The Lobachev results provide a framework for understanding how palindromes might actively undermine genome integrity: breaks are caused by an enzyme designed to act upon an intermediate in homologous recombination when it instead misappropriates a cruciform structure. Resolvases are meant to cleave Holliday junctions, structures comprised of a pair of duplex DNA molecules covalently connected to one another by two shared strands (Fig. 3A-ii). Identified junction-resolving enzymes allow physical separation of the two duplexes by introducing positionally-correlated nicks across the four-way junction in the two shared strands (for a review see [27]). Known resolvase-generated nicks permit recombined duplexes to go their separate ways (Fig. 3A). Known resolvases do not have an inherent ability to discriminate between a Holiday junction and the four-way junction of an extruded cruciform (Fig. 3B [28]). For example T4 DNA resolvase and RuvC both act by making cross-diagonal single strand cleavages at a cruciform base *in vitro*, breaking apart the four-stranded structure into two linear, hairpin-capped cleavage products [28,29]. In fact the appearance of a T4 resolvase-sensitive structure is often taken as proof of cruciform extrusion. Thus, while resolution is beneficial in the context of a Holliday junction – two duplex DNAs are successfully separated – "resolution" is definitely undesirable in the context of an extruded cruciform. Resolvases break a once-contiguous duplex into two parts, creating hairpinned ends on either side of the interruption (Fig. 3B) [28].

Moving to humans, the genetic literature supports the notion that pathogenic breaks may be caused by the structure-forming potential of DNA palindromes. Pioneering work, principally by Emanuel and colleagues has demonstrated that the chromosomal exchanges seen for recurrent translocations involving Chr 22, 11 and 17 localize to the *centers* of large pre-

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