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Review

Interstitial telomeric sequences in vertebrate chromosomes: Origin, function, instability and evolution

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ABSTRACT

By definition, telomeric sequences are located at the very ends or terminal regions of chromosomes. However, several vertebrate species show blocks of (TTAGGG)n repeats present in non-terminal regions of chromosomes, the so-called interstitial telomeric sequences (ITSs), interstitial telomeric repeats or interstitial telomeric bands, which include those intrachromosomal telomeric-like repeats located near (pericentromeric ITSs) or within the centromere (centromeric ITSs) and those telomeric repeats located between the centromere and the telomere (i.e., truly interstitial telomeric sequences) of eukaryotic chromosomes. According with their sequence organization, localization and flanking sequences, ITSs can be classified into four types: 1) short ITSs, 2) subtelomeric ITSs, 3) fusion ITSs, and 4) heterochromatic ITSs. The first three types have been described mainly in the human genome, whereas heterochromatic ITSs have been found in several vertebrate species but not in humans.

Several lines of evidence suggest that ITSs play a significant role in genome instability and evolution. This review aims to summarize our current knowledge about the origin, function, instability and evolution of these telomeric-like repeats in vertebrate chromosomes.

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1. Introduction. What are interstitial telomeric sequences?

1.1. Telomeres

Telomeres are specialized nucleoproteic complexes localized at the physical ends of linear eukaryotic chromosomes that maintain their stability and integrity [1]. They provide a protective "cap" for chromosomal DNA against illegitimate recombination, exonucleolytic attack and degradation, and oxidative damage [1,2]. In all vertebrates, the DNA component of telomeres consists of extended arrays of the TTAGGG hexamer [3,4]. Interestingly, this "vertebrate" telomere motif was also found in most Metazoa (except nematodes and arthropods) and in the unicellular metazoan sister group Choanozoa (see [5] for review). Telomeric DNA is bound by a specialized multiprotein complex known as shelterin, constituted by six proteins (POT1, TPP1. TIN2, TRF1, TRF2 and RAP1) and their variants (for example, mice have two forms of POT1, POT1a and POT1b) [1,6]. Besides telomeric repeats and shelterin, telomeres also comprise (UUAGGG)n-containing RNA molecules (telomeric repeat containing RNA or TERRA), a novel class of RNA transcribed from the subtelomere towards the telomere which plays critical roles in telomere biology, such as heterochromatin formation at chromosome ends and regulation of telomerase activity [7–11]. Spontaneous or induced telomere shortening is usually prevented by telomerase, a reverse transcriptase which adds telomeric repeats to the chromosome ends, thus elongating telomeres [1,12–14]. Telomerase activity is usually inactive in somatic cells, so telomere shortens with each cell division, but it is active in germline cells, stem cells, immortalized cell lines, activated lymphocytes, and most of the tumor cells analyzed so far [14]. Alternatively, telomere elongation can occur in the absence of telomerase through the so-called ALT (for 'Alternative Lengthening of Telomeres') mechanism, which involves homologous recombination between telomeres and has been described in several tumor cells and immortalized cell lines [14–17]. Interestingly, telomerase and ALT mechanisms of telomere elongation coexist in some human tumor cells [14].

1.2. Interstitial telomeric sequences

By definition, telomeric sequences are located at the very ends or terminal regions of chromosomes. However, several vertebrate species show blocks of (TTAGGG)n repeats present in non-terminal regions of chromosomes, the so-called interstitial telomeric sequences (ITSs), interstitial telomeric repeats or interstitial telomeric bands, which include those intrachromosomal telomeric-like repeats located near (pericentromeric ITSs) or within the centromere (centromeric ITSs) and those telomeric repeats located between the centromere and the telomere (i.e., truly interstitial telomeric sequences) of eukaryotic chromosomes [18–20] (Fig. 1). The presence of ITSs has been assumed to be the result of tandem chromosome fusions (telomere–telomere fusions) during evolution or the insertion of telomeric DNA within unstable sites during the repair of DNA double-strand breaks (DSBs) [4,18,19,21]. We will consider the origin and evolution of ITSs in detail in sections 3 and 4 of this review.

1.3. Relationship between ITSs and true telomeres

It has been shown that ITSs do not represent a functional telomere [4]. The only exception reported so far is represented by an Indian Muntjac cell line, where in a small percentage of cells ITSs get amplified and chromosomes fall apart into many small fragments with functional telomeres on most chromosome ends [22]. Moreover, unlike terminal telomeric sequences (i.e., true telomeres), ITSs seem not to be directly associated with the nuclear matrix [23]. Nevertheless, ITSs can interact with telomeres, as demonstrated by the recent discovery of structures named "interstitial telomere loops" or ITLs. These ITLs are chromosome-end structures which result from the interaction of telomeres and ITSs, and are dependent on the telomere-repeat binding factor 2 (TRF2, from the shelterin complex) and lamin A/C (a canonical component of the nucleoskeleton) [24,25]. This structure has important implications in organismal aging, telomere and genome stability, regulation of gene expression and chromosome condensation [25].

1.4. ITSs detection

ITSs are usually detected at the chromosome level by using Fluorescence *in situ* hibridization (FISH) with a DNA or PNA (Peptide Nucleic Acid) telomeric probe or the primed *in situ* labeling (PRINS) technique, but for most short ITSs (<100 bp) molecular methods such as Southern blot or pulsed field gel electrophoresis (PFGE) are necessary to detect these sequences and to determine the exact co-localization of ITSs and the associated breakage or recombination sites. Only a few short ITSs can be detected by FISH or PRINS, due to the relatively low sensitivity of these techniques (about 1 kb, being PRINS more sensitive than FISH) [26,27]. It is important to note that when we refer to ITSs, we