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Review

Haploinsufficiency and telomere length homeostasis

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ABSTRACT

In humans, autosomal dominant or X-linked disease can arise through a phenomenon termed haploinsufficiency, where one remaining wild-type allele is insufficient for function. In model organisms, the impact of heterozygosity can be tested directly with engineered mutant alleles or in a hemizygous state where the expression of one allele is abrogated completely. This review will focus on haploinsufficiency as it relates to telomerase and telomere length maintenance and, citing selected examples in various model organisms, it will discuss how the problem of gene dosage relates to telomere function in normal and diseased states.

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1. Introduction

Haploinsufficiency is a very interesting phenomenon that has the potential to shed significant mechanistic insight into the cellular process it affects. Although this review will focus on the role of insufficient gene dosage as it relates to telomerase and telomere function, it may be useful to first consider what is meant by haploinsufficiency, and how researchers postulate why gene dosage may, in some instances, be limiting.

Haploinsufficiency is defined as insufficient function to maintain a wild-type phenotype in the presence of one wild-type allele and one mutant allele. Haploinsufficiency can arise through mutations that lead to loss of function, or partial or complete loss of expression of one allele. Occasionally haploinsufficiency can be additive, for example when reduced function at two separate loci manifests a phenotype when present in combination (termed unlinked non-complementation) [1]. Although specific instances of unlinked non-complementation will be described for telomere maintenance below, one classic and historical example is described by Stearns and Botstein, who noted a gene-specific and allele-specific lethality when a mutation in beta-tubulin was combined with a cold-sensitive mutation in alpha-tubulin [1].

Such genetic interactions are interesting to biologists for numerous reasons, and it is helpful to consider these reasons when discussing specific examples related to telomere maintenance later. Unlinked non-complementation can provide evidence that two gene products physically interact or cooperate in a single network, as in the example noted above [1]. Sex-linked or autosomal dominant diseases linked to mutation of one gene copy may identify pathways that are limiting for cellular function. In the case of autosomal dominance, it is important to distinguish those mutations that are co-dominant because they interfere with wild-type function from those mutations that do not interfere with function of the remaining wild-type allele. Model

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organisms such as *Saccharomyces cerevisiae*, *Caenorhabditis elegans* and *Drosophila melanogaster* have proven instrumental in underscoring the broad biological relevance of haploinsufficiency. As one example, a genome-wide screen across *S. cerevisiae* strains heterozygous at individual loci revealed that approximately 3% of loci are haploinsufficient for growth in rich media, and these loci were enriched for gene products that associate in multiprotein complexes [2, reviewed in 3]. In another example, a recent study in *D. melanogaster* determined that haploinsufficiency of specific ribosomal protein genes is associated with cardiomyopathy [4]. Thus, many critical cellular processes must be exquisitely sensitive to the dosage of their effectors.

Several interesting hypotheses are postulated regarding the mechanistic and evolutionary forces that drive haploinsufficiency. Heterozygosity may be deleterious in diploid organisms because it may disrupt a proper balance between various components within a complex or network [5]. Others have proposed that the evolution of enzyme pathways favors dosages close to the equilibrium concentration of the rate-limiting step, so that the pathway can remain responsive to changing environmental conditions [6]. We will return to these (non-exclusive) mechanisms at the conclusion of this review.

2. Haploinsufficiency of telomerase function was first described in *S. cerevisiae*

A seminal genetic screen for haploid mutations that suppressed new telomere formation identified three yeast telomerase components whose mutation led to ever-shorter telomeres: *EST2* (telomerase reverse transcriptase), *EST3*, and *EST4*/*CDC13* [7]. The authors made the astute observation that haploid progeny with a mutation in one of the above genes possessed shorter telomeres and entered senescence earlier when the diploid from which they were derived was heterozygous for more than one mutation [7]. For example, *est2-1* progeny derived from an *EST2*/*est2-1 EST3*/*est3-1* diploid exhibited senescence sooner than *est2-1* progeny derived from an *EST2*/*est2-1* diploid. This phenomenon was observed with multiple combinations of *EST* genes, and it was suggested that inadequate telomere maintenance in doubly heterozygous diploid parents led to shorter telomeres in the progeny [7–9]. This phenomenon was termed 'additive haploinsufficiency' and is conceptually similar to the unlinked non-complementation described by Stearns and Botstein [1] (Fig. 1C). The telomerase RNA component of *S. cerevisiae*, *TLC1*, is haploinsufficient even in the absence of other mutations, and *TLC1*/*tlc1Δ* diploids possess shorter

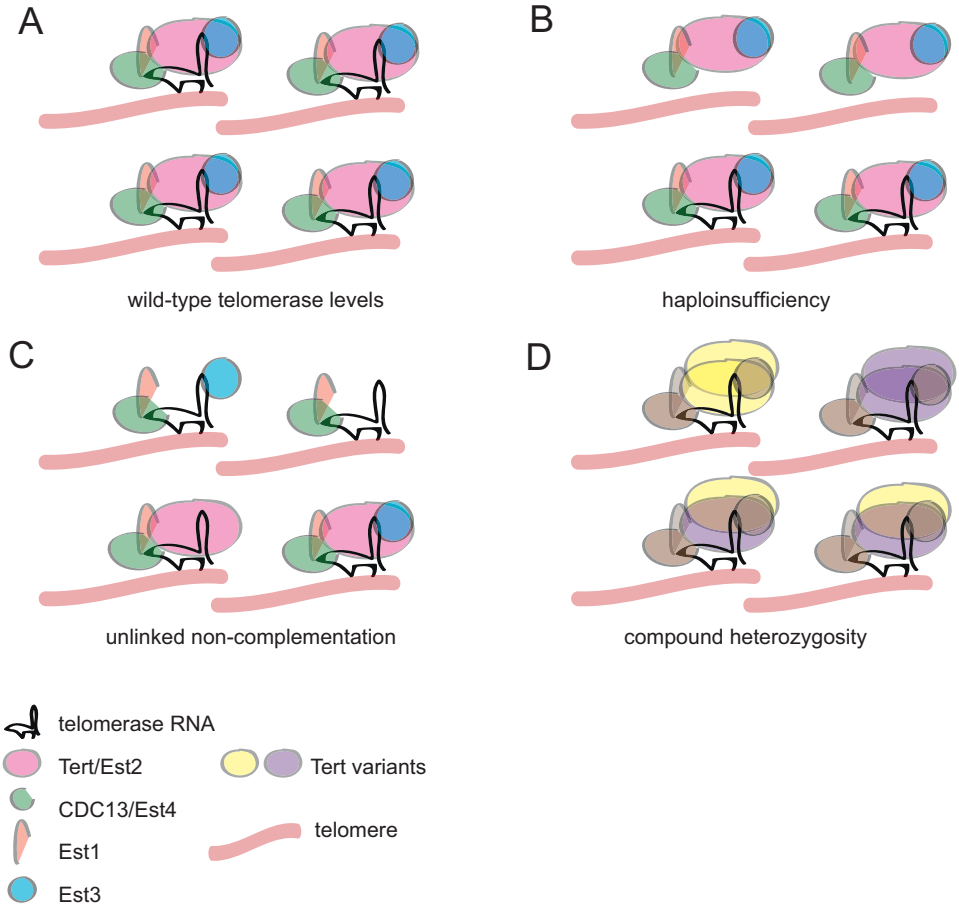

Fig. 1. A simplified schematic of dosage-dependent effects upon telomerase function. (A) Wild-type function. There exists a sufficient level of telomerase to maintain average length at all chromosome ends. (B) True haploinsufficiency. When the dosage of one component is reduced by 50% (e.g. note the absence of the telomerase RNA, *TLC1*, in upper (B) versus (A)), and making an assumption that functional dosage is less than or equal to the concentration of substrate, there will be insufficient levels of telomerase present to elongate every telomere and shortening will ensue. (C) Additive haploinsufficiency or unlinked non-complementation. When the functional dosage of two components within a same complex is reduced by one-half (e.g. TERT/Est2 and Est3, as shown here), and assuming that components are assembled randomly, on average fewer than 50% of complexes may be functional. (D) Compound heterozygosity. In a recent unusual example, two *Tert* mutations were inherited in a young patient suffering from DC, while at the time of the report neither parent exhibited disease [22]. One possible explanation for the disease may be if telomerase existed as a dimer, where yellow/yellow or purple/purple complexes may be functional, but yellow/purple complexes may be non-functional, or the disease may be the result of compound heterozygosity, where all complexes may be slightly less proficient than wild-type, and the effects may be additive rather than allele-specific. Complexes are not presented in comprehensive form, and this schematic represents only a subset of the types of genetic/phenotypic interactions possible.