Année de publication : 2007

Hong-Yan Du, Rachel Idol, Sara Robledo, Jennifer Ivanovich, Ping An, Arturo Londono-Vallejo, David B Wilson, Philip J Mason, Monica Bessler (2007 Sep 19)

Telomerase reverse transcriptase haploinsufficiency and telomere length in individuals with 5p- syndrome.

Aging cell : 689-97

Résumé

Telomerase, which maintains the ends of chromosomes, consists of two core components, the telomerase reverse transcriptase (TERT) and the telomerase RNA (TERC). Haploinsufficiency for TERC or TERT leads to progressive telomere shortening and autosomal dominant dyskeratosis congenita (DC). The clinical manifestations of autosomal dominant DC are thought to occur when telomeres become critically short, but the rate of telomere shortening in this condition is unknown. Here, we investigated the consequences of de novo TERT gene deletions in a large cohort of individuals with 5p- syndrome. The study group included 41 individuals in which the chromosome deletion resulted in loss of one copy of the TERT gene at 5p15.33. Telomere length in peripheral blood cells from these individuals, although within the normal range, was on average shorter than in normal controls. The shortening was more significant in older individuals suggesting an accelerated age-dependent shortening. In contrast, individuals with autosomal dominant DC due to an inherited TERC gene deletion had very short telomeres, and the telomeres were equally short regardless of the age. Although some individuals with 5p- syndrome showed clinical features that were reminiscent of autosomal dominant DC, these features did not correlate with telomere length, suggesting that these were not caused by critically short telomeres. We conclude that a TERT gene deletion leads to slightly shorter telomeres within one generation. However, our results suggest that several generations of TERT haploinsufficiency are needed to produce the very short telomeres seen in patients with DC.

J Arturo Londoño-Vallejo (2007 Aug 31)

Telomere instability and cancer.

Biochimie : 73-82

Résumé

Telomeres are required to preserve genome integrity, chromosome stability, nuclear architecture and chromosome pairing during meiosis. Given that telomerase activity is limiting or absent in most somatic tissues, shortening of telomeres during development and aging is the rule. In vitro, telomere length operates as a mechanism to prevent uncontrolled cell growth and therefore defines the proliferation potential of a cell. In vitro, in somatic cells that have lost proliferation control, shortening of telomeres becomes the main source of genome instability leading to genetic or epigenetic changes that may allow cells to become immortal and to acquire tumor phenotypes. In vivo, mice models have indisputably shown both the protective and the promoting role of very short telomeres in cancer development. In

humans, although telomere shortening and other types of telomere dysfunction probably contribute to the genome instability often detected in tumors, the specific contributions of such instability to the development of cancer remain largely undetermined.

Eric Gilson, Arturo Londoño-Vallejo (2007 Aug 30)
Telomere length profiles in humans: all ends are not equal.
Cell cycle (Georgetown, Tex.) : 2486-94

Résumé

Telomere length is an important parameter of telomere function since it determines number of aspects controlling chromosome stability and cell division. Since telomeres shorten with age in humans and premature aging syndromes are often associated with the presence of short telomeres, it has been proposed that telomere length is also an important parameter for organismal aging. How mean telomere lengths are determined in humans remains puzzling, but it is clear that genetic and epigenetic factors appear to be of great importance. Experimental evidence obtained from many different organisms has provided the basis for a widely accepted counting mechanism based on a negative feedback loop for telomerase activity at the level of individual telomeres. In addition, recent studies in both normal and pathological contexts point to the existence of chromosome-specific mechanisms of telomere length regulation determining a telomere length profile, which is inherited and maintained throughout life. In this review, we recapitulate the available data, propose a synthetic view of telomere length control mechanisms in humans and suggest new approaches to test current hypotheses.

Année de publication : 2006

Maria Antonietta Cerone, J Arturo Londoño-Vallejo, Chantal Autexier (2006 Aug 8)
Telomerase inhibition enhances the response to anticancer drug treatment in human breast cancer cells.
Molecular cancer therapeutics : 1669-75

Résumé

Breast cancer is the most common malignancy among women. Current therapies for breast tumors are based on the use of chemotherapeutic drugs that are quite toxic for the patients and often result in resistance. Telomerase is up-regulated in 95% of breast carcinomas but not in adjacent normal tissues. Therefore, it represents a very promising target for anticancer therapies. Unfortunately, the antiproliferative effects of telomerase inhibition require extensive telomere shortening before they are fully present. Combining telomerase inhibition with common chemotherapeutic drugs can be used to reduce this lag phase and induce tumor cell death more effectively. Few studies have analyzed the effects of telomerase inhibition in combination with anticancer drugs in breast cancer cells. In this study, we inhibited telomerase activity in two breast cancer cell lines using a dominant-

negative human telomerase reverse transcriptase and analyzed cell viability after treatment with different anticancer compounds. We found that dominant-negative human telomerase reverse transcriptase efficiently inhibits telomerase activity and causes telomere shortening over time. Moreover, cells in which telomerase was suppressed were more sensitive to anticancer agents independently of their mechanism of action and this sensitization was dependent on the presence of shorter telomeres. Altogether, our data show that blocking telomere length maintenance in combination with anticancer drugs can be used as an effective way to induce death of breast cancer cells.

J Graakjaer, J A Londono-Vallejo, K Christensen, S Kølvraa (2006 Jun 29)

The pattern of chromosome-specific variations in telomere length in humans shows signs of heritability and is maintained through life.

Annals of the New York Academy of Sciences : 311-6

Résumé

This paper characterizes the distribution of telomere length on individual chromosome arms in humans. By fluorescent in situ hybridization (FISH), followed by computer-assisted analysis of digital images, it is shown that the distribution of telomere length on individual chromosome arms is not random, but that humans have a common telomere profile. This profile exists in lymphocytes, amniocytes and fibroblasts, and seems to be conserved during life. A closer look at the overall pattern of the profile shows that the length of the telomeres in general follows the total chromosome length. In addition to the common profile, it is found that each person has specific characteristics, which are also conserved throughout life. Studying both twins and families we have obtained indications that these individual characteristics are at least partly inherited. Altogether, our results suggest that the length of individual telomeres might occasionally play a role in the heritability of life span.

M A Cerone, J A Londoño-Vallejo, C Autexier (2006 Jun 13)

Mutated telomeres sensitize tumor cells to anticancer drugs independently of telomere shortening and mechanisms of telomere maintenance.

Oncogene : 7411-20

Résumé

Telomerase is a ribonucleoprotein complex that maintains the stability of chromosome ends and regulates replicative potential. Telomerase is upregulated in over 85% of human tumors, but not in adjacent normal tissues and represents a promising target for anticancer therapy. Most telomerase-based therapies rely on the inhibition of telomerase activity and require extensive telomere shortening before inducing any antiproliferative effect. Disturbances of telomere structure rather than length may be more effective in inducing cell death. Telomerase RNA subunits (hTRs) with mutations in the template region reconstitute active holoenzymes that incorporate mutated telomeric sequences. Here, we analysed the feasibility of an anticancer approach based on the combination of telomere destabilization

and conventional chemotherapeutic drugs. We show that a mutant template hTR dictates the synthesis of mutated telomeric repeats in telomerase-positive cancer cells, without significantly affecting their viability and proliferative ability. Nevertheless, the mutant hTR increased sensitivity to anticancer drugs in cells with different initial telomere lengths and mechanisms of telomere maintenance and without requiring overall telomere shortening. This report is the first to show that interfering with telomere structure maintenance in a telomerase-dependent manner may be used to increase the susceptibility of tumor cells to anticancer drugs and may lead to the development of a general therapy for the treatment of human cancers.

Jesper Graakjaer, Héra Der-Sarkissian, Annette Schmitz, Jan Bayer, Gilles Thomas, Steen Kolvraa, José-Arturo Londoño-Vallejo (2006 Jan 28)
Allele-specific relative telomere lengths are inherited.
Human genetics : 344-50

Résumé

Previous studies have indicated that single relative telomere lengths are defined in the zygote. In order to explore the possibility that single telomere lengths segregate in families, we compared relative telomere lengths obtained from allelic chromosome extremities transmitted from parent to child, representing a total of 31 independent meiotic events. We find a significant positive correlation of 0.65 (P=0.0004) between these telomere lengths, whereas the correlation between the non-transmitted parental homologue and the transmitted homologue in the child is not statistically significant (r=0.16; P=0.195). This study indicates that, even though there is a telomerase-mediated maintenance/elongation of telomeres in germ cells, allele-specific relative telomere lengths are preserved in the next generation.

Année de publication : 2005

Fred Goldman, Rachida Bouarich, Shashikant Kulkarni, Sara Freeman, Hong-Yan Du, Lea Harrington, Philip J Mason, Arturo Londoño-Vallejo, Monica Bessler (2005 Nov 15)
The effect of TERC haploinsufficiency on the inheritance of telomere length.
Proceedings of the National Academy of Sciences of the United States of America : 17119-24

Résumé

Telomeres protect chromosome ends from end-to-end fusion and degradation. Loss of telomere function causes cell-cycle arrest or cell death. Autosomal dominant dyskeratosis congenita (AD DC), a rare inherited bone marrow failure syndrome, is caused by mutations in TERC, the RNA component of telomerase. Here, we studied the telomere dynamics over three generations in a 32-member extended family with AD DC due to a TERC gene deletion. Our analysis shows that peripheral blood cells from family members haploinsufficient for TERC have very short telomeres. Telomeres are equally short in all individuals carrying the

TERC gene deletion irrespective of their age. Chromosome-specific telomere analysis distinguishing the parental origin of telomeres showed that in gene deletion carriers, paternal and maternal telomeres are similarly short and similar in length to those of the affected parent. In children of affected parents who have normal TERC genes, parental telomeres are again similar in length, but two generations appear to be necessary to fully restore normal telomere length. These results are consistent with a model in which telomerase preferentially acts on the shortest telomeres. When TERC is limiting, this preference leads to the accelerated shortening of longer telomeres. The limited amount of active telomerase in TERC RNA haploinsufficiency may not be able to maintain the minimal length of the increasing number of short telomeres. Thus, the number of cells with excessively short telomeres and the degree of residual telomerase activity may determine the onset of disease in patients with AD DC.

Delphine T Marie-Egyptienne, Maria Antonietta Cerone, J Arturo Londoño-Vallejo, Chantal Autexier (2005 Sep 30)

A human-Tetrahymena pseudoknot chimeric telomerase RNA reconstitutes a nonprocessive enzyme in vitro that is defective in telomere elongation.

Nucleic acids research : 5446-57

Résumé

The phylogenetically-derived secondary structures of telomerase RNAs (TR) from ciliates, yeasts and vertebrates are surprisingly conserved and contain a pseudoknot domain at a similar location downstream of the template. As the pseudoknot domains of Tetrahymena TR (tTR) and human TR (hTR) mediate certain similar functions, we hypothesized that they might be functionally interchangeable. We constructed a chimeric TR (htTR) by exchanging the hTR pseudoknot sequences for the tTR pseudoknot region. The chimeric RNA reconstituted human telomerase activity when coexpressed with hTERT in vitro, but exhibited defects in repeat addition processivity and levels of DNA synthesis compared to hTR. Activity was dependent on tTR sequences within the chimeric RNA. htTR interacted with hTERT in vitro and dimerized predominantly via a region of its hTR backbone, the J7b/8a loop. Introduction of htTR in telomerase-negative cells stably expressing hTERT did not reconstitute an active enzyme able to elongate telomeres. Thus, our results indicate that the chimeric RNA reconstituted a weakly active nonprocessive human telomerase enzyme in vitro that was defective in telomere elongation in vivo. This suggests that there may be species-specific requirements for pseudoknot functions.

Maria A Cerone, Chantal Autexier, J Arturo Londoño-Vallejo, Silvia Bacchetti (2005 Aug 24)

A human cell line that maintains telomeres in the absence of telomerase and of key markers of ALT.

Oncogene : 7893-901

Résumé

In human somatic cells proliferation results in telomere shortening due to the end replication problem and the absence of adequate levels of telomerase activity. The progressive loss of telomeric DNA has been associated with replicative senescence. Maintenance of telomere structure and function is, therefore, an essential requisite for cells that proliferate indefinitely. Human cells that have acquired the immortal phenotype mostly rely on telomerase to compensate for telomere shortening with cell division. However, a certain percentage of immortalized cell lines and human tumors maintain their telomeres by Alternative Lengthening of Telomeres (ALT), a mechanism not fully understood but apparently based on homologous recombination. Here, we report the isolation of an immortal human cell line that is derived from an ALT cell line but maintains telomeres in the absence of key features of ALT and of telomerase. The properties of these cells suggest that the identification of ALT cells may not be reliably based on known ALT markers. This finding is of relevance for discriminating between the mortal and immortal phenotype among telomerase-negative cells in vitro and in vivo, particularly in regard to the development of pharmacological approaches for cancer treatment based on telomerase inhibition.

Maria Antonietta Cerone, Ryan J Ward, J Arturo Londoño-Vallejo, Chantal Autexier (2005 Mar 9)
Telomerase RNA mutated in autosomal dyskeratosis congenita reconstitutes a weakly active telomerase enzyme defective in telomere elongation.
Cell cycle (Georgetown, Tex.) : 585-9

Résumé

Dyskeratosis congenita (DC) is a rare multi-system syndrome characterized by nail dystrophy, abnormal skin pigmentation and mucosal leukoplakia. The gene mutated in the X-linked form of human DC encodes for dyskerin, a nucleolar pseudourydilase that is involved in rRNA maturation. Dyskerin is also involved in telomerase function through its interaction with the telomerase RNA (hTR). Mutations in dyskerin result in low levels of hTR, decreased telomerase activity and telomere shortening. Autosomal dominant DC is characterized by mutations in hTR, supporting the hypothesis that the DC phenotype may be caused by impaired telomere maintenance. Several mutations have been identified in different regions of hTR in patients affected by autosomal dominant DC. Recent reports have shown that coexpression of wild-type hTR with hTR harboring mutations found in the pseudoknot domain does not affect telomerase activity in vitro. However, these studies did not assess the consequences of mutant hTR expression at the telomeres. Here we provide the first direct in vivo evidence that a mutant hTR carrying the GC to AG double substitution in the pseudoknot at nucleotides 107-108 found in patients affected by autosomal dominant DC does not behave as a dominant-negative for telomere maintenance. Rather it reconstitutes a weakly active telomerase enzyme, which is defective in telomere elongation.