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Telomeres and telomerase as targets for anticancer drug development

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Contents

Abstract

In most human cancers, the telomere erosion problem has been bypassed through the activation of a telomere maintenance system (usually activation of telomerase). Therefore, telomere and telomerase are attractive targets for anti-cancer therapeutic interventions. Here, we review

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a large panel of strategies that have been explored to date, from small inhibitors of the catalytic sub-unit of telomerase to anti-telomerase immunotherapy and gene therapy. The many positive results that are reported from anti-telomere/telomerase assays suggest a prudent optimism for a possible clinical application in a close future. However, we discuss some of the main limits for these approaches of antitumour drug development and why significant work remains before a clinically useful drug can be proposed to patients.

Keywords: Targeted anticancer therapy; Telomeres; Telomerase

1. Introduction

The current trend in research on anticancer drugs is to exploit particular traits or hallmarks unique to cancer cells. Despite the fact that cancer displays a great heterogeneity in clinical behaviour, most human tumours, share a limited set of acquired capabilities that define the malignant state [1]. These include self-sufficiency in growth signal, insensitivity to antigrowth signals, avoidance of programmed cell death, unlimited replicative potential, sustained angiogenesis, tissue invasion and metastasis. Among these hallmarks, the acquisition of unlimited replicative potential is a key step to ensure expansive tumour growth.

Activation of a telomere maintenance mechanism seems indispensable for immortalisation of human cells. Telomeres and telomerase, the protein that allows their maintenance, have therefore been proposed as preferential targets for anticancer drug development. This review highlights recent advances in our understanding of mammalian telomere biology and how it relates to cancer, and discusses current approaches that exploit this knowledge to develop novel antineoplastic drugs.

2. Telomere biology and cancer

2.1. Unlimited replication potential: the link to telomeres and telomerase

Normal cultured cells have a finite replicative potential [2] meaning that after a certain number of divisions they stop growing and enter senescence, a stage named mortality 1 (M1). In human fibroblasts the senescence can be bypassed by inactivation of the tumour suppressor genes p53 and pRb. These transformed cells progress through 20–30 doublings before they enter a second state called crisis or mortality 2 (M2). Cells that escape crisis have acquired the ability to divide without a limit, a trait called immortalisation [3]. Over the past decade, emerging evidence has shown that the ends of chromosomes, or telomeres, are essential regulators of life span. Human telomeres which are composed of several thousand repeats of a T2AG3 hexanucleotide sequence element, progressively shorten as normal cells proliferate [4,5], whereas immortalised cells, including most types of tumour cells, maintain a stable telomere length [6]. Thus, telomeres have been proposed to serve as a molecular device that counts the number of cellular divisions and limits life span [7]. In most malignant cells (85–90%), the maintenance of telomeres is achieved by upregulating the expression of the telomerase enzyme, which adds hexanucleotide repeats onto the ends of telomeres [8] whereas, 10–15% of the remainder tumours or tumour cell lines maintain the length of telomeres through a telomerase-independent alternative lengthening of telomere (ALT) mechanism [9,10], a process implicating homologous recombination [11]. However, the maintenance of telomere length above a critical threshold through either mechanism permits unlimited replication of cells. The ALT phenotype is characterized by heterogeneous telomere lengths and the presence of a variant form of the promyelocytic leukaemia (PML) nuclear bodies at the telomeric level, also called APBs (ALT-associated PML bodies) [12]. Immunofluorescent techniques have demonstrated that APBs bodies, in addition to the PML protein, contain telomeric DNA with their usual telomere-associated proteins (e.g. TRF1, TRF2), but also proteins that are implicated in double strand break repair and homologous recombination such as RPA, Pre11/Nbs1/Rad51 and Rad52 [12]. Further, it has been proposed that tumours presenting ALT-phenotypes have potentially a higher chromosomal instability than telomerase positive tumours [13–15]. However, the clinical evolution and sensitivity to treatment of ALT-tumours are still poorly described despite the reported significance of the ALT-pathway in, for instance, sarcomas [16].

2.2. Telomeres, a multi-protein complex

The extremities of eukaryotic chromosomes are composed of specialized DNA nucleoprotein complexes termed telomeres (Fig. 1). Human telomeres consist of a variable number of tandem repeats of the T2AG3 sequence together with a group of specific proteins, and are therefore of variable length. At the 3′ end, the G rich strand of the telomere forms a single stranded extension. Recent ultrastructural evidence in vitro suggests that the telomere repeated sequence folds back on itself to form a duplex loop structure termed T-loop [17]. Both telomeric DNA and telomere-associated proteins have an essential role in stabilizing chromosome ends by forming a cap structure that protects chromosome ends from exonucleolytic degradation and terminal fusions. Some telomere-associated proteins bind directly to the T2AG3 DNA repeats, whereas others are associated with the telomere via protein–protein interactions (Fig. 2). In humans, the