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REVIEW

microRNAs control the function of telomeres in cancer

Roberto Dinami[1, 2, 3], Eleonora Petti[1, 2, 3], Rosanna Sestito[2], Roberta Benetti[1,4], Stefan Schoeftner[1, 2]

[1]*Laboratorio Nazionale Consorzio Interuniversitario Biotecnologie (LNCIB), Padriciano 99, 34149 Trieste, Italy*
[2]*Italian National Cancer Institute, Regina Elena, Via Elio Chianesi 53, 00144 Rome, Italy*
[3]*SDBM School of Molecular Biomedicine (SDBM), Dipartimento di Scienze della Vita, Università degli Studi di Trieste, 34129 Trieste, Italy*
[4]*Dipartimento di Scienze Mediche e Biologiche, Università degli Studi di Udine; p.le Kolbe 1, 33100, Udine, Italy*

Correspondence: Stefan Schoeftner
E-mail: stefan.schoeftner@lncib.it
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Telomeres are located at the end of chromosomes and consist of DNA tandem repeats that recruit the specialized protein complex "shelterin". Shelterin has a crucial role in controlling chromosome end protection, telomere recombination and telomere length. Telomeres shorten with every cell division, finally leading to telomere-dysfunction and the induction of senescence or apoptosis. Cancer formation is paralleled by a change in telomere regulation. Re-activation of telomerase ensures the maintenance of telomere function to facilitate unlimited proliferative potential. Importantly, aberrant function of the shelterin complex contributes to tumor formation and genomic instability in human cancer. miRNAs are important regulators of central cancer pathways and are of high clinical relevance. We recently showed that the onco-microRNA miR-155 controls the expression of TRF1 in human breast cancer to promote increased telomere fragility and genomic instability. Importantly, low TRF1 expression correlates with poor prognosis in estrogen receptor positive cancer patients, underlining the clinical relevance of miR-155 dependent regulation of TRF1 in human breast cancer. Our work suggests the existence of a network of miRNAs that controls telomere function in telomere related pathologies. Identification and functional validation of "telo-miRNAs" is expected to open new avenues in the understanding of telomere related maladies such as cancer and aging.

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Vertebrate telomeres consist of TTAGGG tandem repeats that recruit the specialized protein complex "shelterin" [1,2]. Shelterin controls various aspects of telomere function and consists of six core components. TRF1 and TRF2 bind double stranded telomeric DNA and POT1 binds to the single stranded telomeric 3'overhang [2-5]. The DNA binding shelterin proteins interact with RAP1, TPP1 and TIN2 to form a functional complex. TRF1, TRF2 and POT1 have a key role in telomere protection by suppressing the activation of the DNA damage signaling and repair pathways at chromosome ends [5-7]. In addition, shelterin controls telomere length and the frequency of homologous recombination between telomeric sister chromatids [2, 8]. Telomeres shorten with each cell division, unless the reverse transcriptase telomerase replenishes chromosome ends [1]. Critical telomere shortening provokes telomere dysfunction and the activation of a DNA damage response at chromosome ends that finally leads to apoptosis or senescence [9-11].

The escape from replicative senescence is a key step in tumorigenesis and is achieved by the reactivation of telomerase activity, as observed in 90% of human cancers [12]. A growing body of evidence suggests that shelterin complex components can play a central role during cancer formation or progression. Recurrent POT1 mutations linked

to telomeric and chromosomal abnormalities have been identified in chronic lymphocytic leukemia (CLL) [13]. Wnt/β-catenin signaling drives TRF2 expression to improve telomere function in cancer cells [14]. Finally, loss of TRF1 results in chromosome fragility at telomeres and increased cancer formation in the absence of p53 [6,7]. Together, these findings indicate that understanding mechanisms that control the expression of telomerase or shelterin components during cancer formation is of high relevance.

miRNAs are crucial modulators of gene expression that act across multiple oncogenic pathways and serve as efficient prognostic and predictive biomarkers [15]. Although telomere function is a central aspect in cancer and aging, miRNAs that impact on the regulation of telomere function in human cancer have been identified only very recently. Spurred by a possible direct therapeutic application, a panel of miRNAs was identified that target the catalytic subunit of telomerase, hTERT [16-20]. In particular, miR-138, miR-498, miR-1207-5p and miR-1266 were able to reduce cancer cell proliferation, phenocopying the effect of classic RNAi mediated knock-down of TERT [17-20]. However, among all reported miRNAs targeting hTERT only miR-1266 was found to have clinical relevance, as demonstrated by the negative impact of low miR-1266 levels on the overall survival of gastric cancer patients [17].

In our recent study we aimed to identify clinically relevant miRNAs that control the expression of shelterin components [21]. We found that miR-155 efficiently represses the translation of TRF1 in cell lines derived from different cancer types. miR-155 is a potent onco-miRNA that is involved in leukemia, breast, colon and lung cancer [22-26]. miR-155 is efficiently up-regulated in luminal, $HER2^+$ and triple negative breast cancer subtypes. Importantly, miR-155 upregulation correlates with low TRF1 protein expression levels in luminal breast cancer specimen, supporting a role for miR-155 in regulating TRF1 expression. Low TRF1 expression levels lead to a significantly reduced distant metastasis-free survival and relapse-free survival of estrogen receptor positive luminal breast cancer patients. Importantly, this effect is recapitulated by a panel of validated miR-155 target genes, indicating that miR-155 dependent regulation of TRF1 represents a clinically relevant aspect of the oncogenic potential of miR-155. Studies using genetic mouse model systems demonstrated that loss of TRF1 affects telomere protection, telomere replication, and promotes tumor-formation in the absence of p53 [6, 7]. This highlights the role of TRF1 as tumor suppressor and regulator of genomic stability. Using breast cancer model cell lines we found that miR-155 controls telomere function and homeostasis by limiting the expression of TRF1. In particular, miR-155 increases the frequency of chromosome fragility at telomeric repeats, promotes telomeric sister chromatid fusions and drives telomere dysfunction as indicated by a recruitment of DNA damage factors at chromosome ends. Consistent with the role of TRF1 as negative regulator of telomere length, reducing TRF1 expression by ectopic introduction of miR-155 mediates telomere elongation [27-30]. Together, this demonstrates that miR-155 can promote genomic instability by impairing telomere function in human breast cancer. These data show for the first time that miRNAs can modulate shelterin function in human cancer and suggest the existence of additional "telo-miRNAs" that can link key-events in oncogenesis with telomere function and homeostasis. Telomere dysfunction has been identified as metastasis promoting event in prostate cancer but was also demonstrated to impair the functionality of stem cells by driving senescence, a hallmark of organismal aging [31,32]. In addition, accumulation of short telomeres has a negative impact on longevity [33]. The central role of shelterin in chromosome end protection and telomere length regulation suggest that alterations in telo-miRNA expression might not only have long-term effects on telomere homeostasis in cancer cells but also in differentiated cells or adult stem cells. Consequently, it is tempting to speculate that "telo-miRNAs" can modulate telomere homeostasis during ontogenesis and impact on organismal aging and telomere related pathologies.

The discovery that "telo-miRNAs" can control telomere function and homeostasis has introduced a new level of telomere regulation. Future work will aim to identify additional functionally relevant telo-miRNAs, discover pathways that regulate telo-miRNA expression and link telo-miRNAs to key biological processes related to cancer formation or aging.

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