Telomerase, the Excalibur against Senescence

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Abstract

In humans aging cells have shortened DNA ends, or telomeres, leading scientists to think it the reason for the replicative crisis. Telomere shortening seems to correlate with the rate of senescing cells formation, however, certain cell lines such as stem cells and hematopoietic cells can elongate their telomers indefinitely. Telomere shortening that limits the number of cell division in somatic cells is unique to humans which questions the plausibility and usefulness of the hypothesis that telomeres determine the lifespan. In this review article we explore the recent breakthroughs in the field of molecular biology focused on telomeres structure and function, and how manipulating the related telomerase holoenzyme has potential to devise effective and efficient therapeutics for close to all kinds of cancer. It is thought that this is a tumor suppression mechanism considering that 85-90% of all cancers have reactivated telomerase, the enzyme that elongates telomeres. Telomerase is a big holoenzyme with many ribonucleoproteins that are involved in synthesis and recruitment of telomerase and are potential druggable targets. The rest 10-15% of cancers have alternative telomerase-independent telomeres elongation that involves completely different proteins and mechanisms. To date, only a few FDA approved therapeutics that target telomeres elongating are approved for cancer treatment. Almost all of them exclusively disrupt the function of the catalytic unit of telomerase. Despite not providing a cure for senescence, understanding the elongation and maintenance of telomeres allows us to prolong the time spent being not just alive but healthy.

Commonly used acronyms

TR or TER - *T*elomerase *R*NA

TERT - *te*lomerase *r*everse *t*ranscriptase

TEN - *t*elomerase *e*ssential *N*-terminal domain

TRBD or RBD - *t*elomerase *R*NA *b*inding *d*omain

RT - *r*everse *t*ranscriptase domain

CTE - *C*-*t*erminal *e*xtension or *C*-*t*erminal *e*lement

PK - *p*seudo*k*not

DDR - *D*NA *d*amage *r*esponse

TIF - *t*elomere dysfunction-*i*nduced *f*oci

TAF - telomere-associated DDR foci

Rb - retinoblastoma

DSB – *d*ouble *s*tand *b*reak

TEBP - *t*elomere *e*nd-*b*inding *p*rotein

POT1 - *p*rotection *o*f *t*elomeres

TRF1 - *t*elomeric *r*epeat binding *f*actor 1

TIN2 - TRF interacting factor

TPP1 - To keep things interesting the term "TPP1" is the result of combining the first letter of each name that it was given by the three groups that initially characterized the human protein: *T*INT (*T*IN2 *int*eracting protein *1*); *P*TOP (*P*OT1- and *T*IN2- *o*rganizing *p*rotein); *P*IP1 (*P*OT1- *i*nteracting *p*rotein *1*)

RAP1 - *r*epressor-*a*ctivator *p*rotein

TERRA - *te*lomeric *r*epeat–containing *RNA*

ALT - *a*lternative *l*engthening of *t*elomeres

HDR - *h*omology *d*irected *r*epair

CBs - *C*ajal *b*odies after Santiago Ramón y Cajal, the father of neuroscience; also called coiled bodies

TCAB1 - *t*elomerase *Ca*jal *b*ody protein 1

PML-NBs - promyelocytic leukemia nuclear bodies[1]

PODs - PML oncogenic dots

ATR - ataxia telangiectasia and Rad3-related protein

RPA - *r*eplication *p*rotein *A*

TERC - *te*lomerase *R*NA *c*omponent

DKCI - *d*yskerin pseudouridine synthase 1

NOP10 (nucleolar protein 10, also known as H/ACA ribonucleoprotein complex subunit 3

NHP2 (H/ACA ribonucleoprotein complex subunit 2)

AR1 (H/ACA ribonucleoprotein complex subunit 1

CST - *C*TC1–*S*TN1–*T*EN1 complex

CTC1 - *c*onserved *t*elomere maintenance *c*omponent 1

STN - *s*uppressor of CDC (cell division cycle) *t*hirtee*n*[6]

Introduction

Most eukaryotic lifeforms have many noncoding regions with often unknown functions. Many noncoding DNA regions with no apparent function were thought of, at the first glance, as junk DNA[2]. However, modern molecular techniques allowed us to investigate them more closely and have shown that these regions are far from useless. Rather, they can be modified for chromatin remodeling, be site of recognition for transcription factors, form functionally active DNA structures like hair pins that interact with CRISPR-associated proteins, activate DNA damage response (DDR), or encode noncoding RNA such as miRNA, siRNA, lncRNA, tRNA, rRNA. This arises from the fact that 75% of the human genome is actively transcribed into RNAs, less than 5% of these RNAs are used for coding proteins. Investigating how they work helps us learn how to interact with our genome on the molecular level and enhances our understanding of gene expression. Ability to down- or upregulate genes, silence or completely excise whole regions of DNA, or even introduce a new sequence are some questions genetic engineering is tasked to solve. When applied in medicinal context it is known as gene therapy and is the most promising candidate to cure genetic diseases or even aging. The most important of such noncoding regions are the very ends of our linear chromosomal DNA, known as telomeres, which shall become the subject of our discussion.

The regulation of telomeres is not fully understood although it has been linked to cancer development. Conversely, the therapeutic potential of telomeres is understudied. In this review we will

delve into the key functional parts of telomeres maintenance system and what implications they have as well as take a closer look at the involvement of telomeres in cancer and aging. To achieve these goals, we will first look at the structure of telomeres and the associated proteins relating it to their function. Understanding the structure and function relationship not only elucidates the role of telomeres in the biochemical context but also facilitates development of effective therapeutics.

Structure of the Telomeres

Molecular Structure

Telomeres are long DNA sequences composed of multiple "TTAGGG" repeats followed by a 3' overhang of 50–200 nucleotides of G-rich single-stranded DNA[3] (Fig. 2a). Telomeres form a number of unique structures. Because of high percentage of GC pairs it is prone to form quadruplexes. The long G-rich 3' overhang participates in dsDNA–ssDNA transition (junction)[3] that forms a t-loop (Fig. 2b) that protects DNA from activating DDR by sensing a double strand break (DSB), and G-rich telomeric long non-coding RNA known as TERRA that interact with dsDNA to for an RNA-DNA hybrid known as an R-loop.

Telomeres shorten after each cell division via a complex interplay between many proteins as will become apparent below but the reason for that are of the two features of DNA polymerase. First, it relies on RNA primers to begin base pair annealing as it cannot bind two individual nucleotides; second, DNA polymerase functions only in the 5'-to-3' direction, therefore, it cannot extend blunt ends because it needs a template strand to acquire complementarity from, if the DNA had a 5' overhang it would not be able to build a complementary stand because it works only in in the 5'-to-3' direction, and even with the (actually existing) 3' overhang after building a complementary stand the process results in blunt ends. This dilemma is solved by telomerase reverse transcriptase (TERT), the catalytic unit of telomerase machinery working in conjunction with a short RNA molecule called telomeric RNA (TR) that functions as a primer. The sequence of TR, CCCAAUCCC, is complementary to the telomeric repeats, TTAGGG, and can bind to the

GGG end. TERT then extends the 3’ end of DNA by annealing complementary nucleotides in a mode analogous to DNA polymerase action. After that, telomerase is translocated and bound to the nascent 3’ overhang to perform the cycle anew trotting its way forward with a 6-nucleotide-long stride. DNA polymerase can then extend the complimentary 5’ end.

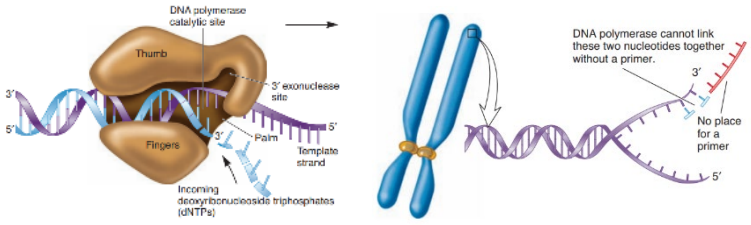


Figure 1. DNA polymerase features that necessitate telomerase. (Taken from *Concepts of genetics, Robert J. Brooker. 1st ed.*)

Telomeric repeats vary from species to species but generally are rich in guanine-cytosine pairs. For example, the ciliate Tetrahymena has $(TTAGGGG)_n$ repeats, Beetles and sea spiders have $(TTAGG)_n$ *Lophotrochoa* (nematodes and arthropods) have so called nematode motif $(TTAGGC)_n$, *Diptera* has unique terminal satellite repeats whose elongation is done through gene conversion. The fruit fly has gone awry and employs telomerase independent terminal insertion of two classes of telomere-specific LINE-like retrotransposable elements.[4] All mammalian telomeres consist of 5’-TTAGGG-3’. Such an evident conservation shows the importance of telomeres and their early evolutionary origin. Despite a few exceptions almost all eukaryotic species have telomeric ends to protect their DNA during cell division.

Synthesis and Maintenance

Although telomeres can be extended essentially endlessly in the presence of telomerase, they need to be replicated during cells division like any other DNA region. Telomeres form unique structures listed above making their replication a difficult task. A regulator of telomere elongation helicase 1 (RTEL1) must remove R-loops and quadruplexes to avoid replicative stress and fork stalling. After the replication the protective t-loop must be reformed. The 5’ end is being resected by the exonuclease Apollo until there is a

long enough 3' overhang to loop onto itself with assistance of TRF1 and TRF2. That causes the daughter cell to have the chromosomes shortened by the length of the 3' overhang which is the true reason for telomeres shortening. TRF1 and TRF2 are part of another key protein complex engaged in telomeres maintenance known as shelterin.

The shelterin complex involves 6 proteins (fig. 2). Of them, TRF1 and TRF2 directly bind double-stranded telomeric DNA4, POT1 is the most highly conserved element; it directly binds the single-strand extension at the chromosome end. TRF1 and TRF2 are bridged through protein–protein interactions with TIN2 that also binds to the third protein, TPP1, that bridges the whole complex to POT1. TPP1 increases the complex affinity to the 3' end as opposed to internal sequences of telomeric DNA and regulates the recruitment of telomerase to the telomere among other functions; molecularly speaking, it acts as a 'sliding clamp', encircling the DNA and preventing dissociation.[5] The sixth protein, RAP1, binds mostly to TRF2 and is thought to be the main processivity (that is, the number base pair attached per unit of time) factor. The main function of the shelterin complex is t-loop formation whereby the 3' overhang locks onto itself protecting the telomeres from double stand break (DSB) that would trigger DDR. Conversely, TPP1 and RAP1 are involved in telomerase catalytic activity by ensuring faithful replication and pose a druggable target not yet explored. Ability to downregulate telomerase activity can suppress cancer growth since around 85% of all cancers show upregulated telomerase expression. Considering the complex interplay among the telomere associated protein it comes as no surprise that their regulation is a convoluted multilayered mechanism. Our current understanding of telomerase regulation in vivo is incomplete.[6]

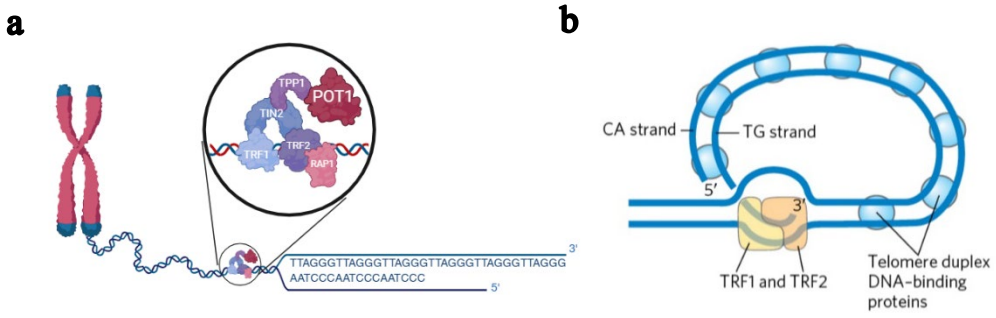


Figure 2. a) Shelterin complex b) a t-loop formation.

Most of the somatic cells show incompetent telomerase activity congruent with the fact that in majority of differentiated tissues the cells stop dividing and become quiescent. The few cells that do show adequate telomerase activity are the stem cells as well T- and B-lymphocytes. In addition, there is a clear correlation between the length of telomeres and the age of a human cell. As will become clear below, very few cell types are allowed to express telomerase because of the inherent threat the immortality or infinite cell division possesses to a multicellular organism, also known as cancer.

Relation of Telomeres to Senescence and its Expression in Different Species

Aging can be thought of as an inadequate response to the molecular and cellular damage that ultimately leads to organismal dysfunction because of either uncontrolled cell proliferation, that is, cancer, or impaired tissue regeneration and accumulation of damaged cells. Although the idea that telomere shortening causes the impaired tissue regeneration seems plausible, it is not usually the case. Even in elderly individuals, in theory, tissue regeneration should not be impaired as long as there is a sustainable stem cell population. In support of this argument, it is worthwhile to look at animals whose somatic cells are not as strictly regulated.

Despite being short lived somatic cells of adult mice show an adequate telomerase expression. Their lifespan seemingly does not depend on telomeric length at all. In humans, on the other hand, most somatic cells seem to have a mitotic clock that limits them to around 50 cell divisions before turning into a senescence cell, so-called Hayflick limit. That number varies slightly, staying between 40 and 60 for most human cells. That has repercussions in carcinogenesis whereby mice showing remarkably similar histopathological course of tumor development and having a similar mutation frequency tend to have rapidly developing malignant tumors where in humans the same process takes years.[7] Interestingly, such large animals like whales rarely, if ever, develop life threatening tumors. Larger animals are not shown to have progressively higher occurrences of cancer – so called Peto's paradox.[8] With a higher number of cells, the likelihood of a malignant mutation increases. One would expect the likelihood of cancer to be off the

charts in whales as their bodies contain hundreds of quadrillions of cells. Despite that, whales do not seem to suffer from cancer at all. Such animals must possess even more sophisticated anticancer mechanisms. Namely, in the case of the long-lived bowhead whale enhanced DNA repair was found to be the most likely anticancer mechanism. Unlike humans, bowhead whale does not have more tumor suppressor genes, instead, it relies on enhanced DNA double-strand break repair capacity and fidelity.[9] Interestingly, bowhead whale fibroblasts required fewer oncogenic hits compared to human fibroblasts showing that while whale cells show lower tumor occurrence overall human cells have more robust tumor suppression mechanisms that can quench an existing mutation. One of such mechanisms that limits cancerous cells proliferation is telomeric shortening.

Role of Telomeres in Cancer Suppression

During meiosis DNA can undergo double-strand breaks resulting in DNA fragments must be fused back together; telomeres help distinguish between such ruptured fragments and the native DNA ends.[10] Because most somatic cells do not express telomerase telomeres shorten with each cell division until they eventually reach the length where they cannot perform their protective function anymore resulting in telomere dysfunction-induced foci (TIF). When that critical length is reached the anticancer function of telomeres becomes apparent.

When telomeres are too short to form a t-loop, however, shelterin proteins are unable to bind and expose the ends to the nucleoplasm. In a well-known pRb pathway whereby retinoblastoma (Rb) protein is a transcription factor that activates synthesis of enzymes necessary for deoxynucleotides products and DNA synthesis during cell division. When MNR complex recognizes TIFs though it activates ATM and ATR kinases that phosphorylate the p53 which acts as a transcription factor to synthesize another protein, p12. The inhibitory effect of p12 renders pRb inactive as a transcription factor causing the cell to enter the growth arrest. The downstream effect of this pathway is retinoblastoma-protein-dependent cellular senescence also known as replicative senescence.

Bypassing either p53 or pRb pathways results in the cells entering a so-called *crisis*, whereby short dysfunctional telomeres cause end-to-end chromosome fusions and rupture of dicentric chromosomes meant to prevent immortalization of cancer cells and their unending growth. During crisis tumorigenic mutations may arise leading to unhindered cell proliferation by means of telomere-maintenance mechanism.[3] These pathways show that telomere shortening has evolved as a major tumor suppression mechanism.[11] If telomerase is reactivated, however, the cell becomes immortal. Reactivation of TERT expression in most cancer types demonstrates that senescence is a tumor suppression mechanism in and of itself. For this reason, somatic cells have such a stringent control of TERT gene, usually completely silenced by histone acetylation.[12] As additional evidence shows, if during tumorigenesis reactivation of telomerase fails the tumor eventually dies of nonspecific necrosis caused by chromosome fusion.

The current consensus is that though telomeres might be involved in some age-related diseases their shortening serves rather as a side effect of the overall wear and tear on the body. Instead of determining the lifespan of a person, they function primarily as a tumor suppression mechanism in humans as well as capping ends during cell division preventing chromosome fusion in most eukaryotic species. That preserves DNA integrity and avoids otherwise imminent crisis.

Despite the unlikelihood of telomeric elongation being a cure for aging, it still has a number of potential uses. Most prominently, reactivation of telomerase can show itself indispensable in autotransplantation[13] whereby the damaged somatic cells are replenished with the donor's cells cultured in vivo by reactivation their telomerase activity. Furthermore, because most cancers rely on heightened telomerase expression levels its inhibition is a potential target for anticancer therapy. To devise a means of suppressing telomerase activity, it is necessary to understand its mechanism and molecular structure.

Telomerase Structure and Function

Telomerase is a ribonucleoprotein complex composed of two essential core components, TR and TERT. The purpose of this section is to elucidate the structure of the latter. Many proteins that bind DNA

crystallize poorly due to their innate flexibility tailored to their function. Hence, the most complete solved structure of TERT was determined by *cryo*genic *e*lectron *m*icroscopy (Cryo-EM) technique.

The two most important parts of telomerase preserved across all eukaryotic species are the TERT protein that catalyzes addition of individual nucleotides and the TR that serves as a template. Several telomerase-associated accessorial proteins with less certainly defined functions are also conserved. Attempts to replicate the telomerase function in vitro with only TERT and TR have failed indicating that its function heavily depends on the structural units. With the development of CryoEM it became possible to investigate the structure of the enzyme more closely as the traditional gold-standard – X-ray crystallography is ill suited for because of their innate flexibility and disorder between subunits. It is now considered that TERT has four main domains: RNA-binding domain (RBD), fingers, palm, and thumb. Reverse transcriptase (RT) is palm with fingers, where the "fingers" are the subdomain of RT that forms a β hairpin structure responsible for nucleotide binding and processivity.[14] Because RT is a domain of a single polypeptide chain it is also covalently attached RBD and the next domain to the other side from it. C-terminal element (CTE) is the thumb that finishes the circular structure of the catalytic core by noncovalently interacting with the RBD domain and anchoring TR. Telomeric RNA is enclosed by TERT and TEN. (Fig. 3) Besides TERT and TR telomerase complex includes the N-terminal domain (TEN)[15] that is connected to the pinched by RBD and CTE anchoring RNA via a flexible linker. It does not directly contribute to telomerase activity, instead, it acts as a clamp fixing TR between itself and CTE; which is possible because TR unzips and wraps around the TERT.

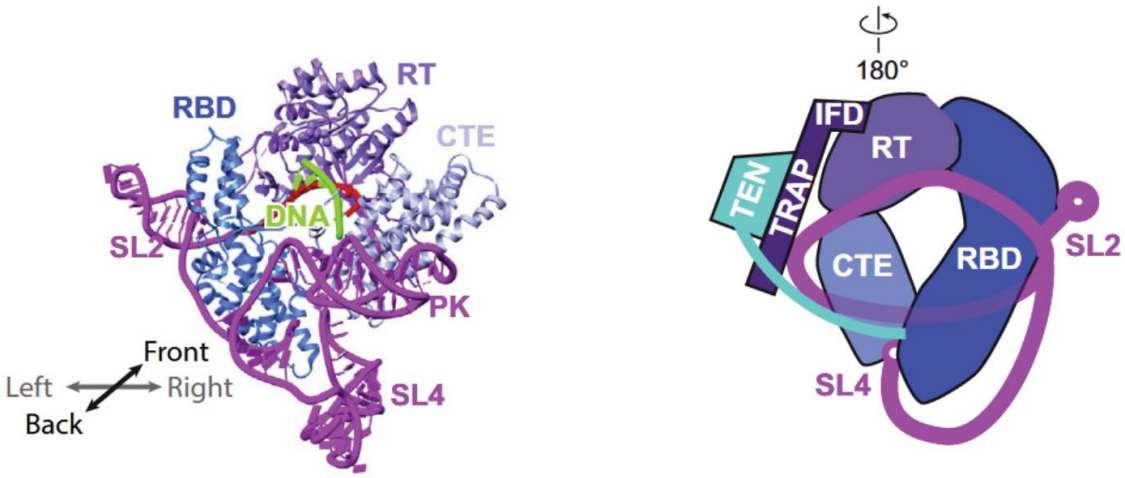


Figure 3 Ring-shaped structure formed by RT (palm, fingers, thumb) and TRBD domains. (Steczkiewicz et al., 2011, p. 9444, PDB code is 3KYL.)

Telomerase is a complex ribonucleoprotein consisting of many more elements than TERT and TR. The synthesis and activation of telomerase involve splicing of precursor rRNA within a so called Cajal body (CB) aided by snoRNAs. CD is also the site of localization of telomerase in humans. A mature telomerase includes the familiar TERT as well as telomerase Cajal body protein 1 (TCAB1) and two sets of the four H/ACA RNPs skewered on the TR.

The H/ACA box includes DKC1, NOP10, NHP2, and GAR1 although it has been shown to associate with the telomerase holoenzyme to a lesser extent. DKC1 is also known as dyskerin, named after the conditioned caused by the lack thereof, dyskeratosis congenita (DC).[16] Despite the name, mutation in any of the genes encoding the holoenzyme counterparts can lead to DC. The disease is characterized by short telomeres in the stem cells which cause exactly what one would expect in the case of uncontrolled telomeres attrition, that is, inability to meet the proliferative demand in growing or regenerating tissues such as epithelium or oral mucosa. In accordance with that, some of the various symptoms include nail dystrophy, hair graying, and oral lesions. It is worth mentioning that the H/ACA box is also involved in posttranscriptional modification of pre-ribosomal ribonucleic acid by the means of pseudouridylation.[17]

Nevertheless, there is evidence of normal functioning of pseudouridylation in DC mutation showing that the cause of DC is primarily impaired function of the telomerase.[18]

Although the lack of telomerase expression can lead to such devastating consequences, it is not much of a problem for cancerous tissues. In fact, some cancer can extend their telomeres via a completely different mechanism known as alternative lengthening.

Alternative Lengthening of Telomeres

In some cases a cell can maintain its telomere lengthening without the participation of telomerase[19], instead, the cell can rely on a recombination-dependent pathway known as alternative lengthening of telomeres (ALT).[20] The origin of ALT active cells is unclear. However, it is thought that promyelocytic leukemia (PML) nuclear bodies must be involved as they are highly characteristic of the cancer types that employ ALT.[20] With some alterations in the proteins involved ALT is a DNA repair process whereby one telomeric 3' end invades the other telomere forming a Holliday junction (HJ). DNA repair proteins readily recognize telomeric HJ and try to resolve it. Because of the repetitive nature of telomeres DNA polymerase can keep extending the 3' overhang until it reaches the end of the telomere in the process of homologous recombination.

DNA recombination is inefficient in the presence of multiple branched DNA structures that stall the replication fork. To circumvent this problem most ALT-positive cancers rely on the protein FANCM that recognizes the branch DNA regions and remodels the molecule by translocating along DNA.[21] FANCM has been explored as a therapeutic target for ALT-positive cancers. Telomerase can be a suitable target too in the more common types of cancer. Though because telomerase is a huge holoenzyme a wide spectrum of therapeutical targets presents itself.

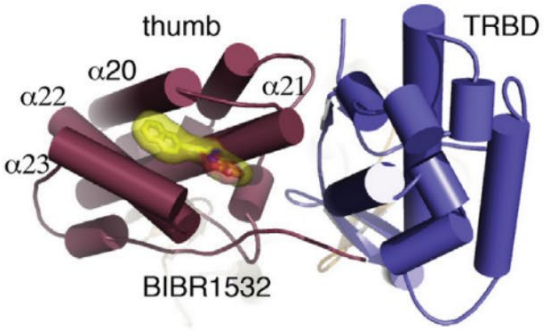
Therapeutic Potential

A potent telomerase inhibitor has been a desirable target due to its potential to mitigate or even eliminate the proliferation of close to all types of cancer, the Excalibur not against aging but Death.

First attempts at designing a therapeutic targeted at suppression of telomerase action involved the use of short oligonucleotides that would bind to the template region of the human TR. One such drug has reached the market under the brand name RYTELO (imetelstat) and is sold as a treatment for myelofibrosis, a disease where activated telomerase is thought to maintain the elevated mitotic activity of myelodysplastic cells.[22]

Another similar approach involves the use of nucleoside analogues. The first cancer treatment of such kind was borrowed from an HIV treatment whereby the antiretroviral drug azidothymidine (sold under the brand name Zidovudine) is used to inhibit HIV's reverse transcriptase. Since telomerase too converts RNA to DNA it poses a perfect druggable target by azidothymidine.

The most successful class of drugs targeted at telomerase are small molecule inhibitors. One such drug was designed after the recent discovery of a novel motif that turned out to be a druggable target. Disrupting with a foreign ligand destabilizes TERT binding to DNA. A hydrophobic pocket named after its four conserved residues F478, V491, Y551, and L554 is snuggly housed between the thumb and RBD domains. FVYL motif can bind BIBR1532 (2-[(E)-3-naphtalen-2-yl-but-2-enoylamino]-benzoic acid) which effectively reduces telomerase activity and showing an antiproliferative effect on leukemia cells but not on normal hematopoietic stem cells.[23]



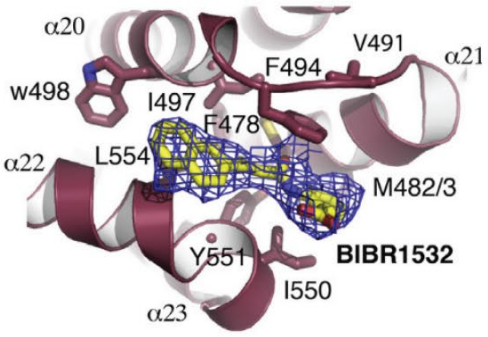


Figure 4. a) BIBR1532 housed between thumb and RBD domains. b) electron map showing that BIBR1532 mainly interacts with the nonpolar residues .

Conclusion

A comprehensive comparison of human telomeres with eukaryotic species that differ in their lifespans is suggestive of the indirect causality between telomeric shortening and senescence. Conversely, lack of telomerase expression in humans is an effective tumor suppression mechanism that can be exploited. Within telomerase inhibition the complexity of the interactions between the telomerase holoenzyme and cell growth factors provides numerous druggable targets with low risk of an off-target influence. Furthermore, reactivation of telomerase expression has potential for facile immortalization of a cell line which can find applications in in-vitro studies as well as cell therapy. Taming DNA degradation may not be the single solution for biological aging, nevertheless, the of telomerase regulation can aid in lowering mortality and extending healthspan, the ultimate goal of scientific research.

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