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Telomerase and Cancer: A Nuclear Enzyme Involving Cell

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Abstract

Enzymes have been used traditionally in the production and treatment of various food products. Recently, enzymes are recombinantly expressed in an appropriate host and are frequently designed to a targeted application by protein engineering methods. Human chromosomes are topped by telomeres that recruit the telomere-binding proteins and short telomeres result in genome instability and cell death. Human telomerase is a rare endogenous enzyme. Four domains namely C-Terminal Extension (CTE), Reverse Transcriptase domain (RT), high-affinity RNA-binding domain (TRBD), and N-Terminal (TEN) domain collectively compose Telomerase Reverse Transcriptase (TERT). Telomerase is a vital factor for normal tissues renewal and long-term proliferation of cancer and stem cell lines. The role of telomerase in apoptosis regulation is also evident in a telomere maintenance-independent manner. In conclusion, the telomerase play key role in aging phenotypes in addition to carcinogenesis by regulating telomere length.

Keywords: Telomerase; Nuclear enzymes; Immortalization

Introduction

Enzymes are the biocatalysts that accelerate the biological reaction at a faster rate. Besides the living system, they have been used since prehistoric times for manufacturing food and beverage. Traditionally the treatment of food and beverages' products was carried out with microorganisms without knowing that those microbes use their enzymes which are involved in the preservation or improvement of food or the manufacturing of desired compounds and aromas. In approximately 3,500 BC, beer was produced in Mesopotamia and Asia, and bacterial amylases and proteases were the significant enzymes for the production of soybean derived foods. Present-day biocatalysis uses isolated enzymes, which are recombinant expressed in an appropriate microbial host; frequently they are designed to a targeted application by protein engineering methods. A new emergent wave around the 1980s acquired advantage of recombinant gene technology that facilitated the cloning and expression of the enzyme of interest in a suitable microbial host. Researchers could then also improve the enzyme chemistry and its properties subjected to site-directed mutagenesis. A step ahead, in the 1990s, the new and advanced protein engineering methods were established such as DNA altering and error-prone Polymerase Chain Reaction (PCR) along with high-throughput sequencing and screening methods which could be called a directed evolution [1]. Bornscheuer et al emphasize what has been achieved: "In the past, an enzyme-based process was designed around the limitations of the enzyme; today, the enzyme is engineered to fit the process specification" [2].

Linear eukaryotic chromosomes including human are topped by telomeres that recruit the telomere-binding proteins. These telomere-binding proteins are critical to differentiate telomeres from DNA breaks and therefore to avoid telomere end-resection and interchromosomal fusions [3,4]. Owing to inherently incomplete genome replication, telomeres are progressively shortened in each cell cycle [5]. Critically short telomeres result in genome instability and cell death [6,7]. To compensate for this sequence loss, a specialized reverse transcriptase, telomerase, adds telomeric repeats to the chromosome 3' end, using TERT and an integral Telomerase RNA subunit (TER) with an internal template for repeat synthesis [8]. Human telomerase activation in embryogenesis and its repression in somatic tissues govern cellular renewal capacity, with telomerase deficiency imposing hematopoietic and epithelial failures and aberrant telomerase activation enabling tumorigenesis [9].

Literature Review

Electron microscopic structure and chemistry

In human telomerase is rarely endogenous. Most of the studies evident that human telomerase is limited to TERT8 and TER (human hTR) overexpression. An hTR domain template with its adjacent pseudoknot (t/PK) is considered crucial for activity along with second 4/5(CR4/5) conserved region domain

organized by P5 and P6 branched junction and stem loop P6.1. All these hTR domains, TERT, and cellular holoenzyme with its repeat addition characteristics sufficiently reconstruct telomerase activity [10]. Four domains namely C-Terminal Extension (CTE), Reverse Transcriptase domain (RT), high-affinity RNA-Binding Domain (TRBD), and N-Terminal (TEN) domain collectively compose TERT. The first three domains form ring and formally known as TERT ring but high-resolution structure analysis of TERT from certain insects like flour beetle Tribolium castaneum revealed the absence of the TEN domain [11]. In such organisms, the TERT ring binds to primer-template duplex but the TERT ring in human supports the synthesis of single repeat [12]. Heterogeneous complexes are resulted in combined overexpression of purification of both TERT and hTR but only a few of them were found to be catalytically active [13]. The exact mechanism of catalytically active enzyme prerequisite remain unclear that either a TERT/hTR dimer or each subunit with only its monomer is required [14-16]. The overall structural layout of telomerase holoenzyme in ciliate Tetrahymena thermophile revealed monomeric TERT-TER catalytic core through landmark 9 A cryo-Electron Microscopy (cryo-EM) [17]. This is the considerable dissimilarity among Tetrahymena and human telomerase holoenzyme in subunit composition but the information about this enzyme in the case of humans is limited to 30 A negative-stain electron microscopy reconstruction.

A recent study characterized the structure and the composition of the human telomerase holoenzyme sub-nanometer resolution showing two flexibly RNA-tethered lobes: The catalytic core with Telomerase Reverse Transcriptase (TERT) and conserved motifs of telomerase RNA (hTR), and an H/ACA Ribonucleoprotein (RNP). In the catalytic core, RNA encircles TERT, adopting a well-ordered tertiary structure with surprisingly limited protein-RNA interactions. The H/ACA RNP lobe comprises two sets of heterotetrameric H/ACA proteins and one Cajal body protein, TCAB1, representing a pioneering structure of a large eukaryotic family of ribosome and spliceosome biogenesis factors. They also obtained negative-stain Electron Microscopy (cryo-EM) reconstructions at 7.7 A and 8.2 A resolution for the catalytic core and H/ACA lobes, respectively, and of the entire holoenzyme at 10.2 A resolution.

Other subunits of telomerase

Additional telomerase subunits also include Dyskerin (DKC) and Nop10 with 58 kDa and 7.7 kDa molecular weights respectively. But both of these subunits are collectively vital for telomerase holoenzyme and are not found to be essential for *in vitro* activity of telomerase [18,19]. However, DKC subunit is essential for the stabilization of TERC for *in vivo* telomerase activity [20]. DKC was also found useful for the proper functioning of ribosomes as well as the biogenesis of p53 [21]. Additional subunits including Pontin and Reptin have their importance for DNA repair and chromatin remodeling [22]. All these subunits function in collaboration with TERC to regulate of activity of telomerase for telomerase assembly and stability *in vivo* [23].

Vital telomerase functions in the cell

In mammals, the telomerase acts as specific reverse transcriptase and maintains telomeric length [24]. In human catalytic subunit, hTERT and an RNA component (hRT) a compose ribonucleoprotein telomerase holoenzyme. This complex acts as a template and directs accessory species specific proteins and at the end of the telomeric DNA add a short repetitive sequence dTTAGGG [25]. Telomerase biogenesis and subcellular localization in addition to *in vivo* functioning are few major roles performed by these accessory proteins. hRT and dyskerin stability is imparted by reptin and pontin ATPases *in vivo*. In recent models, this reptin and pontin jointly form the scaffold which assembles ribonucleoprotein particle of telomerase and stabilize hTR. After formation of this complex the scaffold formed by pontin and reptin is believed to be disassembled hence losing the catalytic ability of the active enzyme by releasing these enzymes which were catalytically active [26]. TCABI which is recently been discovered which regulates the location of telomerase at the subcellular level [27]. In a study evidences were also shown to prove that holoenzyme of human telomerase contains only dyskerin, hTR and TERT, still others do not shows consistent results to this fact.

Dyskerin protein along with its close association to telomerase is a nucleolar protein with highly conserved biochemistry and is considered as specific nucleolar RNP. In spliceosomal snRNA and newly synthesized ribosomal RNAs is acts as a catalyst for pseudouridylation of specific residues. Reptin and pontin have multiple roles along with already mentioned functionality on chromatin remodeling and transcriptional regulation, telomerase activity and DNA repair. Certain oncogenic factors including c-myc and β-catenin were found to regulate their oncogenic functions through interactions of these proteins. Within the telomerase holoenzyme still there is huge gap to understand the significance of the intricate network of protein-nucleic acid and protein-protein interactions at molecular and biochemical level. Furthermore, the pattern of holoenzyme modification in its composition during different stages of cell cycle is important mechanism to investigate and explain [28].

Telomerase is vital factor for normal tissues renewal and long term proliferation of cancer and stem cell lines. However, additional functions are described far beyond telomeric level. TERT also acts as transcriptional regulator in number of pathways such as Wnt-β-catenin signaling pathway [29]. Through interactions with BRG1 (SWI/SNF related chromatin remodeling protein) it functions in a β-catenin transcriptional complex as a cofactor. Additional TERT functions as RNA-dependent RNA polymerase in a complex with RMRP [30]. This TERT-RMRP complex functions as RNA-dependent RNA polymerase or RDRP and process single stranded RMRP into dsRNA which is followed by endoribonuclease Dicer processing into siRNA or small interfering RNA which interfere RMRP endogenous level. In short the whole TERT-RMRP-RDRP acts through negative feedback mechanism to control RMRP level. In some studies role of telomerase in apoptosis regulation is also evident in a telomere maintenance-independent manner [31].

Telomerase activity in cancer and aging

During cellular differentiation due to TERT transcriptional silencing benign tissues and human somatic cells shows limited life spam as their telomerase activity is very low even undetectable [32]. However in case of stem cells as well as adult germ tissues about 80%-90% or above telomerase activity is observed [33,34]. This finding supports the argument that cancer stem line give rise to cancerous cells additional evidences are also present that cancerous cells are originated from somatic cells acquiring stem cell properties or during de-differentiation of progenitor cells [35,36].

Various transcription factors including E-Twenty Six (ETS) family members β-Catenin, C-MYC, p53, E2F, HIF1, NF-kB, AP1, SP1, p21 get attached to various binding sites on TERT promotor [37-42]. Addition to these transcription factors, TERT expression is also regulated by certain hormone receptor-mediated signaling pathways such as Estrogen Receptor (ER)-signaling [43]. In cancers, some of these transcription regulatory factors govern TERT expression, distinct cancers is evident with TERT promoter recurrent mutations ensuing new transcription regulators binding. First in familial and sporadic melanoma the recurrent germline and somatic mutations in promoter region of TERT were identified respectively. Both of these mutations have been resulted in de novo organization of ETS family of transcription factors binding motifs. Somatic TERT promoter mutations are more common as compared to germline mutations in most common cancer types including urothelial cancers, hepatocellular carcinomas, thyroid cancers, including glioblastoma, bladder cancers and human melanoma [44].

During carcinogenesis the neoplastic cells enables them self to multiply ad libitum due to reactivation of telomerase hence acquires necessary genetic variations required for malignant development. Moreover in case of normal stem cells which possess sufficient telomerase activity shows gradual decrease or complete loss of telomerase expression resulting aging and stem cell differentiation [45]. In such stem and somatic cells telomere shortening is one of the major indication for aging and determinant factor for cellular longevity [46]. *In vivo* this telomerase activity is restored by telomerase expression which demonstrated sufficient results in phenotypic regulation of age related signs [47]. In conclusion, the telomerase play key role in aging phenotypes in addition to carcinogenesis by regulating telomere length.

Tissue regeneration and development

During embryonic development of rodents readily detectable activity of telomerase can be seen in their hearts but postnatally being inactivated rapidly [48]. One of key factors limiting activity of telomerase is TERT transcription [49]. Reduced telomerase activity with decreased expression of TERT rightly reflects reduced number of cardiac cells with positive TERT. Limited knowledge is available for mechanism of down regulation of TERT expression in cardiac cells after birth and offers potential area for research. In a recent study to find out the telomerase role in telomerase dysfunction in heart regulation scientists developed a cryoinjury protocol in which neonatal hearts was damaged after one day age.

After neonatal mice cardiac injury results of this study indicated the necessity of ample telomere reserves for proliferation of cardiomyocyte and efficient heart regeneration. Mechanism of forced expression was applied both in new borne and adult individuals and consistent results were found with scar size, reduces apoptosis, cardiac dilation, improved post-MI heart function and survival [50]. The post-acute MI telomerase therapy is found to be cardio-protective in adult mice [51]. Such findings predict about artificial telomerase expression ant its potential towards post cardiac injury to ameliorate heart failure. However, neonatal heart regeneration the consequence of enforced telomerase expression leftovers unknown.

Role in diagnosis of fatal diseases

Patients with pneumonia, tuberculosis, neoplasms and cardiac failure shows frequent complications such as pleural effusion [52]. Malignant tumors are one of the major causes of pleural effusion and metastatic diseases causes 90% of these Malignant Pleural Effusions (MPEs). Their etiologies are necessary to elucidate but from benign to MPE differentiation still remained a clinical challenge [53].

To improve the MPE diagnosis, a number of tumor markers have been studied to improve the sensitivity and specificity. Number of studies has explained diagnostic values for such markers but scientists were failed to identify reliable marker with both the features of high specificity and high sensitivity. So using single marker for MPE diagnosis is highly regretted. Hence new improved method and markers are still need to find for more accurate diagnosis [53].

Conclusion

This contribution shows that the development of gene technology not only enabled recombinant production of the enzyme of interest but also paved the way for protein engineering to tailor enzymes to better meet the demands required for a given process. The more recent achievements in metabolic engineering enable researchers to design entire pathways in microorganisms to accomplish high-level production of products at high titers starting from simple nutrients. In the near future, many further examples are expected in this exciting area of research, allowing the replacement of existing chemical processes as well as inventing routes to new products based on biocatalysis or biotransformation.

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