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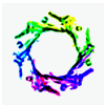

AN IN SILICO ANALYSIS OF TELOMERASE AND TELOMERE BINDING PROTEINS

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Abstract- Telomerase, an enzyme which plays a key role in the maintenance of the ends of chromosome in eukaryotes have been found activated in many cancer cells. Telomerase is an enzyme that adds specific DNA sequence repeats *i.e.,* "TTAGGG" in all vertebrates to the telomere region and thereby maintains the telomere length along with other telomere binding proteins. A group of 6 proteins make up the Shelterin complex which is responsible for telomere capping. The objective of this work is to detect the homologues with the query sequences, identify evolutionarily conserved regions in the query, find patterns of concerted evolution by detecting conserved domain architectures in the query and subject proteins, phylogenetic relationships amongst the query and subject proteins were analyzed to match them with the concerted evolution pattern and Telomerase inhibitors were screened to detect the best fit molecule which could possibly act to prevent carcinogenesis.
Keywords- Telomerase, Shelterin Complex, The Lagging Strand Mechanism, Curcumin

Introduction

The ends of linear chromosomes i.e the telomeric region in the eukaryotic cells undergoes major problems during DNA replication. The lagging strand mechanism of DNA replication cannot copy all the way to the end of the linear molecule resulting in short telomeric regions. The shortening of telomeric region and gradually its disintegration accounts for causing replicative aging and limits the proliferative capacity of normal human cells.

Telomeric sequences have found to be conserved among eukaryotic vertebrates throughout evolution. However the length of telomeres differs between species. Humans telomeric region is restricted up to 20 kb in length while Mus spretus shares nearly same size of the telomeric region of that of human by having a telomere upto 30 kb in size [1]. Telomeres of rodents on the other hand have been reported to be heterogeneous in length with rat telomere lengths ranging from 20 to 100 kb[2]. Mus musculus has been reported to have telomeres up to 150 kb in size [3].

Telomerase is an enzyme that helps to maintain the telomere length by adding specific DNA sequence repeats to the 3' end of the DNA strand in the telomeric region. Being a Reverse transcriptase, it carries its own RNA molecules which functions as a template during the elongation of chromosome in the replication mechanism. Telomerase was discovered by Carol.W.Greider and Elizabeth Blackburn in 1984 in the ciliate Tetrahymena [4] and the protein composition was identified by Scott Cohen and his team in 2007.The protein consists of two molecules, each of telomerase reverse transcriptase (TERT), telomerase RNA (TR or TERC), and dyskerin (DKC1) [5]. The TERC(Telomere RNA component) provides an AAUCCC template to guide the insertion of TTAGGG [6]. The TERT(Telomere Reverse Transcriptase) provides with the catalytic action.

Other than the telomerase other telomere binding protein also provide essential functions in the chromosome maintenance and is thereby suited for analysis in the context of evolution. The first telomere binding protein was identified in the ciliate Oxytricha nova. Telomere binding protein can either be double as well as single stranded ,both of which has been conserved throughout the evolution. Identified in budding and fission yeast and even in humans, double stranded telomere binding proteins are negative regulators of telomerase .They function by counting the number of existing telomere repeats on each chromosome end [7]. While double stranded protein functions in only negative regulation, single stranded telomere binding proteins performs multiple function, both negatively and positively. They influence the extension of telomere telomerase as well as provide a direct link between leading and lagging strand DNA in the replication machinery . The proteins utilizes the oligosaccharide/oligonucleotide fold(OB fold) for efficient binding to telomeric DNA [8]. Some telomere binding proteins are – TRF1(Telomere