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Genome-Wide Studies in Budding Yeast Dissect the Mechanisms that Maintain Telomere Length

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Telomeres are nucleoprotein structures present at the ends of eukaryotic chromosomes. Telomeres play several important roles in maintaining the stability of the genome: they serve to differentiate the natural chromosomal ends, which should not be repaired, from double stranded DNA breaks (DSBs), which may occur by accident and need to be repaired immediately to prevent loss of genomic information. This protection or "capping" is conferred by the special structure of telomeres, created by specific telomeric proteins. In addition, telomeres provide a solution to the end-replication problem: the regular DNA replication machinery is unable to fully replicate the chromosomal ends; as a consequence, information is lost with each cell division, eventually resulting in senescence and cell death. Highly proliferative cells and unicellular organisms solve this problem by expressing telomerase, a specialized reverse transcriptase that uses a dedicated RNA molecule as a template to extend the telomeres. Cancer cells are also highly proliferative and thus also require functional telomeres: in about 80% of tumors, the telomerase gene is expressed; in the rest, an alternative mechanism, ALT, based on homologous recombination, allows telomere length extension. Mutations that affect telomere function result in human diseases, such as Dyskeratosis Congenita, Idiopathic Pulmonary Fibrosis, and others [1]. In addition, telomere length was found to decrease with age in human individuals, suggesting a link between telomere length and aging. Thus, our understanding of the biology of telomeres has significant medical implications, and is especially relevant to the fields of aging and cancer.

Although some differences exist between the organization of telomeres in yeast and mammals, many basic rules are universal. The yeast Saccharomyces cerevisiae, with its sophisticated genetics and molecular biology tools, has been instrumental in providing basic information about telomere biology [2]. Mutant collections in which each nonessential gene was deleted or in which each essential gene was replaced by either a hypomorphic allele or a temperature-sensitive allele are available. The mutant collections allow researchers to carry out systematic mutant screens even if the phenotype of interest is not selectable. Three publications looked for mutants that affect telomere length (telomere length maintenance or tlm mutants). DNA was extracted from each individual yeast strain and telomere length was measured by Southern blot [3-5]. Together, these papers identified ~400 genes affecting telomere length. This list contrasts with the 30 or so genes known to do so at the time the screens were carried out [3]. Moreover, it also demonstrates the complexity of the challenge: each of the ~400 genes participates in determining the equilibrium between elongating and shortening activities at telomeres. Remarkably, each wild type yeast strain exhibits always telomeres of the same size; thus, in a wt cell grown under optimal conditions the equilibrium is always attained at the same telomere length. Thus, a homeostatic mechanism involving hundreds of genes is at play [6]. The screens, as expected, uncovered genes affecting DNA and chromatin metabolism, but almost all functions in the cell are also represented. A large number of these genes are evolutionarily conserved and present in the human genome.

The challenge ahead, of course, is to find out the function of these genes in telomere metabolism and their genetic organization. Using computational approaches and the vast amount of information about protein-protein and genetic interactions in yeast, initial network models of telomere biology have already been established, allowing their dissection [6,7].

Additional genome-wide screens include screens for mutants that affect the three dimensional configuration of telomeres [8] or their capping capacity [9]. Recently, a genome-wide analysis was carried out for mutants that differentially affect the phenotype of two tlm mutants, yku70 (defective for the Ku heterodimer) and cdc13-1 (defective for the CST complex, which positively regulates telomerase). The response to telomere uncapping was shown to be genetically complex, with many genes involved in a variety of processes affecting the outcome [10]. Another genome-wide screen examined, in a systematic fashion, the kinetics of senescence, by looking for mutants exhibiting either retarded or accelerated senescence upon inactivation of telomerase [11]. These studies have started to provide answers about the function of several TLM genes, while uncovering new telomere-affecting genes and thus enlarging the telomere-related genetic network.

The fact that a near-complete list of TLM genes is available opens the door for further exploration of telomere biology. Several secondary screens were already carried out on the tlm mutant collection. In one of these, telomerase RNA levels were measured in all tlm mutants, and 24 were found to affect telomere length via their effect on the level of this RNA [12]. A second screen explored the effect of starvation on telomere length [13]. Starved cells respond by dramatically shortening their telomeres. By screening the tlm mutants for those that do not respond to the starvation signals, it was found that the Ku heterodimer plays a central role in the starvation response. When cells are starved, Ku protein levels are reduced, affecting telomere length. This finding is particularly interesting in light of an apparent paradox: calorie restriction lengthen lifespan, whereas telomere attrition leads to cellular senescence [13]. In another study that followed the response of yeast telomeres to environmental stimuli it was found that exposure to ethanol elongates telomeres, whereas caffeine and high temperature reduce telomere length [14]. Again, a systematic screen of tlm mutants was used to identify the Rap1/Rif1 pathway as necessary for the transduction of different environmental signals. The tlm collection

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was also searched for mutants that affect the survival pathways in the absence of telomerase activity. New functional roles were found for many TLM genes [15].

The Systems Biology revolution is at its infancy; at this stage we can only summarize that the genome-wide studies have greatly extended our view of telomere biology. These studies have underscored the centrality of telomere biology in securing the integrity and replication of the genome, and the remarkable complexity of the processes involved. Yeast with simple biological models, such as yeast cells, greatly accelerates the pace of discovery and provides insights of significant medical implications.

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