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Development of Novel Anti-aging Drugs

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Abstract

It has been thought that cellular senescence is regulated by the total amount of damage to chromosomes, including telomeric regions. Another explanation is that cellular senescence is attributed to oxidative stresses mainly generated in mitochondria. At present, several compounds, such as 2-deoxy-D-glucose (2-DG) and *trans*-Resveratrol (Rsv), are expected to be used as anti-aging drugs for extending life-span. Our previous study indicated that promoter activities of the telomere-maintenance factor-encoding genes are activated by both compounds. The mechanism might be implicated in the concept of hormesis - that the application of low doses of toxic substrates strengthens DNA-repair system. Effective anti-aging drugs could be found by screening compounds that up-regulate expression of the telomere associated genes.

Keywords: Caloric restriction; Cellular senescence; 2-deoxy-D-glucose; Oxidative stress; Resveratrol

All higher organisms, including humans, experience aging and have limited life spans. It has been explained that the aging process is controlled by damage to chromosomes [1] and oxidative stress [2,3]. Telomeres, which are the ends of chromosomes, are composed of TTAGGG repeats with the maintenance factor complex [4]. Repeated replication shortens telomeres [5] and causes chromosomal instability to arise [4]. Mutations of specific genes, such as *WRN* and *LMNA*, are known to cause premature aging syndromes [6,7]. The proteins that are encoded on these genes are thought to regulate chromosomal stability and probably the telomere maintenance system. From studies of model organisms, several genes that encode anti-oxidative enzymes, insulin-signaling proteins, sirtuin (Sir2 in yeast, and SIRT1 in mammalian organisms), tumor suppressor p53, and transcription factor FoxO were shown to affect lifespan [8,9]. These lines of evidence raised the question: how do chromosomal damage and oxidative stress associate with each other to properly regulate the aging process and how can expanding our knowledge of these processes and their association aid in the development of effective anti-aging drugs?

Reactive oxygen species (ROS), which are mainly generated from mitochondria, are thought to cause DNA damage [10]. Recently, it was revealed that telomere dysfunction exerts a signal to mitochondria by reducing transcription of the *PGC-1α* and *PGC-1β* genes that encode mitochondrial regulators [11]. These observations suggest that there is mutual communication between mitochondoria and telomeres.

To date, several candidates for anti-aging drugs have been investigated. For example, 2-deoxy-D-glucose (2DG), which is a potent inhibitor of glucose metabolism, has a caloric restriction (CR) mimetic effect [12]. The natural compound Resveratrol (Rsv), which is contained in grape skins and red wine, activates sirtuin-mediated deacetylation [13]. The life spans of various organisms might be extended by administration of these drugs [12,14]. Besides affecting glucose metabolism and sirtuins, these CR mimetic compounds have the effect of inducing transcription of telomere-associated genes. Our previous study indicated that 2DG and Rsv up-regulate the promoter activities of the *WRN*, *TERT*, and shelterin-encoding genes, along with moderately stimulating telomerase activity [15-17]. This might be a favorable side effect, and may shed light in the search for anti-aging drugs. The anti-aging effect might come from the concept of hormesis [18], the stimulation of the DNA repair or telomere-maintenance system through low doses of toxic substrates. By analyzing the stimulation of telomerase and the gene expression of the telomere-maintenance factors, effective anti-aging drugs might be discovered, isolated, and synthesized in the future.

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