

The Istituto Pasteur-Fondazione Cenci Bolognetti promotes and finances research on telomeres. The chromosomes of multicellular organisms comprise a long DNA double helix, whose ends associate with a protein cap, forming a structure known as telomere. The telomeres “hide” the terminal ends of the chromosome, preventing the cell from recognizing them as DNA breaks and thus activate control mechanisms to block cell division. Furthermore, telomeres play a crucial role in the protection of chromosomes from incomplete replication. For reasons inherent to the DNA duplication process, the DNA termini of the chromosomes are not entirely replicated, leading to a shortening of the chromosome ends at each DNA replication event. To counterbalance this chromosome shortening, telomeres associate with an enzyme, called telomerase, which adds new DNA to chromosome ends. In the absence of telomerase activity, telomeric DNA of actively proliferating cells progressively shortens; when telomere length reaches a critical threshold, the cell stops dividing and enters a resting phase called cellular senescence. In mammals, including humans, telomerase is active in germ cells (functional to reproduction) and in stem cells, but not in somatic cells (the majority of cells in our body). Therefore, the telomeres of elderly people are shorter than those of young people. Consistent with this observation, people who suffer from genetic diseases causing premature aging, such as progeria, exhibit very short telomeres even at an early age.

In tumors, most of which originate from malignant transformation of somatic cells, telomeres are expected to grow shorter at each DNA replication event, resulting in cell growth arrest and senescence. However this is not what happens, because most tumors reactivate telomerase and acquire an unlimited growth capability. Thus, while on the one hand telomerase activity prevents cell aging, on the other it favours tumor development. Therefore, it is conceivable that the ability to control telomerase activity would allow an intervention on both aging and cancer growth. The importance of the studies on telomere biology has recently been acknowledged with the 2009 Nobel Prize for Medicine to Elizabeth Blackburn, Carol Greider and Jack Szostak, the three researchers who discovered telomerase.

Until very recently, an unanswered question was whether short-telomere-associated aging was irreversible, or could be corrected by increasing telomere length. The answer to this question came from a research carried out by Prof. Ronald DePinho group at Harvard University, recently published in *Nature* (Jaskelioff et al., *Nature*, November 28, 2010). By means of genetic engineering techniques, these scientists created a mouse model system in which they were able to inhibit and then reactivate telomerase activity. Using this system, telomerase activity was inhibited for four generations; fourth generation mice displayed very short telomeres, and even at a young age, they showed a series of symptoms generally observed in very old mice, such as neurological problems, a reduced olfactory capability, testicle atrophy and reduced fertility. When DePinho and colleagues reactivated telomerase activity in all mouse cells (somatic, germinal and stem cells), they observed a remarkable rejuvenation of the prematurely aged animals after only four weeks since telomerase reactivation. Neurological defects had strongly decreased, the sense of smell had improved, testicle atrophy had regressed and fertility increased.

These observations, widely publicised by the media, raised a general interest as they clearly demonstrate that aging can be fought and can be made to regress by operating on the mechanisms that control telomere length. However, there are some important issues that remain open. DePinho's research group examined the mice after four weeks since telomerase reactivation, and observed rejuvenation of the animals without an increase in cancer development. But what would happen if telomerase were kept active in somatic cells for over four weeks? Would there be an increase in cancer development? This experiment has not yet been carried out, but we believe that an answer will soon be available. Moreover we expect that sooner or later scientific research will succeed in gaining a complete control of telomerase activity, managing to activate it in senescent cells and inhibit it in cancer cells. The question of whether and when this achievement would lead to medical

applications aimed at delaying aging and defeat cancer, is much harder to foresee. We hope that research on telomeres led by Istituto Pasteur-Fondazione Cenci Bolognetti will help to reach this goal.