Eukaryotic cells possess linear chromosomes. The telomere, a specialized heterochromatin structure, exists at the ends of linear chromosomes. Telomeres contain DNA with an evolutionarily variable repeat sequence: [TG1-3]ₙ in budding yeast, [TTACAG 2-5]ₙ in fission yeast, [TTAGGG]ₙ in most plants and [TTAGGG]ₙ in mammals. Telomere DNA is composed of two parts: double-stranded (ds) DNA in the inner chromosome regions and 3’-protruding G-rich single-stranded (ss) DNA at the very ends of chromosomes. The total length of telomere DNA also varies: ~300 bp in yeasts, ~15 kbp in human germ cells, and ~5–13 kbp in human somatic cells. Telomere DNA serves as a platform for various telomere-binding proteins. The G-rich ssDNA recruits a telomeric ssDNA-binding protein complex, including Pot1, which protects chromosome ends and recruits telomerase for telomere elongation. Telomeric dsDNA recruits other types of protein complexes that include TRF family proteins and Rap1, which negatively regulate the access of telomerase and thus inhibit excessive elongation of telomeres. These ss- and ds-telomere DNA-binding proteins associate with each other and constitute a protein complex called shelterin, which bridges the ssDNA and dsDNA of telomeres. Shelterin protects chromosome ends and plays crucial roles in monitoring and maintaining telomere DNA length by regulating, both positively and negatively, the access of telomerase to chromosome ends.

Recent studies have revealed that telomeres are involved in various biological phenomena, such as protection of chromosome ends, transgenerational preservation of germ cells, regulation of timing of cell senescence, and regulation of chromosome movements in mitosis and meiosis. Yeast cells and human germ cells display high expression levels of telomerase. Thus, these cells are capable of perpetually maintaining their telomere DNA length and continuous cell division. If cells lack some components of shelterin, they gradually lose telomere DNA and eventually lose their ability to divide, resulting in senescence or apoptosis. Even if we have the normal set of shelterin components and telomerase, the expression level of telomerase is severely decreased in differentiated somatic cells, causing a gradual shortening of telomere DNA. Cells with short telomeres will follow paths that lead either to aging or to cancer. In this issue, Makoto Hayashi reviews the history of telomere biology and the various consequences of telomere shortening in mammals.

Apart from the control of lifespan, telomeres also play important roles in the regulation of chromosome movement. Telomere clustering in the nucleus during meiotic prophase is particularly important for the normal progression of meiosis and production of offspring. Furthermore, recent studies have uncovered a link between telomere-binding proteins and DNA replication timing. Interestingly, some telomere-binding proteins are localized near replication origins in non-telomeric regions, as well as at the telomeres, to regulate the timing of DNA replication during S phase. In this issue, Hisao Masai and his colleagues describe how telomere-binding proteins are recruited to the non-telomeric loci near replication origins and how they control genome-wide replication timing and chromatin organization. They also discuss the involvement of telomere-binding proteins in transcriptional control.

Eukaryotic chromosomes possess subtelomeres adjacent to the telomeres. Subtelomeres contain species-specific highly homologous sequences in addition to various genes. In humans, some of the subtelomeric genes are related to diseases, such as intellectual impairment, multiple congenital anomalies and muscular dystrophy. Despite the likely importance of subtelomeres in the regulation of gene expression and chromosome maintenance, the functions of subtelomeres have remained mysterious because technical difficulties resulting from the structural features of subtelomeric homologous sequences, which are very long and present in large numbers of copies, have hampered the progress of research. I describe our recent discoveries about the novel functions of a shugoshin family protein, Sgo2, at subtelomeres in fission yeast. Sgo2 is localized at the centromeres during mitosis for precise chromosome segregation. Upon entry into interphase, it is translocated to the subtelomeres and plays important roles in the formation of highly condensed chromatin structure and in the maintenance of gene expression and DNA replication timing at the subtelomeres. Keiko Muraki and John Murnane review how telomere-binding proteins are recruited to the non-telomeric loci near replication origins and how they control genome-wide replication timing and chromatin organization. They also describe how telomere-binding proteins are recruited to the non-telomeric loci near replication origins and how they control genome-wide replication timing and chromatin organization.