cells is also characteristic of other disorders in which patients display some of the manifestations of aging at an increased rate, such as *Bloom syndrome* and *ataxia-telangiectasia*, in which the mutated genes encode a proteins involved in repairing double-strand breaks in DNA (Chapter 7).

Cellular Senescence. **All normal cells have a limited capacity for replication, and after a fixed number of divisions cells become arrested in a terminally nondividing state,** known as replicative *senescence.* Aging is associated with progressive replicative senescence of cells. Cells from children have the capacity to undergo more rounds of replication than do cells from older people. Two mechanisms are believed to underlie cellular senescence:

- *Telomere attrition.* **One mechanism of replicative senescence involves progressive shortening of telomeres, which ultimately results in cell cycle arrest.** *Telomeres* are short repeated sequences of DNA present at the ends of linear chromosomes that are important for ensuring the complete replication of chromosome ends and for protecting the ends from fusion and degradation. When somatic cells replicate, a small section of the telomere is not duplicated and telomeres become progressively shortened. As the telomeres become shorter, the ends of chromosomes cannot be protected and are seen as broken DNA, which signals cell cycle arrest. Telomere length is maintained by nucleotide addition mediated by an enzyme called *telomerase.* Telomerase is a specialized RNA-protein complex that uses its own RNA as a template for adding nucleotides to the ends of chromosomes. Telomerase activity is expressed in germ cells and is present at low levels in stem cells, but it is absent in most somatic tissues (Fig. 2-36) Therefore, as most somatic cells age, their telomeres become shorter and they exit the cell cycle, resulting in an inability to generate new cells to replace damaged ones. Conversely, in immortalized cancer cells, telomerase is usually reactivated and telomere length is stabilized, allowing the cells to proliferate indefinitely. This is discussed more fully in Chapter 7. The causal links between telomere length and cellular senescence have been established in mouse models. Genetically engineered mice with shortened telomeres exhibit reduced life spans that can be restored to normal by telomere activation. As discussed in other chapters, telomere shortening has also been associated with premature development of diseases, such as pulmonary fibrosis (Chapter 15) and aplastic anemia (Chapter 14).
- *Activation of tumor suppressor genes.* In addition to telomere attrition, activation of certain tumor suppressor genes, particularly those encoded by the *CDKN2A* locus, also seems to be involved in controlling replicative senescence. The CDKN2A locus encodes two tumor suppressor proteins, expression of one of which, known as p16 or INK4a, is correlated with chronologic age in virtually all human and mouse tissues examined. By controlling G1 to S phase progression during the cell cycle (Chapter 1), p16 protects the cells from uncontrolled mitogenic signals and pushes cells along the senescence pathway. This is discussed further in Chapter 7.

Defective Protein Homeostasis. Protein homeostasis involves two mechanisms: those that maintain proteins in there correctly folded conformations (mediated by chaperones) and others that degrade misfolded proteins by the autophagy-lysosome system and ubiquitin-proteasome system. There is evidence that both normal folding and degradation of misfolded proteins are impaired with aging. Mutant mice deficient in chaperones of the heat shock protein family age rapidly, and conversely, those that overexpress such chaperones are long-lived. Similar data exist for the role of autophagy and proteasomal degradation of proteins. Of interest, administration of rapamycin, which inhibits the mTOR pathway, increases the life span of middle aged mice. Rapamycin has multiple effects including promotion of autophagy. Abnormal protein homeostasis can have many effects on cell survival, replication, and functions. In addition, it may lead to accumulation of misfolded proteins, which can trigger pathways of apoptosis.

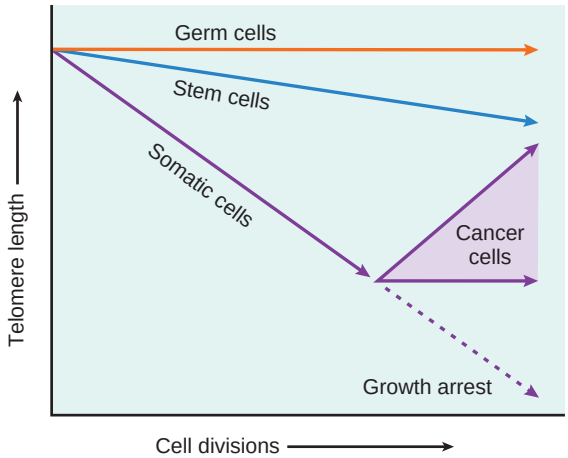

Figure 2-36 The role of telomeres and telomerase in replicative senescence of cells. Telomere length is plotted against the number of cell divisions. In most somatic cells there is no telomerase activity and telomeres progressively shorten with increasing cell divisions until growth arrest or until senescence occurs. Germ cells and stem cells both contain telomerase, but only germ cells have sufficient levels of the enzyme to stabilize telomere length completely. In cancer cells, telomerase is often reactivated. (Data from Holt SE, et al: Refining the telomere-telomerase hypothesis of aging and cancer. Nat Biotechnol 14:836, 1996, MacMillan Publishers Ltd.)

Deregulated Nutrient Sensing. Paradoxical though it may seem, eating less increases longevity. Caloric restriction increases life span in all eukaryotic species in which it has been tested, with encouraging results even in nonhuman primates and a few usually disciplined people who are the envy of others! Because of these observations, there has been much interest in deciphering the role of nutrient sensing in aging. The following paragraphs review two major neurohormonal circuits that regulate metabolism.

- *Insulin and insulin-like growth factor 1 (IGF-1) signaling pathway.* IGF-1 is produced in many cell types in response to growth hormone secretion by the pituitary. IGF-1, as indicated by its name, mimics intracellular signaling by insulin and thereby informs the cells of the availability of glucose, promoting an anabolic state as well as cell growth and replication. IGF-1 signaling has multiple downstream targets; relevant to this discussion are two kinases: AKT and its downstream target, mTOR (mammalian target of rapamycin), which, as the name implies, is inhibited by rapamycin.
- *Sirtuins.* Sirtuins are a family of NAD-dependent protein deacetylases. There are at least seven types of sirtuins