Nevertheless, most hematopoietic and solid tumors overexpress at least one member of the BCL2 family of anti-apoptotic proteins, suggesting that evasion of apoptosis is generally important in cancer development and progression. Furthermore, chemotherapy and radiation therapy kill cancer cells mainly by inducing apoptosis via the intrinsic pathway, and overexpression of BCL2 family members is believed to have an important role in the resistance of tumors to therapy. This appears to be particularly true for MCL-1, a BCL-2 family member that is normally subject to proteasomal degradation in the setting of DNA damage, but which is often found to be stabilized and overexpressed in drug-resistant cancers.

As mentioned earlier, p53 is an important pro-apoptotic protein that induces apoptosis in cells that are unable to repair DNA damage. The actions of p53 are mediated in part by transcriptional activation of BAX and PUMA, but there are also other connections between p53 and the apoptotic machinery. Thus, the apoptotic machinery in cancer may be thwarted by mutations affecting the component proteins directly, as well as by loss of sensors of genomic integrity such as p53.

The extrinsic pathway in less frequently altered in cancers, but nevertheless also has a role in some types, particularly certain lymphomas. Reduced levels of CD95/Fas may render the tumor cells less susceptible to apoptosis by CD95L/FasL. Other tumors have high levels of FLIP, a protein that can bind the death-induced signaling complex and prevent activation of caspase 8.

KEY CONCEPTS

Evasion of Apoptosis

- Apoptosis can be initiated through intrinsic or extrinsic pathways, both of which result in the activation of a proteolytic cascade of caspases that destroys the cell.
- Abnormalities of both pathways are found in cancer cells, but lesions that incapacitate the intrinsic (mitochondrial) pathway appear to be most common.
- In greater than 85% of follicular B-cell lymphomas, the anti-apoptotic gene *BCL2* is overexpressed due to a (14;18) translocation.
- Overexpression of other BCL2 family members such as MCL-1 is also linked to cancer cell survival and drug resistance.

Limitless Replicative Potential: The Stem Cell–Like Properties of Cancer Cells

All cancers contain cells that are immortal and have limitless replicative potential. Some cell lines established from cancers have now been proliferating ceaselessly in laboratories for more than 60 years, and it is reasonable to expect that they will continue to grow for as long as there are scientists to tend to them. How can it be that cancer cells have seemingly discovered the proverbial fountain of eternal youth? The answers are not completely known, but three interrelated factors appear critical to the immortality of cancer cells: (1) evasion of senescence; (2) evasion of mitotic crisis; (3) the capacity for self-renewal.

- **Evasion of senescence**. As was discussed in the section on cellular aging (Chapter 2), most normal human cells have the capacity to divide 60 to 70 times. After this, the cells become senescent, permanently leaving the cell cycle and never dividing again. The mechanisms that produce senescence are still not well understood, but the senescent state is associated with upregulation of tumor suppressors such as p53 and INK4a/p16 (perhaps in response to the accumulation of DNA damage over time). These tumor suppressors are believed to contribute to senescence in part by maintaining RB in a hypophosphorylated state, which favors cell cycle arrest. As already discussed, the RB-dependent G_1/S cell cycle checkpoint is disrupted in virtually all cancers by a wide variety of acquired genetic and epigenetic aberrations.
- **Evasion of mitotic crisis**. While cells that are resistant to senescence have increased replicative capacity, they are still not immortal; instead, they eventually enter into a phase referred to as *mitotic crisis* and die. This phenomenon has been ascribed to progressive shortening of *telomeres* at the ends of chromosomes. Telomeres are special DNA sequences at the ends of chromosomes that bind several types of protective protein complexes (Chapter 2). Most somatic cells do not express *telomerase*, the enzyme that is responsible for the maintenance of telomeres, and with each cell division their telomeres shorten. When the telomeric DNA is eroded, the exposed chromosome ends are "sensed" as double-stranded DNA breaks. If the affected cells have functional p53, the cell arrests its growth and may undergo apoptosis, but if p53 is dysfunctional, the nonhomologous end-joining pathway is activated and may join the "naked" ends of two chromosomes. This results in dicentric chromosomes that are pulled apart at anaphase, resulting in new double-stranded DNA breaks. The snowballing genomic damage caused by repeated "bridge-fusion-breakage" cycles eventually produces mitotic catastrophe and cell death (Fig. 7-34). Telomerase is expressed at very low levels in most somatic cells, and thus any cells that escape from senescence are very likely to die in mitotic crisis. However, if cells in crisis reactivate telomerase, the cells can restore their telomeres and survive; such cells may have suffered damage to oncogenes and tumor suppressor genes during crisis and are at high risk for malignant transformation. Alternatively, cancers may arise from stem cells (described later), which are normally long-lived in part because they continue to express telomerase. Whatever the mechanism, telomere maintenance is seen in virtually all types of cancers, and in 85% to 95% of cases this is due to upregulation of telomerase. The remaining tumors use another mechanism to maintain their telomeres termed *alternative lengthening of telomeres* that probably depends on DNA recombination.
- **Self-renewal**. Unlike most cells, tissue stem cells and germ cells express telomerase, making them resistant to mitotic crisis, and also somehow avoid the genetic and epigenetic alterations that trigger senescence. In addition, long-lived stem cells also possess another critical property, the capacity for self-renewal. In simple terms, self-renewal means that each time a stem cell divides at least one of the two daughter cells remains a stem cell.