

angiogenesis such as vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF1/2) which can be activated by different mechanisms as shown for VEGF in Figure 21.1.

Angiogenesis is attractive in anticancer therapy because its inhibition is expected to have no implications for normal cells in the body regardless of their proliferation rate.

6. *Resisting cell death*: Resistance to apoptosis, or programmed cell death, is also a key acquired capacity of cancer cells. In normal cells, apoptosis targets cells for self-destruction when their DNA is damaged beyond repair or when the cells do not receive the proper pro-survival signals from its environment. A key family of apoptosis regulatory proteins is the Bcl-2 family containing pro-apoptotic (Bax, Bak, Bid, and Bim) and antiapoptotic (Bcl-2, Bcl-XL, and Bcl-W) proteins. The Bcl-2 protein itself is frequently upregulated in cancer cells, leading directly to resistance toward drug-induced apoptosis. Furthermore, deletion or mutational inactivation of the tumor suppressor gene *TP53* represents another way of evading apoptosis because p53 normally induces upregulation of pro-apoptotic Bax protein upon DNA damage. p53 is inactivated in 50% of all human tumors.
7. *Deregulating cellular energetics*: Cancer cells display an enhanced cellular energy metabolism through glycolysis, the so-called Warburg effect, a switch from normal respiration to anaerobic glycolysis. In order to support continuous cell growth and proliferation, cancer cells consume >20 times as much glucose and produce energy in the form of ATP almost 100 times faster as a normal cell. Hypoxia-inducible factor is an important factor that activates genes supporting anaerobic glycolysis when triggered by, e.g., DNA damage, protein signaling, and growth factors. This metabolic switch is controlled by phosphoinositide 3 kinase (PI3K) which in turn activates key regulatory proteins such as AKT and mTOR leading to the altered energy metabolism.
8. *Avoiding immune destruction*: An active immune system continuously recognizes and eliminates the vast majority of cancer cells before they establish themselves and form a tumor. The action of the immune system include three phases, elimination of cancer cells, immunological control of cancer cell growth, and the “escape” of tumor cell not affected by the immune system. A defect or suppressed immune system will lead to the “escape” of tumor cells that can continue to proliferate and cause tumors. In many cancers, malignant progression is accompanied by profound immune suppression; in addition, tumors have themselves the ability to promote the production of pro-inflammatory cytokines and other factors leading to suppression of immunity. Cancer immunotherapy, be it cellular-, antibody-, or cytokine-based, is at present one of the most promising new cancer treatment approaches. This is primarily due to the fact that whereas the benefits of molecular targeted therapies are each time negated by the rapid development of drug resistance, patients that respond to immunotherapies such as ipilimumab (Yervoy) or nivolumab (Opdivo) show durable long-term responses.

21.1.2 ENABLING CHARACTERISTICS OF CANCER CELLS

1. *Genome instability*: In addition to the hallmarks mentioned in the previous section, cancer cells display a number of additional alterations that can be construed as enabling cancer growth. One of the most important alterations is genome instability. The number of individual mutations required to induce all eight hallmarks of cancer would not normally accumulate in a single cell if not for genome instability. Genome instability is caused by mutations of DNA repair/checkpoint surveillance mechanisms which normally results in cell cycle arrest until the damaged DNA has been repaired, or in case DNA cannot be efficiently repaired results in elimination of the cell via apoptosis. The genome guarding protein p53 as well as proteins sensing DNA damage such as ATR, ATM, and their downstream signal kinases Chk1 and Chk2 play an important role in such checkpoints, and their loss often precedes genome instability.