oxidative phosphorylation but also as a central regulatory structure of the apoptotic process.

The evolution of tumor cells to a more malignant phenotype requires the acquisition of genetic changes that subvert apoptosis pathways and promote cancer cell survival and resistance to anticancer therapies. However, cancer cells may be more vulnerable than normal cells to therapeutic interventions that target the apoptosis pathways that cancer cells depend on. For instance, overexpression of Bcl-2 as a result of the t(14;18) translocation contributes to follicular lymphoma. Upregulation of Bcl-2 expression is also observed in prostate, breast, and lung cancers and melanoma. Targeting of antiapoptotic Bcl-2 family members has been accomplished by the identification of several low-molecular-weight compounds that bind to the hydrophobic pockets of either Bcl-2 or Bcl-XL and block their ability to associate with death-inducing BH3-only proteins. These compounds inhibit the antiapoptotic activities of Bcl-2 and Bcl-XL at nanomolar concentrations in the laboratory and are entering clinical trials.

Preclinical studies targeting death receptors DR4 and DR5 have demonstrated that recombinant, soluble, human TRAIL or humanized monoclonal antibodies with agonist activity against DR4 or DR5 can induce apoptosis of tumor cells while sparing normal cells. The mechanisms for this selectivity may include expression of decoy receptors or elevated levels of intracellular inhibitors (such as FLIP, which competes with caspase-8 for FADD) by normal cells but not tumor cells. Synergy has been shown between TRAIL-induced apoptosis and chemotherapeutic agents. For instance, some colon cancers encode mutated Bax protein as a result of mismatch repair (MMR) defects and are resistant to TRAIL. However, upregulation of Bak by chemotherapy restores the ability of TRAIL to activate the mitochondrial pathway of apoptosis. However, clinical studies have not yet shown significant activity of approaches targeting the TRAIL pathway.

Many of the signal transduction pathways perturbed in cancer promote tumor cell survival (Fig. 102e-5). These include activation of the PI3K/Akt pathway, increased levels of the NF-κB transcription factor, and epigenetic silencing of genes such as *APAF-1* and *caspase-8*. Each of these pathways is a target for therapeutic agents that, in addition to affecting cancer cell proliferation or gene expression, may render cancer cells more susceptible to apoptosis, thus promoting synergy when combined with other chemotherapeutic agents.

Some tumor cells resist drug-induced apoptosis by expression of one or more members of the ABC family of ATP-dependent efflux pumps that mediate the multidrug-resistance (MDR) phenotype. The prototype, P-glycoprotein (PGP), spans the plasma membrane 12 times and has two ATP-binding sites. Hydrophobic drugs (e.g., anthracyclines and vinca alkaloids) are recognized by PGP as they enter the cell and are pumped out. Numerous clinical studies have failed to demonstrate that drug resistance can be overcome using inhibitors of PGP. However, ABC transporters have different substrate specificities, and inhibition of a single family member may not be sufficient to overcome the MDR phenotype. Efforts to reverse PGP-mediated drug resistance continue.

Cells, including cancer cells, can also undergo other mechanisms of cell death including *autophagy* (degradation of proteins and organelles by lysosomal proteases) and *necrosis* (digestion of cellular components and rupturing of the cell membrane). Necrosis usually occurs in response to external forces resulting in release of cellular components, which leads to inflammation and damage to surrounding tissues. Although necrosis was thought to be unprogrammed, evidence now suggests that at least some aspects may be programmed. The exact role of necrosis in cancer cell death in various settings is still being determined. In addition to its role in cell death, autophagy can serve as a homeostatic mechanism to promote survival for the cell by recycling cellular components to provide necessary energy. The mechanisms that control the balance between enhancing survival versus leading to cell death are still not fully understood. Autophagy appears to play conflicting roles in the development and survival of cancer. Early in the carcinogenic process, it can act as a tumor suppressor by preventing the cell from accumulating abnormal proteins and organelles. However, in established tumors, it may serve as a mechanism of survival for cancer cells when they are stressed by damage such as from chemotherapy. Inhibition of this process can enhance the sensitivity of cancer cells to chemotherapy. Better understanding of the factors that control the survival-promoting versus death-inducing aspects of autophagy is required in order to know how to best manipulate it for therapeutic benefit.

METASTASIS

The metastatic process accounts for the vast majority of deaths from solid tumors, and therefore, an understanding of this process is critical. The biology of metastasis is complex and requires multiple steps. The three major features of tissue invasion are cell adhesion to the basement membrane, local proteolysis of the membrane, and movement of the cell through the rent in the membrane and the ECM. Cells that lose contact with the ECM normally undergo programmed cell death (anoikis), and this process has to be suppressed in cells that metastasize. Another process important for metastasizing epithelial cancer cells is epithelial-mesenchymal transition (EMT). This is a process by which cells lose their epithelial properties and gain mesenchymal properties. This normally occurs during the developmental process in embryos, allowing cells to migrate to their appropriate destinations in the embryo. It also occurs in wound healing, tissue regeneration, and fibrotic reactions, but in all of these processes, cells stop proliferating when the process is complete. Malignant cells that metastasize undergo EMT as an important step in that process but retain the capacity for unregulated proliferation. Malignant cells that gain access to the circulation must then repeat those steps at a remote site, find a hospitable niche in a foreign tissue, avoid detection by host defenses, and induce the growth of new blood vessels. The rate-limiting step for metastasis is the ability for tumor cells to survive and expand in the novel microenvironment of the metastatic site, and multiple host-tumor interactions determine the ultimate outcome **(Fig. 102e-6)**. Few drugs have been developed to attempt to directly target the process of metastasis, in part because the specifics of the critical steps in the process that would be potentially good targets for drugs are still being identified. However, a number of potential targets are known. HER2 can enhance the metastatic potential of breast cancer cells, and as discussed above, the monoclonal antibody trastuzumab, which targets HER2, improves survival in the adjuvant setting for HER2-positive breast cancer patients. Other potential targets that increase metastatic potential of cells in preclinical studies include HIF-1 and -2, transcription factors induced by hypoxia within tumors; growth factors (e.g., cMET and VEGFR); oncogenes (e.g., *SRC*); adhesion molecules (e.g., focal adhesion kinase [FAK]); ECM proteins (e.g., matrix metalloproteinases-1 and -2); and inflammatory molecules (e.g., COX-2).

The metastatic phenotype is likely restricted to a small fraction of tumor cells (Fig. 102e-6). A number of genetic and epigenetic changes are required for tumor cells to be able to metastasize, including activation of metastasis-promoting genes and inhibition of genes that suppress the metastatic ability. Cells with metastatic capability frequently express chemokine receptors that are likely important in the metastatic process. A number of candidate metastasis-suppressor genes have been identified, including genes coding for proteins that enhance apoptosis, suppress cell division, are involved in the interactions of cells with each other or the ECM, or suppress cell migration. The loss of function of these genes enhances metastasis. Gene expression profiling is being used to study the metastatic process and other properties of tumor cells that may predict susceptibilities.

An example of the ability of malignant cells to survive and grow in a novel microenvironment is bone metastasis. Bone metastases are extremely painful, cause fractures of weight-bearing bones, can lead to hypercalcemia, and are a major cause of morbidity for cancer patients. Osteoclasts and their monocyte-derived precursors express the surface receptor RANK (receptor activator of NF-κB), which is required for terminal differentiation and activation of osteoclasts. Osteoblasts and other stromal cells express RANK ligand (RANKL), as both a membrane-bound and soluble cytokine. Osteoprotegerin (OPG), a soluble receptor for RANKL produced by stromal cells, acts as a decoy receptor to inhibit RANK activation. The relative balance of RANKL