marrow–damaging agents, the tumor also seems to sense when tumor cell numbers have been reduced and can respond by increasing growth rate. However, the critical difference is that the marrow stops growing when it has reached its production goals, whereas tumors do not.

Additional tumor cell vulnerabilities are likely to be detected when we learn more about how normal cells respond to "stop" signals from their environment and why and how tumor cells fail to heed such signals.

IS IN VITRO SENESCENCE RELEVANT TO CARCINOGENESIS?

When normal cells are placed in culture in vitro, most are not capable of sustained growth. Fibroblasts are an exception to this rule. When they are cultured, fibroblasts may divide 30–50 times and then they undergo what has been termed a "crisis" during which the majority of cells stop dividing (usually due to an increase in p21 expression, a CDK inhibitor), many die, and a small fraction emerge that have acquired genetic changes that permit their uncontrolled growth. The cessation of growth of normal cells in culture has been termed "senescence," and whether this phenomenon is relevant to any physiologic event in vivo is debated.

Among the cellular changes during in vitro propagation is telomere shortening. DNA polymerase is unable to replicate the tips of chromosomes, resulting in the loss of DNA at the specialized ends of chromosomes (called *telomeres*) with each replication cycle. At birth, human telomeres are 15- to 20-kb pairs long and are composed of tandem repeats of a six-nucleotide sequence (TTAGGG) that associates with specialized telomere-binding proteins to form a T-loop structure that protects the ends of chromosomes from being mistakenly recognized as damaged. The loss of telomeric repeats with each cell division cycle causes gradual telomere shortening, leading to growth arrest (called *senescence*) when one or more critically short telomeres trigger a p53-regulated DNA-damage checkpoint response. Cells can bypass this growth arrest if pRb and p53 are nonfunctional, but cell death usually ensues when the unprotected ends of chromosomes lead to chromosome fusions or other catastrophic DNA rearrangements. *The ability to bypass telomere-based growth limitations is thought to be a critical step in the evolution of most malignancies*. This occurs by the reactivation of telomerase expression in cancer cells. Telomerase is an enzyme that adds TTAGGG repeats onto the 3′ ends of chromosomes. It contains a catalytic subunit with reverse transcriptase activity (hTERT) and an RNA component that provides the template for telomere extension. Most normal somatic cells do not express sufficient telomerase to prevent telomere attrition with each cell division. Exceptions include stem cells (such as those found in hematopoietic tissues, gut and skin epithelium, and germ cells) that require extensive cell division to maintain tissue homeostasis. More than 90% of human cancers express high levels of telomerase that prevent telomere shortening to critical levels and allow indefinite cell proliferation. In vitro experiments indicate that inhibition of telomerase activity leads to tumor cell apoptosis. Major efforts are under way to develop methods to inhibit telomerase activity in cancer cells. For example, the protein component of telomerase (hTERT) may act as one of the most widely expressed tumor-associated antigens and be targeted by vaccine approaches.

Although most of the functions of telomerase relate to cell division, it also has several other effects including interfering with the differentiated functions of at least certain stem cells, although the impact on differentiated function of normal non-stem cells is less clear. Nevertheless, a major growth industry in medical research has been discovering an association between short telomeres and human diseases ranging from diabetes and coronary artery disease to Alzheimer's disease. The picture is further complicated by the fact that rare genetic defects in the telomerase enzyme seem to cause pulmonary fibrosis, aplastic anemia, or dyskeratosis congenita (characterized by abnormalities in skin, nails, and oral mucosa with increased risk for certain malignancies) but not defects in nutrient absorption in the gut, a site that might be presumed to be highly sensitive to defective cell proliferation. Much remains to be learned about how telomere shortening and telomere maintenance are related to human illness in general and cancer in particular.

SIGNAL TRANSDUCTION PATHWAYS IN CANCER CELLS

Signals that affect cell behavior come from adjacent cells, the stroma in which the cells are located, hormonal signals that originate remotely, and from the cells themselves (autocrine signaling). These signals generally exert their influence on the receiving cell through activation of signal transduction pathways that have as their end result the induction of activated transcription factors that mediate a change in cell behavior or function or the acquisition of effector machinery to accomplish a new task. Although signal transduction pathways can lead to a wide variety of outcomes, many such pathways rely on cascades of signals that sequentially activate different proteins or glycoproteins and lipids or glycolipids, and the activation steps often involve the addition or removal of one or more phosphate groups on a downstream target. Other chemical changes can result from signal transduction pathways, but phosphorylation and dephosphorylation play a major role. The proteins that add phosphate groups to proteins are called kinases. There are two major distinct classes of kinases; one class acts on tyrosine residues, and the other acts on serine/threonine residues. The tyrosine kinases often play critical roles in signal transduction pathways; they may be receptor tyrosine kinases, or they may be linked to other cell-surface receptors through associated docking proteins **(Fig. 102e-2)**.

Normally, tyrosine kinase activity is short-lived and reversed by protein tyrosine phosphatases (PTPs). However, in many human cancers, tyrosine kinases or components of their downstream pathways are activated by mutation, gene amplification, or chromosomal translocations. Because these pathways regulate proliferation, survival, migration, and angiogenesis, they have been identified as important targets for cancer therapeutics.

Inhibition of kinase activity is effective in the treatment of a number of neoplasms. Lung cancers with mutations in the epidermal growth factor receptor are highly responsive to erlotinib and gefitinib **(Table 102e-2)**. Lung cancers with activation of anaplastic lymphoma kinase (ALK) or ROS1 by translocations respond to crizotinib, an ALK and ROS1 inhibitor. A BRAF inhibitor is highly effective in melanomas and thyroid cancers in which BRAF is mutated. Targeting a protein (MEK) downstream of BRAF also has activity against BRAF mutant melanomas. Janus kinase inhibitors are active in myeloproliferative syndromes in which JAK2 activation is a pathogenetic event. Imatinib (which targets a number of tyrosine kinases) is an effective agent in tumors that have translocations of the *c-Abl* and BCR gene (such as chronic myeloid leukemia), mutant c-Kit (gastrointestinal stromal cell tumors), or mutant platelet-derived growth factor receptor (PDGFR; chronic myelomonocytic leukemia); second-generation inhibitors of BCR-Abl, dasatinib, and nilotinib are even more effective. The third-generation agent bosutinib has activity in some patients who have progressed on other inhibitors, whereas the third-generation agent ponatinib has activity against the T315I mutation, which is resistant to the other agents. Sorafenib and sunitinib, agents that inhibit a large number of kinases, have shown antitumor activity in a number of malignancies, including renal cell cancer (RCC) (both), hepatocellular carcinoma (sorafenib), thyroid cancer (sorafenib), gastrointestinal stromal tumor (GIST) (sunitinib), and pancreatic neuroendocrine tumors (sunitinib). Inhibitors of the mammalian target of rapamycin (mTOR) are active in RCC, pancreatic neuroendocrine tumors, and breast cancer. The list of active agents and treatment indications is growing rapidly. These new agents have ushered in a new era of personalized therapy. It is becoming more routine for resected tumors to be assessed for specific molecular changes that predict response and to have clinical decision-making guided by those results.

However, none of these therapies has yet been curative by themselves for any malignancy, although prolonged periods of disease control lasting many years frequently occur in chronic myeloid leukemia. The reasons for the failure to cure are not completely defined, although resistance to the treatment ultimately develops in most patients. In some tumors, resistance to kinase inhibitors is related to an acquired mutation in the target kinase that inhibits drug binding. Many of these kinase inhibitors act as competitive inhibitors of the ATP-binding pocket. ATP is the phosphate donor in these phosphorylation