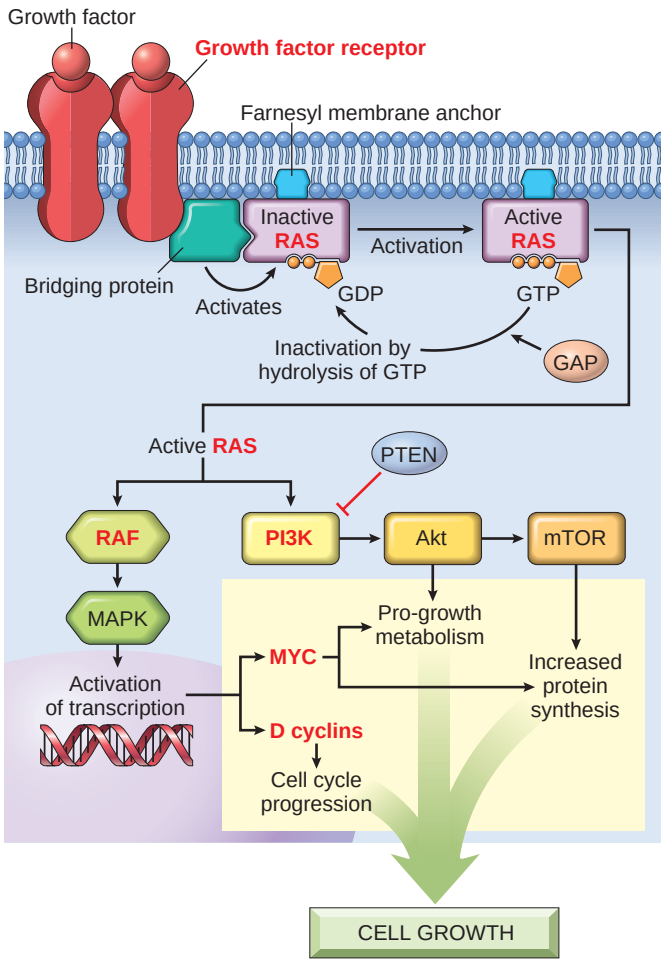

Figure 7-25 Growth factor signaling pathways in cancer. Growth factor receptors, RAS, PI3K, MYC, and D cyclins are oncoproteins that are activated by mutations in various cancers. GAPs apply brakes to RAS activation, and PTEN serves the same function for PI3K.

greatest impact on the malignant phenotype. Based on this logic, the signal transducer RAS, which operates immediately downstream from receptor tyrosine kinases, and two signaling "arms" that are downstream of RAS, the mitogen-activated protein kinase (MAPK) pathway and the phosphoinositidyl-3-kinase (PI3K)/AKT pathway, appear to be particularly important in promoting cancer cell growth (Fig. 7-25). Most (and possibly all) human cancers have molecular defects that affect one or more components of these pathways; examples are highlighted in Fig. 7-25 and are discussed in some detail below.

Growth Factors. Normal cells require stimulation by growth factors to proliferate. Most soluble growth factors are made by one cell type and act on a neighboring cell to stimulate proliferation (paracrine action). Some cancer cells, however, acquire the ability to synthesize the same growth factors to which they are responsive, creating an autocrine loop. For example, many brain tumors called *glioblastomas* express both platelet-derived growth factor (PDGF) and the PDGF receptor tyrosine kinases, and many sarcomas overexpress both transforming growth factor α (TGF-α) and its cognate receptor, epidermal growth factor receptor (EGFR), another member of the receptor tyrosine kinase family. In tumors in which an autocrine loop is an important pathogenic element, the growth factor gene itself is usually not altered or mutated. More commonly, signals transduced by other oncoproteins cause overexpression and increased secretion of growth factors , thereby initiating and amplifying the autocrine loop.

Growth Factor Receptors. A large number of oncogenes encode growth factor receptors, of which receptor tyrosine kinases are arguably the most important in cancer. Recall that receptor tyrosine kinases are transmembrane proteins with an extracellular ligand-binding domain and a cytoplasmic tyrosine kinase domain (Chapter 1). Normally, the receptor's kinase activity is activated transiently by binding of a specific growth factor to the extracellular domain, an event that induces a rapid change in receptor conformation to an active dimeric state. The activated receptor then autophosphorylates tyrosine residues in its own intracellular tail, and these modified residues serve as sites for recruitment of a number of signaling molecules, including RAS and PI3K, which have already been described as key players in receptor tyrosine kinase signaling. The oncogenic versions of these receptors are associated with mutations that lead to constitutive, growth factor–independent tyrosine kinase activity. Hence, the mutant receptors deliver continuous mitogenic signals to the cell, even in the absence of growth factor in the environment.

Receptor tyrosine kinases can be constitutively activated in tumors by multiple mechanisms, including point mutations, gene rearrangements, and gene amplifications. A few of the better characterized oncogenic mutations involving growth factor receptors are listed in Table 7-5; the following are salient examples of clinical importance:

- ***ERBB1*** encodes the epidermal growth factor receptor (EGFR), which is involved by point mutations in certain cancers. Of greatest clinical importance are several different *ERBB1* point mutations that are found in a subset of lung adenocarcinomas. These mutations result in constitutive activation of the EGFR tyrosine kinase.
- ***ERBB2*** encodes a different member of the receptor tyrosine kinase family, HER2. Rather than being activated by point mutations, the *ERBB2* gene is amplified in certain breast carcinomas, leading to overexpression of the HER2 receptor and constitutive tyrosine kinase activity.
- **Gene rearrangements** activate other receptor tyrosine kinases, such the tyrosine kinase ALK. For example, a deletion on chromosome 5 fuses part of the *ALK* gene with part of another gene called *EML4* in a subset of lung adenocarcinomas. The resulting *EML4-ALK* fusion gene encodes a chimeric EML4-ALK protein, again with constitutive tyrosine kinase activity.

The role of each of the mutations described earlier in promoting the growth and survival of tumor cells has been proven in no small part by the response of tumors bearing these mutations to therapeutic agents that specifically bind and inhibit these mutated receptor tyrosine kinases. For example, breast cancers with *ERBB2* amplification and overexpression of HER2 generally respond to treatment with antibodies or drugs that block HER2 activity. These inhibitors not only cause the cessation of tumor growth but also induce apoptosis and tumor regression, reflecting the