Table 7-5 Selected Oncogenes, Their Mode of Activation, and Associated Human Tumors

Category	Proto-Oncogene	Mode of Activation in Tumor	Associated Human Tumor
Growth Factors			
PDGF-β chain	*PDGFB*	Overexpression	Astrocytoma
Fibroblast growth factors	*HST1* *FGF3*	Overexpression Amplification	Osteosarcoma Stomach cancer Bladder cancer Breast cancer Melanoma
TGF-α	*TGFA*	Overexpression	Astrocytomas
HGF	*HGF*	Overexpression	Hepatocellular carcinomas Thyroid cancer
Growth Factor Receptors			
EGF-receptor family	*ERBB1 (EGFR)* *ERBB2 (HER)*	Mutation Amplification	Adenocarcinoma of lung Breast carcinoma
FMS-like tyrosine kinase 3	*FLT3*	Point mutation	Leukemia
Receptor for neurotrophic factors	*RET*	Point mutation	Multiple endocrine neoplasia 2A and B, familial medullary thyroid carcinomas
PDGF receptor	*PDGFRB*	Overexpression, translocation	Gliomas, leukemias
Receptor for KIT ligand	*KIT*	Point mutation	Gastrointestinal stromal tumors, seminomas, leukemias
ALK receptor	*ALK*	Translocation, fusion gene formation Point mutation	Adenocarcinoma of lung, certain lymphomas Neuroblastoma
Proteins Involved in Signal Transduction			
GTP-binding (G) proteins	*KRAS* *HRAS* *NRAS* *GNAQ* *GNAS*	Point mutation Point mutation Point mutation Point mutation Point mutation	Colon, lung, and pancreatic tumors Bladder and kidney tumors Melanomas, hematologic malignancies Uveal melanoma Pituitary adenoma, other endocrine tumors
Nonreceptor tyrosine kinase	*ABL*	Translocation Point mutation	Chronic myelogenous leukemia Acute lymphoblastic leukemia
RAS signal transduction	*BRAF*	Point mutation, Translocation	Melanomas, leukemias, colon carcinoma, others
Notch signal transduction	*NOTCH1*	Point mutation, Translocation Gene rearrangement	Leukemias, lymphomas, breast carcinoma
JAK/STAT signal transduction	*JAK2*	Translocation	Myeloproliferative disorders Acute lymphoblastic leukemia
Nuclear Regulatory Proteins			
Transcriptional activators	*MYC* *NMYC*	Translocation Amplification	Burkitt lymphoma Neuroblastoma
Cell Cycle Regulators			
Cyclins	*CCND1* (Cyclin D1)	Translocation Amplification	Mantle cell lymphoma, multiple myeloma Breast and esophageal cancers
Cyclin-dependent kinase	*CDK4*	Amplification or point mutation	Glioblastoma, melanoma, sarcoma

daughter cells. Cell growth pathways implicated in oncogenesis also initiate signals that promote and coordinate the biosynthesis of all of these cellular components (discussed later). This insight has led to the idea that it may be possible to target many aspects of oncogenic "pro-growth" signaling to therapeutic advantage, including the altered cellular metabolism that is characteristic of cancer cells.

Building on this framework, we next discuss the mechanisms by which cancer cells acquire self-sufficiency in growth signals.

Proto-oncogenes, Oncogenes, and Oncoproteins

Proto-oncogenes have multiple roles, but all participate at some level in signaling pathways that drive proliferation. Thus, pro-growth proto-oncogenes may encode growth factors, growth factor receptors, signal transducers, transcription factors, or cell cycle components. The corresponding oncogenes generally encode oncoproteins that serve functions similar to their normal counterparts, with the important difference that they are usually constitutively active. **As a result of this constitutive activity, pro-growth oncoproteins endow cells with self-sufficiency in growth**.

Two questions follow: (1) what are the functions of pro-growth oncoproteins and (2) how do the normally "civilized" proto-oncogenes turn into "enemies within?" The ensuing discussion uses receptor tyrosine kinases and downstream signaling components as examples. Receptor tyrosine kinase signaling is complex and has a number of major branchpoints and signaling nodes. Amongst these, Darwinian selection picks out the factors that have the