Prior to the early 1990s, the mechanisms by which growth factors and cytokines modulate cell behavior were largely unknown. In the mid-1980s, with the discovery of the first mitogen-activated protein kinase (MAPK) pathway, and with subsequent discoveries of other MAPK family pathways in the early 1990s, our understanding of the hormonal control of cell biology was provided with a greater degree of molecular underpinning. In light of these findings, the ability of cytotoxic drugs and ionizing radiation to control the activity of MAPK family (and other) signaling pathways was first investigated in the mid-1990s. It was discovered that radiation and many noxious drugs, in a cell-type-dependent manner, can activate multiple intracellular signal transduction pathways: the activation of some pathways has been reported to be DNA-damage-dependent, that of others by generation of lipids such as ceramide, whereas others have been noted to be dependent on mitochondria-derived reactive oxygen/nitrogen species and the activation of growth factor receptor tyrosine kinases. The precise roles of growth factor receptors and signal transduction pathways in cellular responses following exposure to noxious stresses are presently under intense investigation. Generally, in a cell-type and dose-dependent manner, inhibition of the extracellular-regulated kinase 1/2 (ERK1/2), and to a greater extent phosphatidylinositol 3 kinase (PI3K)/AKT, pathways can enhance cell killing. The modulation of cell survival by the ERK1/2 and AKT pathways has been correlated to the expression of mutant active RAS isoforms and to growth factor receptors of the ERBB and insulin/insulin-like growth factor (IGF) families. The activation of the c-Jun NH2-terminal kinase 1/2 (JNK1/2), ERK1/2, and PI3K/AKT pathways in tumor cells has also been linked to the expression of paracrine ligands—ligands that can promote cell growth and survival after exposure to a noxious stress and ligands that are generally only expressed at high levels in transformed cells. This chapter will discuss the signaling pathways activated by cytotoxic drugs and ionizing radiation and the roles each pathway can play in cellular responses of tumor cells.

**Key Words:** Radiation; signaling; kinase; phosphatase; reactive oxygen/nitrogen species; receptor.
1. SELF-LIMITING EFFECTS OF CANCER THERAPIES: AGENTS THAT CAUSE INCOMPLETE KILLING AND THE COMPENSATORY ACTIVATION OF GROWTH FACTOR RECEPTORS AND SURVIVAL SIGNALING PATHWAYS

As judged by the findings of many groups using a wide variety of noxious xenobiotic agents, cellular stresses cause pleiotropic activation of multiple receptor proteins in the plasma membranes of cells. The activation of death receptors by xenobiotic agents, such as the FAS and tumor necrosis factor α (TNFα) receptors, has been linked to the generation of ceramide, resulting in the clustering of activated death receptors in the plasma membrane, and the activation of apoptotic pathways. However, lethal cellular stresses also promote activation of growth factor receptors that when activated by their natural ligands are normally linked to cell growth and survival. Hence, conflicting signals are generated.

For example, xenobiotic agents can activate ERBB family receptors, and signaling by ERBB family of receptors is, in general, believed to be pro-proliferative and cytoprotective (1,2). Because both ERBB receptor expression and autocrine growth factor levels are often increased in carcinoma cells compared with normal tissue, many laboratories have studied signaling by the ERBB family in tumor cell growth and survival control after exposure to therapeutic agents. Thus, when signaling from ERBB family receptors is blocked, by use of inhibitory antibodies (e.g., C225, 4D5 Herceptin, and monoclonal antibody 806), small molecular weight inhibitors of receptor tyrosine kinases (e.g., PD183805 (also called CI1033), PKI166, AG1478, PD153035, ZD1839, PD169414, OSI774, AG825, and AG879), dominant-negative truncated receptors (e.g., dominant-negative EGFR-CD533), or antisense approaches (antisense EGFR), that tumor cell growth can be reduced and the sensitivity of these cells to being killed by noxious stresses increased (3–21).

In part, the above findings can be explained by the fact that growth factor receptors, including ERBB1, ERBB2, ERBB3, VEGF-R (Flt-1), and the insulin-like growth factor-1 (IGF-1), are all known to be activated, in a cell-type-dependent manner, after radiation/drug exposure (22–24). Recent publications have tended to argue that reactive oxygen and nitrogen species (ROS/RNS) play an important role in the activation of ERBB family receptors and the signaling by protective downstream pathways following exposure to ionizing radiation (25,26). In the case of receptor tyrosine kinases, the primary target of ROS/RNS is most likely to be protein tyrosine phosphatase (PTPase) enzymes that contain an ROS/RNS-sensitive cysteine residue within their active site, which is a residue that is essential for phosphatase activity (27). As PTPases are approximately 100-fold more active as enzymes than protein kinases, a small reduction in cellular PTPase activity will result in an increase in the steady-state tyrosine phosphorylation of the protein kinases, for example, receptor tyrosine kinases, whose phosphorylation the PTPases act to suppress. Many cytotoxic drugs also have been shown to directly or indirectly generate ROS/RNS as part of the mechanism by which they kill both non-transformed and tumor cells, for example, cisplatinum, histone deacetylase inhibitors, rituximab, doxorubicin, and NSAIDs (28–32). Hence, both cytotoxic drugs and radiation have the potential to both kill tumor cells and simultaneously activate protective pathways, for example, ERBB receptor signaling into downstream survival signal transduction pathways, by which their toxicity is blunted.