Growth Factor Signaling in Cell Survival: Implications for Cancer Treatment

SUNIT TALAPATRA and CRAIG B. THOMPSON
Department of Cancer Biology, Abramson Family Cancer Research Institute, University of Pennsylvania, Philadelphia, Pennsylvania
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ABSTRACT
Cells of multicellular organisms require extracellular signals to survive. Numerous studies have implicated a variety of intracellular signaling pathways, including PI-3 kinase/Akt, Ras/mitogen-activated protein kinase, and Jak/signal transducers and activators of transcription, as effectors of these extracellular trophic factors. Binding of growth factors to their respective receptors results in the activation of individual and combined pathways resulting in pleiotropic effects on cellular biochemistry. Over the past decade, investigation of these pathways has provided insight into the mechanism of cell survival and apoptosis itself. The results of these studies are providing new clues for therapeutic intervention in human disease. In this review, we focus on advances in our current understanding of the receptor signaling pathways that regulate apoptosis. Implications for the pharmacological manipulation of apoptosis in the treatment of cancer are also discussed.

Extracellular cues govern the differentiation, development, proliferation, and survival of cells in multicellular organisms. Increasing evidence suggests that diffusible growth factors both direct and shape the development of organs. Limitations in growth factor availability and signaling lead to death. In fact, the availability of growth factors is thought to define the size of various tissues by dictating the delicate balance between proliferation and cell death within a particular organ (Conlon and Raff, 1999). Although normal cells require growth factor stimulation to remain viable, transformed cells often circumvent this requirement. Indeed, in many cases, tumors possess oncogenes that lead to the hyperactivation of growth and survival pathways, liberating them from the need for exogenously derived signals. Despite a wide array of distinct trophic factors and receptors that govern the survival of specific cells, many of these receptors use common intracellular signaling molecules and pathways to mediate their signals. Three pathways that have taken center stage in survival signaling are the phosphatidylinositol 3-kinase (PI3K)/Akt, the Ras/mitogen-activated protein kinase, and the Jak/signal transducers and activators of transcription (STAT) pathways. These pathways have been shown to mediate survival signals in several cell types and model organisms and in response to a diverse array of growth factors. This review will present an overview of our current understanding of programmed cell death, also referred to as apoptosis, focusing on growth factor signaling pathways in the context of cell survival and the role of these pathways in carcinogenesis. Current attempts and opportunities for therapeutic intervention are also discussed.

Initiation and Execution of Programmed Cell Death
The morphological features of programmed cell death were first described 30 years ago and include chromosome condensation, DNA fragmentation, and membrane blebbing. For dying cells to adopt these features, the activation of a family of cysteine proteases, termed caspases, is required. Although the activation of caspases irreversibly commits a cell to death, their activation is not required to effect cell death under many circumstances. In fact, perturbations in cell metabolism, growth factor availability, and genotoxic agents, which result in the loss of mitochondrial function, can induce cell death even in the absence of caspase activation. In the absence of mitochondrial dysfunction, however, an otherwise healthy cell may be com-

ABBREVIATIONS: PI3K, PI-3 kinase; Akt, c-Akt; BH, Bcl-2 homology; DD, death domain; FasL, Fas ligand; MAPK, mitogen-activated protein kinase; PTEN, phosphatase and tensin homolog deleted from chromosome 10; PI, phosphatidylinositol; PIP, PI-3’ phosphate; PH, pleckstrin homology; STAT, signal transducers and activators of transcription; IBID, truncated BID; TNF, tumor necrosis factor; TNFR, TNF receptor; VDAC, voltage-dependent anion channel; S136, serine 136; Rsk, ribosomal S6 kinase; NF-κB, nuclear factor κB; IL, interleukin.
mitted to death through engagement of cell surface death receptors. Therefore, cell death can be categorized based on the method of initiation: 1) that which is initiated from cell surface death receptor engagement or 2) death arising from mitochondrial dysfunction.

**Death Receptor-Induced Apoptosis.** Engagement of receptors of the tumor necrosis factor receptor (TNFR) family, including CD95 (Fas/APO-1) and TNFR-1, leads to the activation of caspases to initiate death (Enari et al., 1995; Los et al., 1995). Receptor engagement then leads to the recruitment of death domain (DD) containing proteins as the Fas-associated DD, which serve to bind and activate caspase-8 that in turn ultimately initiates a cascade of caspase activation (Fig. 1). In many cell types, death receptor stimulation is sufficient to generate enough caspase activity to complete cell death. However, cells where caspase induction is not sufficient for death following CD95 stimulation require further caspase initiation generated from loss of mitochondrial function and cytochrome c release.

**Cell Death following Mitochondrial Dysfunction.** The critical role of the mitochondria in the regulation of apoptosis has become evident in the past several years. Cell damage that leads to perturbations in mitochondrial homeostasis and cytochrome c release from the inner mitochondrial space and into the cytosol commits a cell to death. Once in the cytoplasm, cytochrome c binds to apoptotic protease-activating factor-1, which binds and activates caspase-9 leading to initiation of the caspase cascade and cell death (Zou et al., 1997) (Fig. 1). Unlike death receptor-mediated death, most cells appear committed to dying once cytochrome c is released from the mitochondria and cannot be rescued by caspase inhibitors. The Bcl-2 family comprises proteins that are able to regulate mitochondrial homeostasis, and can be classed into two groups: those that initiate death typified by BAX and BAK, and those that function to prevent death, such as Bcl-2 and Bcl-xL (Kelekar and Thompson, 1998). Several models have been proposed as to the biochemical function of the Bcl-2 proteins (Vander Heiden and Thompson, 1999; Desagher and Martinou, 2000). What is consistent, however, is that the expression of the pro-apoptotic Bcl-2 proteins leads to cytochrome c release and the anti-apoptotic Bcl-2 proteins serve to prevent cytochrome c redistribution.

Bcl-2 proteins can be grouped on the basis of their homology in one of four Bcl-2 homology (BH) domains. A subclass of the pro-apoptotic proteins that only share homology in BH3, BAD and BID, are thought to function in trans by inactivating Bcl-xL or activating BAK and BAX. In the presence of survival factors, BAD is phosphorylated and sequestered in the cytoplasm by virtue of 14-3-3 proteins (Zha et al., 1996). Upon dephosphorylation, BAD is released from 14-3-3 and translocates to the mitochondria, where it is thought to induce death by inactivating pro-survival Bcl-2 family members. The ratio of pro- to anti-apoptotic Bcl-2 proteins is an important determinant of cell survival. BID is the precursor to the death-inducing form of truncated BID (tBID). Following death receptor engagement, activated caspase-8 binds and cleaves BID. The resulting tBID has been shown to bind and oligomerize BAX or BAK at the mitochondrial outer membrane and induce cytochrome c release (Eskes et al., 2000; Wei et al., 2000). Thus, the tBID pathway connects death receptors to the mitochondrial pathway of caspase activation.

**Fig. 1.** Cell death pathways. Apoptosis can be initiated following death receptor engagement. Alternatively, inadequate survival signaling leads to the inactivation of pro-survival Bcl-2 proteins, as Bcl-xL, and the redistribution of cytochrome c. Release of cytochrome c from the inner mitochondrial space results in caspase activation and death. See text for details. FADD, Fas-associated DD; Apaf-1, apoptotic protease-activating factor 1; PKA, cAMP-dependent protein kinase; ANT, adenine nucleotide transporter.
Growth Factors Prevent the Initiation of Apoptosis

It is evident that growth factors prevent cell death. Inadequate growth factor signaling leads to apoptosis, and several lines of evidence suggest that the death may be attributed to loss of mitochondrial homeostasis. As detailed below, progress has been made over the past decade in identifying and elucidating growth factor signaling pathways and maintenance of viability.

PI3K/Akt Pathway. Many receptors, including those for cytokines [interleukin-3 (IL-3), IL-2], neurotrophic factors [nerve growth factor], brain-derived neurotrophic factor, and growth factors [insulin-like growth factor-1, platelet-derived growth factor] transmit survival signals through the PI3K pathway. Induction of tyrosine phosphorylation results in the activation of PI3K, which catalyzes the transfer of a phosphate group from ATP to the D3 position of phosphatidylinositol (PI), thus generating 3'-phosphate group from ATP to the D3 position of phosphatidylinositol (PI), thus generating 3'-phosphatidylinositol phosphates (PIPs) (Fig. 2). PIPs have been termed lipid messengers because they serve as binding sites for proteins that possess a pleckstrin homology (PH) domain. One such protein is c-Akt (referred to through this review as Akt), also identified as protein kinase B and related to A- and C-protein kinase. Binding of the Akt PH domain to the phospholipids results in its translocation to the plasma membrane and phosphorylation at two critical residues, threonine 308 and serine 473. Phosphorylation at threonine 308 is achieved through additional kinases such as PI-dependent kinase 1, which also contains a PH domain and requires PI3K activity for membrane localization (Alessi et al., 1997). The enzyme that phosphorylates serine 473 has yet to be identified, but the Ca\(^{2+}\)/CaM-dependent protein kinase kinase or the cAMP-dependent protein kinase have been suggested (Yano et al., 1998; Harada et al., 1999).

The evidence suggests that regulation of Akt function is controlled both by localization to the membrane, which is dependent on available PIPs, and by the level of its phosphorylation. The generation of 3'-phosphoinositols is counter-balanced by lipid phosphatases that dephosphorylate PIPs. The tumor suppressor phophatase and tensin homolog deleted from chromosome 10 (PTEN), also referred to as mutated in multiple advanced cancers or TGF-β-regulated and epithelial cell-enriched phosphatase-1, is one such lipid phosphatase with specificity for 3'-phosphorylated PIPs. PTEN knockout studies revealed high concentrations of PIPs and a concomitant hyperactivation of Akt (Di Cristofano et al., 1999). While inactivating mutations of PTEN render cells resistant to apoptosis, overexpression of wild-type PTEN sensitizes cells to cell death following detachment from its extracellular matrix. This potentially explains the frequency of PTEN mutations in late stage, invasive tumors.

Inhibition of PI3K activity is sufficient to induce death even in the presence of survival factors. This death can be overcome by constitutive Akt activity. Although it is thought that Akt is a major if not the sole effector of PI3K survival, the mechanism by which Akt suppresses death is not known. Several Akt targets have been identified that may promote cell survival; however, no one substrate or model has emerged as the clear candidate.

Akt in Signal Transduction. The current understanding of Akt targets can be sorted into essentially two categories: proteins directly involved in signal transduction and enzymes of glucose metabolism. Among the former is BAD, a pro-apoptotic member of the Bcl-2 family. Akt phosphorylates BAD at serine 136 (S136) (del Peso et al., 1997). When phosphorylated, BAD is sequestered in the cytoplasm by 14-3-3 proteins, unable to heterodimerize with and inactivate the anti-apoptotic protein, Bcl-xL. Overexpression of BAD alone commits a cell to death, which may be rescued by coexpression of activated Akt. However, Akt is incapable of protecting cells expressing BAD with an S136-Alanine mutation. Clearly, Akt can mediate growth factor-dependent survival by reversing the apoptotic activity of BAD. However, it is uncertain that this is the primary means of Akt protection, as Akt-dependent survival can be observed in cells that contain little to no BAD. Therefore, in these cells, Akt-mediated survival is likely to involve other mechanisms.

In Caenorhabditis elegans, a homologous PI3K pathway regulates development and longevity. Mutations in Daf-2 (mammalian insulin receptor homolog) or AGE-1 (mammalian PI3K homolog) lead to developmental arrest at the dauer larval stage. This phenotype can be suppressed by mutations of the Daf-16 allele. Search for mammalian orthologs of the Forkhead transcription factor Daf-16 have revealed three members to date, AFX, FKH, and FKHRL1. As with BAD, in the presence of survival factors, Forkhead proteins are phosphorylated and retained in the cytosol by 14-3-3 proteins, suggesting a general role of 14-3-3 proteins in Akt-induced inhibition. Nonphosphorylatable mutants of FKHRL1 induce apoptosis in a variety of cell lines, while expression of Forkhead mutants with aspartic acid residues to mimic phosphorylation renders cells resistant to death.

Transcriptional activity is required for Forkhead function, as

![Fig. 2. Survival signaling pathways. Three major survival pathways can be activated in response to extracellular growth factors (GF), as described in text. A schematic of downstream effectors of the Jak/STAT, PI3K, and Ras/MAPK are shown. PDK1, PI-dependent kinase 1.](image-url)
substrates. Moreover, unlike Bcl-xL-expressing cells, the mitochondrial integrity at reduced levels of electron transport can be abated in the presence of antibodies that block Fas activation (Brunet et al., 1999). Consistent with this model, PTEN heterozygous mice develop a lethal polycyonal autoimmune disorder similar to Fas-deficient mice. Fas-mediated apoptosis is impaired in PTEN(+/-) mice, which can be restored in the presence of PI3K inhibitors. Moreover, neurons fail to induce apoptosis in the presence of inhibitors of translation or transcription. These data suggest that a significant aspect of Akt-mediated cell survival may be inactivation of Forkhead.

Additional transcription factors have more recently been identified as targets of Akt; however, their relevance in Akt-dependent survival is not yet clear. Akt directly phosphorylates cAMP response element binding protein, which has been implicated in brain-derived neurotrophic factor and Bcl-2 expression (Pugazhenthi et al., 2000). Induction of NF-kB by Akt has been reported (Madrid et al., 2000). Akt survival function in response to platelet-derived growth factor and TNF requires the activation of NF-kB transcriptional activity (Kane et al., 1999; Ozes et al., 1999; Romashkova and Makarov, 1999). Gene targets of the transcription factor NF-kB include a pro-survival member of the Bcl-2 family, A1, and the inhibitors of apoptosis proteins.

Akt in Metabolism Regulation. Several lines of evidence in insulin receptor signaling have emphasized the role of PI3K/Akt in cellular metabolism. Indeed, direct substrates of Akt that mediate glucose metabolism include the glucose transporter 4, phosphofructokinase 2, and glycogen synthase kinase 3 (Cross et al., 1995; Barthel et al., 1999). Interestingly, cells protected from IL-3 withdrawal-induced cell death by constitutively active Akt have high rates of glycolysis and increased mitochondrial potential while remaining viable over extended periods of growth factor deprivation. In Drosophila melanogaster, Akt null flies die during embryogenesis of systemic apoptosis. In contrast, ectopic expression of Akt during wing development results in enlarged wings composed of larger cells (Verdu et al., 1999). Recent data suggest that Akt promotes cell survival in part by maintaining elevated levels of glycolysis, thereby maintaining the cellular supply of mitochondrial substrates (Piras et al., 2001). This allows the mitochondria to use electron transport to produce the inner membrane potential that is required to maintain the integrity of the organelle in the absence of growth factor signaling. In contrast, Bcl-xL sustains mitochondrial integrity at reduced levels of electron transport substrates. Moreover, unlike Bcl-xL-expressing cells, the dependence on glycolysis for survival renders Akt-expressing cells susceptible to death induced from nutrient limitation. Additional studies will be required to determine whether an elevated level of metabolism or glycolysis alone is sufficient to protect cells from death in the absence of growth factors.

Ras/MAPK Pathway. Many of the same growth factors that activate the PI3K pathway can also stimulate the MAPK pathway. In addition to contributing to cell proliferation and differentiation, several studies have attributed a role in cell survival to this pathway. Upon recruitment and activation via receptor tyrosine kinases, the small guanosine triphosphatase protein Ras activates Raf, which leads to a phosphorylation signaling cascade involving the activation of the MAP kinases (Fig. 2).

The significance of the receptor tyrosine kinase in signaling through the MAPK pathway is evident. Deletion of the cytoplasmic tail that mediates Granulocyte and Macrophage-Colony Stimulating Factor/IL-3 survival signaling in BaF3 cells abrogates the activation of the Ras/MAPK pathway. Overexpression of an activated Ras in cells expressing the receptor mutation rescues the defect in Granulocyte and Macrophage-Colony Stimulating Factor/IL-3-induced survival. These data suggest the importance of the Ras/MAPK pathway in growth factor survival signaling. Ras transformation may also activate PI3K in this system; however, overexpression of downstream effectors of Raf that do not appear to affect PI3K activity also suppress cell death. Expression of oncogenic Raf inhibits apoptosis induced by IL-3 withdrawal in 32D and BaF3 cells, while inhibition of MAPK activation with dominant negative mutants suppresses IL-3-dependent survival in BaF3 cells. Additionally, activation of Src-like kinase, Lyn, thought to act upstream of the Ras/MAPK pathway, is necessary for survival in growth factor-treated eosinophils and neutrophils (Yousefi et al., 1996).

Several targets of MAPK activity in survival have been proposed, including the family of 90-kDa ribosomal S6 kinases (Rsks), which have been implicated in cell survival (Shimamura et al., 2000). In the IL-3-dependent 32D cell line, inhibition of Raf target mitogen-activated protein kinase kinase antagonizes IL-3-modulated survival, and expression of a constitutively active Rsk1 is sufficient to rescue the cells. Rsk activity protects cells from death through phosphorylation of BAD at S136 in multiple tissues (Shimamura et al., 2000). In other Ras/MAPK survival studies, evidence points to a role of the anti-apoptotic proteins of the Bcl-2 gene family in mediating survival. Protection from growth factor withdrawal-induced cell death through enforced expression of anti-apoptotic Bcl-2 family members is well documented.

Evidence from D. melanogaster also suggests that the Ras pathway may be important in cell survival (Meier and Evan, 1998). Expression of constitutively active Ras in the fly embryo suppresses normal developmental apoptosis, and the poor viability of cells lacking Ras can be rescued by reintroduction of wild-type Ras (Diaz-Benjumea and Hafen, 1994; Prober and Edgar, 2000). In the developing eye, gain of function mutations in the Ras/MAPK pathway suppress cell death while mutations that abrogate function of Ras/MAPK activity induce apoptosis (Kurada and White, 1998). In this model, Ras/MAPK activity promotes cell survival by inhibiting the expression and function of the pro-apoptotic protein, Hid. A vertebrate homolog for Hid has been difficult to establish. Murine knockout studies of B-Raf demonstrate an essential role of Raf gene function in endothelial cell survival. However, it should be noted that some reports ascribe no survival function to this pathway while others report a death-promoting effect.

Jak/STAT Pathway. The Janus family of kinases (Jaks) plays a major role in signaling from cytokine receptors to a family of STAT transcription factors (Fig. 2). The Jak/STAT pathway has been shown to transduce cytokine-mediated survival signals in several cell types. However, the mechanism is poorly understood. In some models, STAT activation...
leads to cell cycle arrest and cell death (Chin et al., 1996). STAT1 has been reported to trigger cell death through expression of caspase-1 (Chin et al., 1997). This apparent contradiction is probably the consequence of at least four Jak isoforms and seven STAT molecules, which may be activated by several cytokines and have distinct DNA binding properties. Knockout studies of the STAT family reveal STAT3 to have a role in cell survival (Takeda et al., 1997). STAT3 was shown to be required for growth colony stimulating factor-dependent cell survival in BaF-BO3 cell lines, and cells expressing dominant negative STAT3 were subject to apoptosis even in the presence of granulocyte factor. Downstream effectors of STAT-mediated survival are unclear, but when survival is apparent, increased Bcl-2 protein expression has been reported. Elevated Bcl-2 expression was demonstrated in cells expressing wild-type STAT3, but not dominant negative versions. However, it remains to be seen whether STAT activity is directly responsible for Bcl-2 induction.

**Pharmacological Inhibition of Survival Pathways**

Akt expression is amplified in 12% of ovarian carcinomas, 3% of breast carcinomas, and 10% of pancreatic carcinomas; PTEN mutations are found in over 80% of patients that suffer from Cowden disease, Lhermitte-Duclos disease, and Bannayan-Zonana syndrome (Bellacosa et al., 1995; Cheng et al., 1996). These findings suggest the importance of the PI3K pathway in tumor progression and suppression. Activating mutations of Ras are also prevalent in 90% of pancreatic adenocarcinomas and in 50% of colon and thyroid tumors (Bos, 1989). Although the contribution of the Jak/STAT pathway in oncogenesis is still unclear, constitutive Jak activity and STAT activation is found in virally transformed cells and in leukemia (Lacroix et al., 1997). Thus, there is considerable interest in counteracting these survival pathways through therapeutic intervention, which has spawned several pharmacological agents.

Early attempts at inhibiting Ras/MAPK function focused on Ras farnesyltransferase (FTase) activity, which catalyzes the posttranslational modification of Ras, required for plasma membrane localization. Several classes of peptide and small molecule inhibitors have been discovered, some of which are highly selective for Ras FTase and have little effect on normal cells (Leonard, 1997). In fact, small molecule inhibitors are currently in clinical phase I trials (Adjei et al., 2000). The synthetic molecule PD98059 completely inhibits mitogen-activated protein kinase kinase activity in most cases and has been widely used in in vitro studies.

Although there are many pharmacological agents to study Ras/MAPK signaling, inhibition of the PI3K/Akt pathway is currently possible with two inhibitors of PI3K (Srivastava, 1998). Wortmannin is a fungal metabolite of *Penicillium wortmannii* that inhibits PI3K activity by irreversibly modifying K802 of the catalytic subunit. The structurally unrelated PI3K inhibitor, LY294002, is a competitive inhibitor of the ATP binding site of the catalytic subunit of PI3K. Both drugs appear to be functionally equivalent. Although successfully applied in in vitro studies, wortmannin and LY294002 have not been effectively translated to human therapy. To our knowledge, no inhibitor of the PI3K/Akt pathway has entered clinical trials.

Pharmacological activation of cell intrinsic mechanisms for death has been an attractive model for cancer therapy. Accordingly, a search for agents to induce caspases has been an objective for cancer therapeutics in recent years. Vitamin D3 related compounds induce cell cycle arrest and apoptosis in breast cancer cells. Because Vitamin D3 has profound effects on calcium metabolism, synthetic analogs have been sought to avoid the side effects. A phase I study with the Vitamin D3 analog EB1089 showed reduced calcemia, and in vitro experiments demonstrate clear reduction in MCF-7 breast cancer cell line proliferation (Colston et al., 1992; Guillford et al., 1998). Recently, EB1089 was shown to induce death by caspase-3 activation, but other mechanisms of action are possible (Mathiasen et al., 1999; Park et al., 2000). Although many extracellular stimuli induce caspase activity, such as hydrogen peroxide, radiation, and FasL, these compounds appear to induce apoptosis in both normal and transformed cells. Thus, challenges remain to specifically target caspase activation to tumors.

As mentioned, Bcl-2 family proteins have been implicated as the effectors of survival in all the major survival signaling pathways. In chemotherapy studies, Bcl-2 expression or BAX deficiency correlates with drug resistance (Minn et al., 1995). Therefore, the efficacy of any therapeutic effort to counteract hyperactivation of survival signaling needs to take the function of Bcl-2 proteins into account. In fact, Bcl-2 expression protects cells from chemotherapeutic drug-induced death (Kamesaki et al., 1993). A Bcl-2 antisense oligonucleotide approach has been investigated to reduce Bcl-2 expression and thwart its anti-apoptotic effect and has been reportedly effective in the treatment of lymphomas (Cotter et al., 1999). A phase I study using the Bcl-2 antisense molecule G3139 was shown to reduce tumor mass and circulating lymphoma cells, concomitant with a reduction in Bcl-2 expression (Webb et al., 1997; Waters et al., 2000). The preliminary evidence suggests that Bcl-2 antisense nucleotides have anti-tumor activity, with the efficacy and low toxicity similar to current chemotherapy. However, as with all antisense approaches, specific uptake and compartmentalization issues as well as questions of nonspecific nucleotide interactions will need to be addressed. In addition, further studies are required to discern the efficacy of Bcl-2 antisense therapy in nonlymphoid tissue and to sensitize cells to apoptosis in conjunction with chemotherapy.

An alternative approach to inhibiting Bcl-2 function comes from functional studies of Bcl-xL, which suggest that the protein may promote cell survival by facilitating adenine nucleotide exchange between the mitochondria and cytoplasm. It has been proposed that Bcl-xL may promote mitochondrial ATP/ADP exchange in the absence of growth factors by holding the voltage dependent anion channel (VDAC) in the open configuration (Vander Heiden et al., 2000). In line with this idea, an alternative method of inhibiting Bcl-2 function may be to inhibit VDAC or the associated molecule adenine nucleotide transporter.

**Concluding Remarks**

The regulation of survival has emerged as having a significant role in oncogenesis and human disease. As growth factors dictate growth, proliferation, and survival, much interest has centered on the cellular biology of growth factor signaling. Ex-
tensive use of specific inhibitors has allowed investigation of each of the pathways and their specific contribution to signaling cellular functions. Recently, however, the concept of cross-talk between the pathways has added a new dimension for study. Although there has been a greater understanding of the control of the pathways, downstream effectors of the signals remain elusive or uncertain. The PI3K pathway, for example, has several targets that may function as effectors of survival, and Akt, which is a known survival gene, has numerous direct targets that may work in preventing cell death. Furthermore, all of the pathways can influence the expression of Bcl-2 family members, which may also enhance survival. It will be necessary to learn which genes are critical in respective tissues to effectively determine which will be appropriate targets for therapeutic intervention. However, in light of recent data concerning the role of genes that prevent apoptotis in the development of malignancy, inhibition of genes involved in cancer cell survival may provide new pharmacological approaches to cancer treatment.

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References

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Address correspondence to: Craig B. Thompson, Department of Cancer Biology, University of Pennsylvania, 421 Curie Boulevard, Philadelphia, PA 19104-6160. E-mail: dr@tl.med.upenn.edu

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