COMMENTARY

Unraveling the Mysteries of IGF-1 Signaling in Melanoma

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The inherent ability of a cell to undergo apoptosis governs a number of developmental processes essential to proper mammalian development. Into adulthood, the pathways that potentiate the apoptotic response are extremely diverse and finely regulated to prevent potential diseases. Of these, cancer is often associated with loss of an apoptotic response. Hanahan and Weinberg (2000) list evasion of apoptosis as a hallmark feature acquired during neoplastic transformation. The impact of this event is dramatic on several levels; avoidance of apoptosis not only prevents programmed cell death in an array of cell types but also promotes chemotherapeutic resistance during anticancer regimens.


In mammalian systems, there are currently 12 known members of the Bcl-2 family of apoptotic regulators (Yuile and Strasser, 2008); this group is divided into anti-apoptotic members (Bcl-2, Bcl-XL, Mcl-1, etc.) and pro-apoptotic proteins (BID, BAX, BAD, NOXA, etc.). A delicate balance of these proteins dictates the fate of a given cell; a rheostat exists between pro- and anti-apoptotic Bcl-2 family members to modulate cell death or survival, whereby whichever is more highly expressed determines the cellular outcome (Olthuis et al., 1993). Survivin (encoded by BIRC5) is a member of the inhibitors of apoptosis family of proteins and functions similarly to anti-apoptotic Bcl-2 family members (Altieri, 2008). Collectively, these apoptotic proteins control fundamental cell fate decisions that underlie the difference between homeostasis and onset of disease.

Metastatic melanoma is a complex malignancy that is refractory to nearly all known chemotherapeutics; as a result of the relative dearth of available therapies, the 5-year survival rate for patients afflicted with metastatic melanoma is approximately 15%. The inherent drug resistance observed in melanoma may be due, in part, to the network of signaling pathways that are activated during malignant transformation (Bennett, 2008). Although the cooperative phenotype that results from activation of these pathways is similar, their individual contributions and overall significance to disease may greatly contrast; thus, it is paramount to understand how each pathway can contribute to disease initiation, progression, and clinical manifestation.

The IGF-1 signaling axis originates from the IGF-1 receptor. IGF-1R is a heterotrimer consisting of two extracellular α subunits and two β subunits that encompass the transmembrane and tyrosine kinase domains (Hartog et al., 2007). After ligand binding, IGF-1R initiates a series of signaling events that positively affect the mitogen-activated human papillomavirus serology based on in situ-purified glutathione S-transferase fusion proteins. Clin Chem 51:1845–53


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protein kinase and phosphatidylinositol-3-kinase pathways, among others. Because these pathways are commonly activated in a variety of cancers, it is not surprising that a number of monoclonal antibodies and small-molecule inhibitors of IGF-1R are currently in clinical development (Hartog et al., 2007).

Somewhat surprisingly, IGF-1 is not expressed in melanoma cells (Rodeck et al., 1991); however, IGF-1R expression is correlated with melanoma progression (Kanter-Lewensohn et al., 2000). These observations suggest that paracrine-derived signals may be responsible for activation of IGF-1R during advancement of melanocytic disease. Indeed, our laboratory previously demonstrated that fibroblast-derived IGF-1 promotes growth and survival of early-stage melanoma cells (Satyamoorthy et al., 2001). In this issue, Hilmi et al. (2008) bolster a role for IGF-1 in melanoma pathophysiology by revealing that resistance to apoptosis in melanoma may be due to IGF-1-mediated expression of the anti-apoptotic proteins Bcl-2, Bcl-X, and survivin (Hilmi et al., 2008). The results from this study shed additional light on the mechanisms by which micro-environmental influences promote the chemoresistant phenotype associated with most advanced-stage melanomas.

Using two melanoma cell lines (MeWo and A375), the authors demonstrated that IGF-1 is sufficient to inhibit tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis; this antagonistic effect appeared to bypass caspase-8 activation and, instead, was dependent on caspases-9 and -3. This latter observation is intriguing because TRAIL is generally thought to induce apoptosis through a binding event with an appropriate death receptor, thereby initiating the “extrinsic” apoptotic pathway characterized by caspase-8 activation; here, caspases-3 and -9 were activated rather than caspase-8. These caspases (9 and 3) are associated with the “intrinsic” pathway that is affiliated with compromised mitochondrial function. Experiments measuring mitochondrial membrane potential validated those data and supported the premise that IGF-1 rescues TRAIL-induced apoptosis via prevention of the intrinsic apoptotic signaling cascade. Finally, upregulation of the anti-apoptotic proteins Bcl-2, Bcl-X, and survivin was provided as the mechanistic evidence for the biological effects of IGF-1.

Previous studies have demonstrated a role for IGF-1 in the proliferation of early-stage melanoma cells but not metastatic melanomas (Satyamoorthy et al., 2001), suggesting that IGF-1 has little effect on melanoma growth after the radial-growth phase of disease; this new report assigns a novel role to IGF-1 during disease progression: evasion of apoptosis. The malignant phenotype of melanoma is undeniably resistant to an assortment of anticancer therapeutics. The mechanisms responsible for drug resistance in melanoma are likely not limited to a single pathway or effector; instead, the chemoresistant nature of melanomas is probably the additive result of a number of drug efflux pumps, activation of cell survival pathways, and, potentially, the presence of a slow-cycling tumor-initiating cell population. The IGF-1 growth factor is now described as another potential mediator of cell survival in melanoma, thereby implicating IGF-1 signaling in additional biomolecular processes essential for maintenance of disease.

The precise cell type that produces IGF-1 in the tumor microenvironment is still uncertain. It is apparent that melanoma cells themselves express minimal amounts of IGF-1, indicating that the presence of IGF-1 is from a paracrine source. Others have suggested that stromal components are responsible for IGF-1 production in other cancer lesions (Cullen et al., 1991; van der Laan et al., 1995), and melanoma appears to be no different. Our laboratory has extensive gene expression data for a large panel of melanoma cell lines; Figure 1 depicts the expression profiles of the target genes of IGF-1 signaling (Bcl-2, Bcl-X, and survivin), as described by Hilmi et al. Our data suggest that the expression of these survival factors varies greatly across melanoma samples, rather than

**Figure 1. Expression profiling of Bcl-2, Bcl-X, and survivin in a panel of melanoma cell lines.** Gene transcription profiling of 30 melanoma cell lines was performed using Affymetrix U133A microarrays. An absolute expression analysis was performed using Affymetrix MAS 5.0 and the data were normalized per gene in GeneSpring GX 7.3.1. The target genes Bcl-2, Bcl-X (BCL2L2), and survivin (BIRC5) were visualized using supervised clustering analysis. The color bar indicates the fold expression level from the normalized value of 1 (yellow). Red indicates high expression and blue indicates decreased expression compared with the normalized value per gene.

**IGF-1 may mediate expression of anti-apoptotic proteins.**
being highly expressed; the apparent discrepancy between our data and those reported by Hilmi et al. may be due to one of several factors. First, the authors used only two cell lines in their studies, which might have not been enough lines to accurately predict a similar association across a larger sample size. Next, our gene expression profiling was performed in the continued presence of excess (5 µg/ml) insulin, rather than a transient treatment with IGF-1 to serum-starved cells; this minor experimental difference could account for the discrepancy between the two sets of data.

Although the results of Hilmi et al. (2008) help to establish a role for IGF-1 signaling in expression of anti-apoptotic molecules, they leave other questions unanswered. For example, what are the molecular mechanisms by which IGF-1 is able to induce expression of Bcl-2, Bcl-X, and survivin—are these proteins coregulated or similarly affected by distinct downstream mediators of the IGF-1 signaling axis? Likewise, MeWo and A375 cells represent metastatic melanomas—is the prosurvival phenotype after IGF-1 treatment a function of disease stage or is this observation merely coincidental? Furthermore, does inhibition of IGF-1 signaling (via IGF-1R monoclonal antibodies, for example) synergize with traditional chemotherapeutics to initiate disease regression? These types of studies appear promising in preclinical investigations (Ji et al., 2007; Maloney et al., 2003), whereas results from early clinical trials are still pending.

CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES

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First-Class Delivery: Getting Growth Factors to Their Destination

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Growth factor bioavailability in therapeutic applications such as wound healing is limited by extracellular matrix sequestration, proteolysis, and clearance. Local, transient delivery by gene transfer is an attractive concept. Many transfection strategies are available, and adenoviral vectors are in clinical trials. Keratinocyte growth factor-1 (KGF-1), an epithelial-specific member of the fibroblast growth factor (FGF) family, has achieved limited success in protein formulations. Matrix- and cell-based strategies for delivering a KGF-1 virion to target tissue may improve the reproducibility and efficiency of the process, although the advantages of cell-based therapy must be weighed against its added cost and complexity.


Despite two decades of advancement in the understanding and use of growth factors for wound healing, there has been limited clinical success (Leahy and Lawrence, 2007; Papanas and Maltezos, 2007). Numerous strategies for transient gene delivery of growth factor cDNA, by driving sustained, local overexpression of the factor, appear to overcome obstacles to delivery of and response to these proteins in the hostile wound environment (Eming et al., 2007). Transient gene delivery avoids many of the challenges of stable transformation needed to correct genetic defects. Among the many potential approaches for DNA transfer, early clinical findings with adenoviral recombinant platelet-derived growth factor-BB (PDGF-BB) therapy have been promising. Using a humanized mouse model, Escámez et al. (2008, this issue) have compared several methods.

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