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Invited Review

Apoptosis regulating genes in neuroendocrine tumors

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Summary. Neuroendocrine turnors (NETs) are a heterogeneous group of neoplasms. They are relatively uncommon and characterised by a relatively indolent clinical course. The indolent nature of NETs has long been enigmatic and recent advances in apoptosis research have led to speculation regarding the role of programmed cell death in NET tumorigenesis. It is hoped that a fundamental molecular understanding will help explain these variant behaviors that are so evident to the clinician, and ultimately yield novel and more effective therapies.

Recent studies have demonstrated that deregulation of programmed cell death may be a critical component in the multistep tumorigenesis of NETs and that the frequent expression of the BCL-2 oncoprotein in these tumors may contribute to their pathogenesis. The genetic complementation of simultaneously deregulated BCL-2 and c-MYC may be implicated in the multistep tumorigenesis of human NETs. It is also clear that numerous cellular gene products can and will be shown to impact upon apoptosis in NETs; some of these may even be molecules identified as oncoproteins or tumor suppressors. The major challenge will be to ascribe primary pathogenetic significance to tumor-associated derangements in expression of these molecules, and hopefully to then exploit our knowledge toward therapeutic benefit.

Key words: Neuroendocrine tumor, Apoptosis, Tumorigenesis

Introduction

It is widely recognized that alterations in oncogenes and tumor suppressor genes may result in enhanced rates of cellular proliferation. More recently, it has become clear that genetic regulation of apoptosis is also of critical importance during tumorigenesis and that oncogene and tumor suppressor genes can regulate the rate, or susceptibility of cells to undergo apoptosis (McDonnell, 1993; Williams and Smith, 1993).

The specific application of general principles of neoplasia to neuroendocrine tumors (NETs) has been a productive area of research and has already begun to be translated into direct clinical relevance, a process that is certain to accelerate. Neuroendocrine tumorigenesis also involves some special, if not unique, features which must be considered in moving toward the goal of a full understanding of its origins. NETs are a heterogeneous group of neoplasms which arise from a diverse cell system that shares histologic and biochemical features (Bolande, 1974; Pearse, 1980). They are relatively uncommon and characterised by a relatively indolent clinical course. These tumors secrete active hormones and may be associated with distinctive clinical syndromes. Despite their rather uniform histological pattern, these tumors often display a remarkable degree of intertumoral and intratumoral heterogeneity and there are considerable differences in their behavior and in their responsiveness to therapy. The initial genetic changes in the development of the familial multiple endocrine neoplasia (MEN) syndromes (MEN 1 and MEN 2) have recently been characterised (Eng, 1996; Chandrasekharappa et al., 1997; Eng and Mulligan, 1997; Lemmens et al., 1997). Somatic mutations of these genes have also been identified in a subset of sporadic NETs (Debelenko et al,.1997a,b; Eng and Mulligan, 1997; Heppner et al., 1997; Zhuang et al., 1997; Prezant et al., 1998; Tanaka et al., 1998). However, little is known about the molecular pathogenesis of the sporadic variants of the tumors which account for the majority of NETs. Clearly, other etiologies need to be sought.

Apoptosis is a ubiquitous physiologic and genetically controlled mode of cell death and an important feature in many normal biological processes, such as embryogenesis, morphogenesis, development of the immune system, cell maturation and differentiation. Apoptosis plays a complementary but opposite role to mitosis in the regulation of tissue homeostasis and is distinct from necrosis, the other type of cell death (Kerr

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Table 1. Expression of BCL-2, c-MYC, p53, and p53 mutation in neuroendocrine tumors.

TUMOR TYPE	Bcl-2	c-Myc	p53	REFERENCES
MTC	+	+	-	Yana et al., 1992; Viale et al., 1995; Wang et al., 1995, 1996a,b; Basolo et al., 1997
Pheochromacytoma	+	+	-	Yana et al., 1992; Dahia et al., 1995; Wang et al., 1995, 1997a
Neuroblastoma	+	N-myc	-	Castle et al., 1993; Reed et al., 1993; Vogan et al., 1993; Castresana et al., 1994; Ramani and Lu, 1994; Krajewski et al., 1995
Pituitary tumor	+	+	-	Herman et al., 1993; Levy et al., 1994; Wang et al., 1996b
Melanoma	+	+	-	Lubbe et al., 1994; Van den Oord et al., 1994; Hartmann et al., 1996; Miracco et al., 1998
Parathyroid tumor	+	NA	-	Hakin and Levine 1994; Uda et al., 1996; Wang et al., 1996d; Vargas et al., 1997
Carotid body tumor	+	+	-	Wang et al., 1995; Wang et al., 1996c, 1997b
PNT	+	+	-	Yoshimoto et al., 1992; Lohmann et al., 1993b; Wang et al., 1995, 1997c
Carcinoid tumor	+	+	-	Yoshinoto et al., 1992; Lohmann et al., 1993b; Wang et al., 1995, 1997c, 1998a; Brambilla et al., 1996

MTC: madullary thyroid carcinoma; PNT: pancriatic neuroendoctine tumor; NA: not available.

and Harmon, 1991; Vaux et al., 1993). However, when the balance is disturbed, abnormal cellular accumulations in the form of hyperplasia (an increase in cell number) and/or neoplasia may result. Apoptotic cell loss can inhibit tumor growth and the regulation of this process is a likely target for genetic changes associated with transformation. Recent studies have suggested that deregulation of programmed cell death may be a critical component in the multistep tumorigenesis of NETs.

BCL-2

The protein product of the BCL-2 oncogene, which was initially discovered as a result of its involvement in the common t(14;18) translocation in human follicular lymphomas, blocks a distal step in an evolutionarily conserved pathway for programmed cell death and apoptosis without affecting cell proliferation (Hockenbery et al., 1990; Wang and Reed, 1998). The discovery of BCL-2 marked the emergence of an entirely new class of genes with an important role in cancer.

Mah et al. (1993) and Lindenboim et al. (1995) reported that BCL-2 inhibits apoptosis in rat pheochromocytoma cells (PC12 cells) induced by deprivation of growth factors and cytotoxic drugs. It is hypothesized that BCL-2 expression in PC12 cells abrogates the requirement for stimulation by nerve growth factor (NGF) for survival (Mah et al., 1993). Moreover, significant expression BCL-2 has recently been reported in small cell lung carcinomas (SCLC) (Ben-Ezra et al., 1994; Jiang et al., 1995, 1996; Brambilla et al., 1996; Wang et al., 1998a) and other NETs (Table 1). These results indicated that the dysregulation of apoptotic through a pathway involving BCL-2 may be common in human NETs.

Furthermore, BCL-2 is frequently expressed in NETs, which are usually slow-growing and less aggressive tumors, suggesting that in these tumors, BCL-2 expression might also act in this capacity leading to indolent tumor growth. This has been borne out by recent studies in transgenic mice, generated from bcl-2 minigene constructs, which were used to assess the contribution of *bcl-2* gene deregulation to lymphomagenesis (Hockenbery et al., 1990; McDonnell et al., 1990). The disease process was initially indolent, as is also seen in follicular lymphoma, but after an extended latency period the mice developed clonal, high-grade B-cell malignancies (McDonnell and Korsmeyer, 1991). This model suggests that *bcl-2* overexpression may contribute to indolent tumor growth. Moreover, Konwlton et al. (1998) recently demonstrated that despite antiapoptotic effects favoring tumor survival, BCL-2 prolongs cell cycle and slows tumor cell proliferation. A growth advantage due to cell survival with a low mitotic rate, together with slower acquisition of additional genetic defects, could help explain the indolent progress of many NETs as is the case with follicular lymphomas (Vaux et al., 1988; McDonnell et al., 1990; McDonnell and Korsmeyer, 1991), in which BCL-2 expression is a frequent primary aberration. For example, tumors of the carotid body are rare and slow growing neoplasms. The genetic etiology of carotid body tumors is suggested by the familial occurrence of the neoplasm (Parry et al., 1982), and genetic linkage analysis localized the abnormal gene to the long arm of chromosome 11 (11q23) (Heutink et al., 1992; Baysal et al., 1997). Environmental influences are also implied by the fact that the tumor is more common in those living at high altitude (Saldana et al., 1973). However, the development of sporadic tumors occurring at sea level, which account for the majority of cases, remains unknown. Recently, it has been revealed that oncogenes, particularly the expression of apoptosis suppressing gene *bcl-2*, may play a important role in the pathogenesis suggesting that deregulation of apoptosis pathway may be involved in the genesis of such tumors (Wang et al., 1996c, 1997b). Furthermore, this hypothesis was also supported by the observation of BCL-2 expression in C-

cell hyperplasia (Wang et al., 1998b). C-cell hyperplasia is the precursor of medullary thyroid carcinoma (MTC) (Wolfe et al., 1973) in patients with familial MEN 2A, MEN 2B, and familial medullary thyroid carcinomas (FMTC) (Jackson et al., 1973; Hazard, 1977). The fact that MTCs are monoclonal neoplasms means that one of the multitude of C-cells bearing the pathogenetic inherited RET oncogene mutation must acquire additional genetic aberrations that confer a selective advantage. Apoptotic block would be the type of alteration that would be consistent with the development of often indolent neoplasia in such patients.

Neuroendocrine tumors are generally refractory to conventional chemotherapy and radiation treatment. In patients with metastatic or recurrent disease after surgery, however, chemotherapy is often considered. Over the last few years there has been increasing evidence that modulation of apoptosis may influence resistance to chemotherapy and therefore affect the outcome of cancer treatment. The expression of certain genes, such as p53 and *bcl-2*, may affect the cellular response to an apoptotic stimulus and therefore modulate the sensitivity of cells to cancer drugs. It has been demonstrated that many types of current anticancer drugs, with completely disparate cell targets, induce apoptosis in susceptible cells (Hickman, 1992). Imam et al. (1997) have recently shown the induction of apoptosis in NETs during treatment with somatostatin analogues. Previously, the expression of BCL-2 has been associated with poor response to chemotherapy (Sentman et al., 1991; Campos et al., 1993; Fisher et al., 1993). The finding in some NETs of seemingly constitutive and high level expression of BCL-2 protein may well be linked to the intrinsic resistance of these tumor cells to chemotherapeutic agents.

The mechanisms by which BCL-2 inhibits apoptosis have not been defined precisely. However, interactions among BCL-2 family members, including BAX, which promotes cell death, and BCL-XL, which inhibits cell death, appear to modulate the propensity of the cell to undergo apoptosis (Yang and Korsmeyer, 1996; Wang and Reed, 1998). In MTCs and a human MTC cell line (TT cells), very low level BAX expression was detected compared to high level BCL-2 expression (Wang et al., 1998b). A low level of BAX expression and high BCL-2/BAX ratio seem to protect tumor cells from the apoptotic pathway (Korsmeyer et al., 1993; Reed 1994). Indeed, using DNA nick end labeling techniques Wang et al. (1996a) and Basolo et al. (1997) have recently shown a very low prevalence of apoptotic tumor cells in human MTCs.

c-MYC

The *c-myc* proto-oncogene, usually implicated in cell transformation, differentiation and cell-cycle progression also has a central role in some forms of apoptosis (Evan et al., 1992). The opposing roles for myc in cell growth and death require that other gene products dictate the outcome of *c-myc* expression on a cell regarding oncogene complementarity (or cooperativity) in multistep carcinogenesis. Although BCL-2 alone is insufficient to cause transformation (Vaux et al., 1988), the surviving cells could provide the substrate for further genetic changes to conventional oncogenes, such as *c-myc*. Eventually a malignant clone could be produced. The direct evidence of the complementarity between myc and *bcl-2* was provided by studying Eμ-*myc* and Eμ-*bcl-2* transgenic mice (Strasser et al., 1990). It was shown that myc/*bcl-2* double-transgenic mice had a much shorter latency to tumor development than did either the Eμ-myc or Eμ-*bcl-2* single-transgenic mice. Moreover, documented evidence demonstrates that apoptotic cell death induced by c-MYC is inhibited by BCL-2, and simultaneously, BCL-2 expression does not prevent cell proliferation (Strasser et al., 1990; Fanidi et al., 1992; Wagner et al., 1993). Therefore, the cells generated as a consequence of the enhanced proliferation imparted by c-MYC would remain viable and result in tumor formation.

Khosla et al. (1994) showed that the expression of *c-myc* mRNA increased in the apoptotic MTC cells induced by TGF-ß1. Furthermore, an association between the expression of BCL-2 and c-MYC was also observed in NETs including MTCs (Wang et al., 1998b), pheochromocytomas (Wang et al., 1997a), pituitary tumors (Wang et al., 1996b), carotid body tumors (Wang et al., 1996c), melanomas (Miracco et al., 1998) and some carcinoid tumors (Wang et al., 1997c). Unlike *bcl-2*-lg transgenic mice, there is no evidence of B-cell hyperplasia in the prelymphomatous Eμ-myc mice despite an augmentation in cellular proliferation (Langdon et al., 1986). It is, therefore, tempting to speculate that the expression of c-MYC in NETs may be a secondary event critical for the tumor development. This co-expression of BCL-2 and c-MYC could indicate that BCL-2, by mitigating the apoptotic effects of deregulated c-MYC expression without affecting its ability to promote continuous cell growth, so provides a mechanistic basis for the oncogenic synergy between these two proto-oncogenes in NETs.

It must be stressed, however, that *bcl-2* expression does not always coincide with *c-myc* expression. Indeed, in SCLCs (Brambilla et al., 1996) and neuroblastomas (Ikegaki et al., 1995) there was no correlation between the expression of *bcl-2* and *c-myc*, suggesting that other genetic mechanisms must be also involved in the tumour genesis of such tumors. For example, the association between the expression of BCL-2 and p53 has been found in SCLCs (Brambilla et al., 1996; Wang et al., 1998a), and Castle et al. (1993) have reported that the expression of *bcl-2* in neuroblastoma is associated with N-myc gene amplification. However, the extent to which BCL-2 over-expression and inactivation of p53 in SCLC and N-myc amplification in neuroblastoma may have additive or synergistic effects in conferring resistance to apoptosis in such tumors has yet to be determined.

p53

The p53 protein, by regulating normal responses to DNA damage and other forms of genotoxic stresses, is a key element in maintaining genomic stability. When *p53* is mutated, control of the cell cycle may be lost, leading to tumourigenesis (Lane, 1992; Vogelstein and Kinzler 1992). Modulation of apoptosis appears to be one of the biological activities of the *p53* tumor suppressor gene, this is partly through upregulation of cell death promoting factor BAX or death factor FAS, because wild-type *p53* is a transcriptional activator of these genes (Miyashita and Reed 1995; Owen-Schaub et al., 1995). Moreover, wild-type *p53* is also involved in the mediation of c-MYC induced apoptosis (Hermeking and Eick, 1994). Loss of will-type *p53* function is also associated with chemoresistance in some systems (Lowe et al., 1993).

Tumor suppressor gene *p53* is the most commonly mutated gene in human cancers, and is involved in a number of different type of cancer (Hollstein et al., 1991). In contrast, *p53* mutations and overexpression are less common in NETs (Table 1) than other common tumors with exception of SCLCs (Takahashi et al., 1991; Sameshima et al., 1992). It might be that some types of NETs are uncommon with relatively benign behaviour as these tumors bear the wild-type *p53* protein. Nonetheless, *p53* mutations are associated with disease progression and poor prognosis in a number of NETs, such as SCLCs (Takahashi et al., 1991; Sameshima et al., 1992), metastatic melanomas (Stretch et al., 1991) and malignant insulinomas (Pavelic et al., 1995). NETs of the lung, for example, SCLCs, which bear a high frequency of *p53* mutations, are a highly malignant disease marked by rapid and disseminated tumor growth in the majority of patients. Whereas, pulmonary carcinoid tumors, which bear wild-type *p53* (Lohmann et al., 1993a), are slow growing and have a low malignant potential and excellent prognosis. This suggests that fundamentally different molecular changes occur between lung carcinoid tumors and SCLCs in their tumorigenesis (Wang et al., 1998a).

Interestingly, it was shown by Heise and colleagues (1997) that the E1B-deleted adenovirus not only killed *p53*-negative tumor cells, but in addition killed tumor cell lines with *p53*-wild type status. In another study, Freytag et al. (1998) showed that the combined gene therapies do not only kill *p53*-wild type tumor cells, but it was shown in vitro to not kill normal *p53*-wild type cells. The *p53*-wild type tumor cells should be more sensitive to suicide gene therapy and radiotherapy because they can undergo *p53*-mediated apoptosis. It has been previously demonstrated that tumor cells with normal *p53* status are more sensitive to the cytotoxic effects of chemotherapeutic drugs and radiation than tumor cells lacking functional *p53* (Lowe et al., 1993, 1994). The heightened sensitivity of tumor cells with normal *p53* is thought to be due to their increased propensity to undergo *p53*-mediated apoptosis following injury. This may hold the promise for the treatment of NETs which contain the wild-type *p53*, Li et al. (1998) have recently shown that melanoma cell lines containing wild-type *p53* are sensitive to drug therapy, whereas those containing mutant *p53* exhibit treatment resistance.

Other apoptosis regulating genes

In *Caenorhabditis elegans*, the protein products of the genes *ced-3* and *ced-4* are required for the execution of apoptosis (Yuan and Horwitz, 1990), and the product of the ced-9 gene prevents apoptosis by inhibiting activation of ced-3 and ced-4 (Hengartner et al., 1992). In mammals, several central mediators of apoptosis have similar molecular shapes and signaling roles as *ced-3*, *ced-4*, and *ced-9*. The human *bcl-2* and *C. elegans ced-9* gene products appear to be functionally equivalent (Hengatner and Horvitz, 1994), and as in *C. elegans*, humans have a CED-4 homologue that induces apoptosis, called Apaf-1 (apoptosis protease activating factor-1) (Liu et al., 1996; Zou et al., 1997). The product of *ced-3* has sequence and functional similarities to the mammalian cysteine protease interleukin-1ß converting enzyme (ICE/caspase-1) (Cerreti et al., 1992; Thornberry et al., 1992). Recently, Simizu et al. (1996) have shown that in SCLC cells the generation of intracelluar H_2O_2 and BAX expression in tyrosine kinase inhibitor-induced apoptosis were modulated by the activation of caspase-3 (-like) proteases. Since it has been suggested that NETs may be caused by an inability to correctly regulate apoptosis, the possibility that dysfunction of ICE family proteins and other proteins of BCL-2 family could be involved in these tumors clearly merits further investigation.

In mammals, apart from these three group of genes that are involved in the actual killing of the cell, there are other signal transduction pathways involved in the regulation of apoptosis. Current evidence indicates that the signal transduction pathways for controlling apoptosis and the cell cycle overlap and under certain circumstaces, cyclin and cyclin dependent kinases (CDKs) seem to be required for apoptosis (Rubin et al., 1994). Evidence supporting involvement of deregulation of the cell cycle with induction of apoptosis comes from analysis of cell cycle proteins in apoptotic cells. The activation of cyclin/CDK complexes during apoptosis has been observed in a number of differentiated cell types, including in rat pheochromocytoma cells (PC12 cells) (Park et al., 1996; Dobashi et al., 1998). Moreover, recent studies have demonstrated the alterations of some CDKs and CDK inhibitors in some NETs (Maelandsmo et al., 1996; Wang et al., 1996a-d; Lloyd et al., 1997; Iolascon et al., 1998; Takeuchi, 1998; Tominaga et al., 1999), suggesting that these cell cycle regulators may be also involved in the regulation of apoptotic pathway in these NETs.

Other proto-oncogenes have also been found to be involved in the signaling pathway of apoptosis. For example, the proto-oncogene c-jun is a member of the

early response gene family that initiates phenotypic changes in response to a variety of extracellular stimuli (Bohmann et al., 1987). Recently jun has been shown to be involved in the onset of programmed cell death, particularly in the area of neuronal death (Estus et al., 1994; Schlingensiepen et al., 1994). Ferrer et al. (1996) showed that strong c-Jun immunoreactivity is associated with apoptotic cell death in human tumors of the central nervous system. More recently, the expression of c-Jun has been also found in a proportion of NETs (Wang, unpublished data) indicating that the expression of c-jun may be also involved in the regulation of apoptosis in these tumors. Moreover, the cell can induce apoptosis through another pathway involving the FAS receptor and FAS ligand. This receptor is a member of the tumor necrosis factor (TNF) family (Itoh and Nagata, 1993; Tartaglia et al., 1993) and plays a prominent role in T-cell apoptosis, especially in the context of recognizing self-antigens and suppressing T-cell activity in immunologically privileged areas such as the eye (Griffith et al., 1995). In this pathway, a cell that expresses the membrane-bound FAS receptor will undergo apoptosis when it encounters the FAS ligand. Some cutaneous melanomas have taken advantage of this system to eliminate tumor-infiltrating lymphocytes by producing FAS ligand (Hahne et al., 1996). A killer T cell that happens to recognize the tumor will begin apoptosis once it enters the tumors and is exposed to the Fas ligand. In this way, the tumor is able to create its own immunologically privileged space and protect itself from any tumor surveillance that might occur.

In addition, for many years, hormonal effects on "normal" tissue homeostasis have been known although these earlier studies focused primarily on cellular proliferation and differentiation. Recently, however, it has been shown that many hormones, cytokines and growth factors act as general and/or tissue specific survival factors preventing the onset of apoptosis. In addition, many hormones and growth factors are also capable of inducing or facilitating programmed cell death under physiological or pathological conditions, or both. Steroid hormones are potent regulators of apoptosis in steroid-dependent cell types and tissues such as the mammary gland, prostate, ovary and testis. The role of glucocorticoids and sex steroids in the regulation of apoptosis were the subjects of recent reviews (Thompson, 1994; Evans-Storms and Cidlowski, 1995; Cidlowski et al., 1996; Hsu and Hsueh, 1997; Kiess and Gallaher, 1998). Interestingly, Tallett et al., (1996) showed that inhibition of neuropeptide-stimulated tyrosine phosphorylation and tyrosine kinase activity stimulates apoptosis in SCLC cells and this is through a *p53*- and BCL-2-independent mechanism. Kato et al. (1997) also reported that adrenomedullin, which is a potent vasorelaxant/hypotensive peptide isolated from human pheochromocytoma, significantly suppressed apoptosis without inducing cell proliferation in rat endothelial cells. Another study showed that the calcitonin gene-related peptide enhanced apoptosis of thymocytes (Sakuta et al., 1996). Moreover, Ohmori et al. (1999) recently showed that Bcl-2 protein expression and gut neurohormonal polypeptide/amine production in colorectal carcinomas and tumor-neighboring mucosa closely correlate to the occurrence of the tumor suggesting that Bcl-2 protein may act not only as an inhibitor of apoptosis but also as an inducer of neuroendocrine differentiation. Clearly, the neuropeptides from neuroendocrine cells or tumors may influence programmed cell death in some tissues and may be even involved in the generation of those tumors. Further studies are needed to elucidate what role apoptosis may play in these cell behaviors and the mechanism by which the neuropeptides are involved in the regulation of apoptosis.

Conclusions

Acquired resistance to apoptosis in NETs may promote clonal expansion and enhance the likelihood that subsequent mutations lead to growth or persistence of the neoplastic clone. Recent studies have demonstrated that deregulation of programmed cell death may be a critical component in the multistep tumorigenesis of NETs and that the frequent expression of the Bcl-2 oncoprotein in these tumors may contribute to their pathogenesis. The genetic complementation of simultaneously deregulated Bcl-2 and c-Myc may be implicated in the multistep tumorigenesis of human NETs.

Furthermore, because the efficacy of cytotoxic chemotherapy relies on its ability to induce programmed cell death, resistance to apoptosis typically correlates with chemoresistance, a phenomenon that is typical in NETs. Consideration of how oncogenes affect rates of cell death, in addition to augmenting growth, has already provided valuable insights into the biology of cancer. Understanding the molecular and cellular features of this process may enable the development and application of more effective and potentially curative treatment strategies in which the induction of programmed cell death is an integral component.

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