

Foreword

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Last year, the Nobel Prize in medicine was awarded to Sidney Brenner, H. Robert Horvitz, and John Sulston, in part for their elucidation of the genetics of programmed cell death using *Caenorhabditis elegans* as a model organism. It is fitting therefore that this issue of *ONCOGENE* is devoted to reviews on apoptosis, from a cancer perspective. Furthermore, I am honored to have served as organizing editor for this special edition.

The study of programmed cell death, and its morphological equivalent, apoptosis, has emerged as one of the fastest growing areas of biomedical research today, as tracked by the number of publications devoted to the topic, according to the Institute for Scientific Information. To tumor biologists, defective apoptosis is recognized as one of the six pillars upon which cancer occurs and progresses, along with defective cell cycle regulation, growth factor autonomy, overcoming senescence, angiogenesis, and cell invasion and metastasis. Defects in apoptosis contribute in several important ways to tumor pathogenesis and progression, allowing neoplastic cells to survive beyond their normally intended lifespans and thereby promoting clonal expansion, subverting the need for exogenous survival factors, providing protection from hypoxia and oxidative stress as tumor mass expands, and allowing time for accumulative genetic alterations that deregulate cell proliferation, interfere with differentiation, promote angiogenesis, and increase cell motility and invasiveness during tumor progression. Apoptosis defects are also recognized as an important complement to proto-oncogene activation, as many deregulated oncoproteins that drive cell division also trigger apoptosis (e.g. Myc; E1a; Cyclin-D1). Defects in apoptosis facilitate metastasis by allowing epithelial cells to survive in a suspended state, without attachment to extracellular matrix. They also promote resistance to the immune system, in as much as many of the weapons cytolytic T-cells (CTLs) and Natural Killer (NK) cells use for attacking tumors depend on integrity of the apoptosis machinery. Finally, cancer-associated defects in apoptosis play a role in chemoresistance and radioresistance, increasing the threshold for cell death, and thereby requiring higher doses for tumor killing.

Thus, defective apoptosis regulation is truly a fundamental aspect of the biology of cancer. Perhaps not surprisingly, it is cancer research that has provided many of the milestone discoveries that have forwarded our understanding of the fundamental molecular mechanisms responsible for apoptosis and its regulation. For example, in 1985, the first anti-apoptotic gene (*BCL-2*) was discovered by cancer researchers studying chromosomal translocations commonly found in human

lymphomas. In 1991, cancer researchers in pursuit of monoclonal antibodies that could kill tumor cells discovered the cell surface receptor, Fas (CD95; Apo1), providing the first example of a receptor system that actively triggers cell suicide and solidifying the notion that cell death can be an active, instructed decision. In the early 1990s, studies of the cytotoxic mechanisms of anti-cancer drugs provided evidence of protease involvement, with documentation of cleavage of nuclear lamins, poly-ADP ribosyl polymerase (PARP), and other cellular proteins that would later become recognized as the substrates of Caspases, a family of intracellular cysteine proteases largely responsible for apoptosis. And, in the early 1990's, research on anti-apoptotic proteins commonly over-expressed in cancer highlighted the importance of mitochondria as engines of cell death, setting the stage for an explosion of information about the step-by-step pathways that connect cellular damage and non-nuturing environments to apoptosis mechanisms, in addition to suggesting the likely possibility that many cellular organelles (e.g., endoplasmic reticulum; Golgi; nucleus) have mechanisms for sensing irreparable stress and triggering apoptotic responses.

In this issue of *ONCOGENE*, the reader will find reviews on topics intended to cover a broad spectrum of apoptosis-based research that has built upon the seminal discoveries of the past 25 years and brought us to our current state of enlightenment. The picture that should emerge from these contributions is that an intricate network of connections is being revealed by researchers, linking many facets of tumor biology to mechanisms for either promoting or suppressing apoptosis, ranging from oncogene activation and anchorage-independence, to genetic instability and metastasis. Underlying this progress in our understanding of apoptosis mechanisms is an increasingly abundant menu of options for envisioning new strategies for instructing cancer cells to commit suicide. To date, many of the strategies for promoting apoptosis of malignant cells currently available or in late phase clinical testing have targeted signaling molecules (e.g. kinases; GTPases) or transcription factors (e.g. retinoid receptors; hormone receptors) that indirectly influence the expression or activity of apoptosis-regulatory genes and proteins. However, not far behind are a variety of new agents that strike at core components of the apoptotic machinery, interceding more directly and at points closer the site of cell death commitment. Among these emerging apoptosis-based therapies are antisense oligonucleotides targeting the anti-apoptotic *BCL-2* gene (Phase III), agonistic monoclonal antibodies targeting the TNF-family death receptor, Trail-R1 (DR4) (Phase I), and small-molecule chemicals targeting IAP-family apoptosis suppressors (preclinical). Thus, while the fruits of apoptosis research

in terms of new cancer therapies are yet to be realized, we can look forward with promise and hope to a new era of cancer treatment where pharmacological restoration of apoptosis sensitivity in tumor cells makes our existing anti-cancer drugs more effective and provides

physicians and patients with new weapons to exploit in their daily battles with cancer.

John C Reed
The Burnham Institute