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Guest Editor

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Dr Dan A Liebermann obtained his Ph D degree in 1980 from the Weizmann Institute of Science, Israel and carried out his post-doctoral training at Stanford University School of Medicine, Stanford, CA, USA from 1980–1986. He worked at the University of Pennsylvania School of Medicine as an assistant professor from 1986–1993 and joined the Fels Institute for Cancer Research and Molecular Biology in 1993 where he is currently a Professor. Dr Liebermann has made major contributions in the area of hematopoietic cell differentiation and is the discoverer of MyD gene family of proteins, which play an important role in apoptosis

Apoptosis: Preface

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For almost a century it has been recognized that an intricate balance between cell proliferation, growth arrest and cell death is essential for embryonic development, as well as to maintain cell homeostasis in the adult. Yet , only since the beginning of the last decade the molecular machineries that regulate these cellular processes have started to be investigated. From an historic perspective, the incremental time course of events that have taken place to shape these lines of research is interesting. Around 1980, the discovery of cellular oncogenes has helped to focus research on cell proliferation. About 6 years later, the first tumor suppressor genes were identified, and boosted research in the molecular biology of growth suppression. It took, however, an additional 5 years until the study of cell death has caught the fascination of scientists, and turned it into one of today's hottest fields in biomedical research. Two key findings led to this development. The first is that cell death, as seen in the developing embryo and during tissue turn over in the adult, is an active and highly orchestrated process that involves distinct morphological characteristics (Kerr *et al*., 1972). The second is that this type of cell demise is genetically regulated, as initially observed in studies on cell death (*ced*) genes in the nematode *Canerhabditis elegans* (Ellis and Horvitz, 1986).

The articles assembled in this issue of Oncogene Reviews provide a comprehensive, in depth analysis of the complex biology of this process of cellular self-suicide, which has been termed programmed cell death or apoptosis (from a Greek word describing the process of leaves falling from trees).

Starting this issue is the article of Dragovich *et al*. It provides an overview of apoptosis including pathways of apoptotic signaling, cross talk among these pathways, receptors and second messengers that regulate cell death and survival, and the intracellular network of proteins that protect from or execute cell death signals.

What has been learned on the molecular nature of genetic programs that control cell death and survival, and what still remains to be determined, is highlighted by Bergmann *et al*., who describe genetic studies on programmed cell death in highly accessible invertebrate model systems. These include recent studies on genes controlling cell life and death in the nematode *Canerhabditis elegans*, and lessons learned from studies on the molecular genetics of programmed cell death in *Drosophila melanogaster*.

Reviewed by Reed is how proteins of the bcl-2 family, mammalian homologues of the nematode CED-9 protein, participate in the regulation of cell life and death.

A wide variety of apoptotic stimuli, external and internal, converge on activation of a family of cysteine proteases, termed caspases (the mammalian homologous of CED-3), which are the down stream executors of the death machinery. The article authored by Nunez *et al*. describes in detail the different types of caspases, the cascade of caspase activation by proteololytic cleavage, and how caspases function in the execution of death signals.

The Inhibitor of Apoptosis Protein (IAPs) family has recently emerged as a major player in the inhibition of apoptosis. The anti-apoptotic function of IAPs, that appears to be mediated by inhibition of caspase activation and modulation of NF-κB activity, is covered by LaCasse *et al*. Their interesting role in cancer pathology, is highlighted as well.

One well established apoptotic pathway in mammalian cells is signaling via death receptors, such as the superfamily of the tumor necrosis factor (TNF) receptors or CD95(Fas). The signal transduction pathways that mediate the function of these death receptors are analysed in detail in the articles provided by Baker and Reddy (TNF), and Varadhachary and Salgame (CD95).

A second archetypal pathway in death signaling, is the response of mammalian systems to environmental stress which results in cell injury and DNA damage. The role of ceramide and c-*jun* kinase in mediating stress signals is described in the article of Basu and Kolesnick. Nuclear factors that co-operate in the mammalian response to DNA damage include the tumor suppressor gene *p53*, the ataxia -telangiectasia mutated (ATM) gene, and the c-*abl* proto-oncogene. Their functions in DNA damage signaling is reviewed by Amundson *et al*. (*p53*), Canman and Lim (ATM), and Kharbanda, *et al*. (c-*abl*).

Terminal differentiation represents a distinct form of negative growth control, where in tissues with rapid cell turnover growth arrested and terminally differentiated cells undergo programmed cell death. The article of Liebermann and Hoffman describes the functions of proteins encoded by genes identified as Myeloid Differentiation primary response (MyD) genes (IRF-1, AP-1, EGR-1, MyD88, MyD116, and MyD118) in negative growth control of many cell types.

Interferon -γ is a strong apoptotic agent for some cell types. The article authored by Levy-Strumpf *et al*., describes the apoptotic roles of genes encoding for novel Death Associated Proteins (DAP-kinase, DAP-3, DAP-1, DAP-5) that were isolated as the result of a molecular genetic approach to identify genes which mediate interefron-γ induced apoptosis. The apopotic

role of cathepsin D, a known protease identified by this procedure, is highlighted as well.

Understanding the death pathways which are caused by ischemia and reperfusion, as seen during arterial occlusion, shock, and organ transplantation is of clinical importance. Thus, the article of Saikumar *et al*. provides an inquiring look at the role of apoptosis versus necrosis and mechanisms that mediate cell killing during these different types of tissue injury.

It has become evident that cancer therapy unknowingly has been based on the higher sensitivity of malignant cells, compared to their normal counterparts, to apoptosis induced by anti cancer agents. In recent years it has been recognized that oncogenic mutations that play a role in cancer development, also sensitize cancer cells to apoptosis. Expanding on this team, Hoffman and Liebermann. discuss how deregulated c-*myc* may sensitize cells to undergo programmed cell death, whereas Muschel *et al*. take an inquiring look at the role of oncogenes in the altered radiosensitivity and apopotsis of tumor cells.

Apoptosis and growth suppression are interrelated processes that cooperate to negatively regulate cell proliferation. Thus, also review articles whose main team is growth suppression have been included. Along these lines, Grana *et al*. take a look at the role of proteins of the retinoblastoma family, including pRB, pl07 and pl30, in negative growth control, whereas Ghebranious and Donehower discuss mechanistic insights that have been gained by using tumor suppressor-deficient mice and their usefulness as model systems for human cancer.

References

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