INTRODUCTION

Spotlight on apoptosis

Apoptosis, perhaps one of the most fashionable words in the biological sciences, is especially relevant to hematology and oncology. In this and following issues of *Leukemia*, 'Spotlight on Apoptosis' will review and discuss the current developments in this rapidly evolving field. Although these initial reviews were invited, all readers are encouraged to participate and offer their points of view.

A deeper understanding of the mechanisms underlying apoptotic cell death should lend considerable insight into the origins and progression of cancer and leukemia. Even more importantly that induction of apoptosis in tumor cells is currently considered as a goal of chemotherapy in cancer and leukemia. Ironically, the rapid progress of apoptosis research has also left some key topics undiscussed, and has led in some cases to tremendous confusion. For instance, besides tissue necrosis, are there alternatives to apoptotic death? Surprisingly, although extensively described, apoptosis has no absolute, precise definition. Unless apoptosis and its alternatives are clearly defined, the role of apoptosis in cancer therapy cannot be accurately evaluated. A biochemical definition of apoptosis as caspase-mediated cell death is emerging, and this allows some distinction from cell death occurring in the absence of caspase activation. From this perspective, I will address the dilemma of apoptotic cell death vs non-apoptotic cell death. Frequently, cell death without caspase activation is induced by chemotherapy drugs and by physiological stimuli. I will also discuss the paradoxical ability of some oncogenes such as Ras and Raf as well as growth factors to inhibit apoptosis on the one hand, while promoting non-apoptotic slow cell death on the other hand.

While inhibition of caspase proteases can significantly delay apoptosis, most cells will eventually succumb to a death stimulus. Recent evidence indicates that several non-caspase proteases may participate in apoptotic cell death. A review by Dr D Johnson (USA) will examine the participation of non-caspase proteases in apoptotic execution, and will comment on the integration of pathways initiated by non-caspase proteases with those initiated by caspases.

Cell death can occur without caspase activation, likewise, caspase activation can occur without cell death. Activation of these proteases in the absence of cell death is a physiological process which plays an important role in the proper functioning of the lymphoid system. How does caspase activation regulate development of lymphoid system and what is the role of caspases in the response of tumours of lymphoid origin to treatment? The review by Drs Fadeel, Orrenius and Zhivotovsky (Sweden) will provide insight into these two fascinating phenomena.

The curability of some forms of leukemia and lymphoma, testicular carcinoma and some other malignancies may be related to the capacity of the cancerous cells to undergo apoptosis following chemotherapy. This has fueled the notion

that induction of apoptosis should be a primary goal of cancer therapy. While the mechanism of growth arrest by common chemotherapy drugs is fairly well understood, many questions remain regarding the mechanisms of chemotherapy-induced cell death. The current state of knowledge concerning chemotherapy-induced apoptosis will be discussed by Dr Solary (France).

Caspase activation and the progression of apoptotic events can be regulated on multiple levels by members of the Bcl-2 protein family and by kinases including Bcr-Abl. The role of post-translational modifications of Bcl-2 family members in the regulation of resistance to chemotherapy, however, remains somewhat disputable. The review on anti-apoptotic oncogenes and regulation of progression of apoptosis caused by anti-cancer drugs will clarify important issues pertaining to the topic of regulation of chemotherapy-induced apoptosis.

An increased knowledge of apoptosis signal transduction pathways should lead to the development of novel small molecules which target these pathways. Recent studies have shown that drugs such as the kinase inhibitor flavipiridol, UCN-01, proteasome inhibitors, PS-341, are very potent inducers of apoptosis. These and other experimental therapeutics which are currently in clinical trials will be discussed in the review by Dr Senderowicz (USA).

Apoptosis can result from caspase activation following treatment with chemotherapy drugs or following stimulation of cell surface death receptors. Leukemic cells often originate from cells that are sensitive to death ligands such as FasL, TNF and TRAIL, partially explaining the apoptosis-prone phenotype of these cells. Importantly, it appears that death receptors and death ligands may be regulated by p53 and by DNA damaging drugs, and both p53 and drugs may induce common downstream pathways with positive feedback loops. The relationship between death receptors and p53-dependent pathways activated by DNA damage will be discussed in the following review by Drs Saeed Sheikh and Fornace (USA).

Other studies have shown that nitric oxide interacts with apoptosis pathways and can decrease or increase sensitivity to apoptosis, depending on a number of factors. The expression of nitric oxide synthetase in leukemic cells and the anti-apoptotic activity of nitric oxide will be reviewed by Dr JP Kolb (France).

Lastly, resistance or sensitivity to apoptosis is also determined by the activity of cellular kinases. As the best known example, Bcr-Abl may determine resistance to chemotherapeutic drugs by affecting cytochrome C/caspase-9 activation. Recent advances concerning the action of other kinases as negative or positive regulators of apoptosis will be discussed in the review by Drs RA Franklin and JA McCubrey (USA). Cellular kinases and phosphatases participate in signaling cascades that influence this process. In particular, this review will discuss the ability of the CaM-kinases, I κ B kinases, PI3-kinases, and the MAP kinase signaling pathways (ERK, JNK and p38), to influence apoptotic processes in hematopoietic cells.

As we continue to increase our understanding of apoptosis pathways and regulation, we can anticipate the development of novel therapeutics targeting apoptotic mechanisms. Such therapies should prove useful in the treatment of a variety of different cancers, including leukemias and lymphomas. Moreover, it should become possible to more successfully combat

neoplastic diseases which have become apoptosis-resistant, and hence, drug-resistant.

MV Blagosklonny
Medicine Branch, NCI
NIH, Bethesda, MD 20982, USA