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BOOK REVIEW

Apoptosis and Inflammation

(J. D. Winkler, ed., Birkhäeuser Verlag, Basel-Boston-Berlin, 1999)

The book *Apoptosis and Inflammation* (edited by J. D. Winkler) contains an introduction and twelve chapters.

The editor's introduction "Apoptosis in inflammatory cells and diseases" contains a description of general features of apoptosis and its regulation as well as its role in normal physiology and in pathology. The introduction is intended to direct readers to reviews and other references that are outside the scope of this book.

The chapters of the book can be divided into three groups. The first two chapters refer to the study of signals that initialize apoptosis, especially in inflamed tissues. Among these signals are some growth factors and arachidonate metabolites.

Data on the phenomenology of apoptosis and necrosis are compared in the chapter of C. L. Mann and J. A. Cidlovski "Signaling cascades of apoptosis". Here one finds descriptions of intracellular signal cascades from such initiators of apoptosis in the immune system as glucocorticoids, FAS-type receptors related to the family of TNF (tumor necrosis factor) receptors, and TCR (T-cell receptors) as well as of inhibitors of apoptosis such as FLIP and bcl-2.

The release of arachidonic acid from phospholipids catalyzed by several types of phospholipase A_2 is treated at some length in the chapter of F. H. Chilton, III, F. H. Chilton, Jr., C. L. Clay, A. Trimboli, and A. N. Fonteh "Influence of arachidonic acid metabolism on cell proliferation and apoptosis". This chapter makes special emphasis on oxidative metabolism of the substance both via cyclooxygenase- and lipoxygenase-mediated pathways.

Apoptosis in several types of cells such as lymphocytes, granulocytes, hematopoietic cells, chondrocytes, and keratinocytes both in normal and pathological conditions is discussed in the next five chapters.

The perforin/granzyme-, Fas/FasL-, and TNF-dependent mechanisms of regulation of apoptosis by T-cells are considered by J. H. Russel in his chapter "Apoptosis in the regulation and function of T and B lymphocytes in inflammation". The participation of T and B cells in autoimmune diseases and susceptibility of cells to apoptosis are also given some attention.

The implication of apoptosis in elimination of granulocytes from inflamed tissues, data on the lifespans of neutrophils and eosinophils as well as on the peculiarity of apoptosis in these cells, on participation of phagocytes in removal of granulocytes and their degradation products from tissues during apoptosis, and on the mechanisms of initiation and inhibition of apoptosis in granulocytes are discussed in the chapter "Granulocytes" authored by J. Savill and C. Haslett.

The authors of the chapter "Hematopoietic cells", D. J. Park and M. J. Koury, demonstrate how apoptosis participates in the maintenance of the number of circulating blood cells after bringing into operation mechanisms of action of cytokines produced by the cells and discusses the negative regulatory loop in the cytokine action network. They present some evidence concerning the maintenance of equilibrium between processes of cell proliferation (in the course of myelopoiesis, erythropoiesis, and thrombopoiesis) and apoptosis of corresponding stem cells.

Data on the role of the regulation of apoptosis in the maintenance of functioning of cartilage tissue under normal conditions and in such diseases as rheumatoid arthritis and osteoarthritis are given in the chapter of M. Lotz, S. Hashimoto, R. Ochs, and K. Kuehn, "Chondrocyte apoptosis". The evidence on such inducers of apoptosis as Fas and NO and on the participation of mitochondria in the processes of chondrocyte calcification and mineralization are also presented in the chapter with special emphasis on the role of apoptotic bodies in cartilage tissue metabolism.

The chapter "Keratinocytes" authored by D. A. Norris, Y. Shellman, and G. A. Bellus focuses on keratinocyte location, functions and differentiation, factors of initiation and suppression of apoptosis, and peculiarities of apoptosis in keratinocytes during differentiation as well as under ultraviolet radiation and activation of the immune system, particularly in the case of immune cytotoxicity and immunological skin diseases. The view that epidermis is not a uniform structure in relation to apoptosis in keratinocytes is justified by the different susceptibility of the cells in different layers of skin to inducers of or protectors from apoptosis.

The last five chapters describe some manifestations of disturbances in apoptosis or its individual processes in some immune and inflammatory diseases such as rheumatoid arthritis, lupus and lupus-like syndromes, osteoarthritis, psoriasis, and inflammatory renal diseases.

The chapter of P. P. Tak and G. S. Firestein "Apoptosis in rheumatoid arthritis" focuses on the reac-

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tion of T-cells, especially $CD4^+$ cells, that take part in the immune response of patients with rheumatoid arthritis. The authors consider that macrophages, fibroblast-like synoviocytes, and pannocytes can be draw into the inflammation at a latter stage and play a role in destruction of connective tissue cells through the induction of apoptosis by cytokines, proteases, and NO.

Apart from the inducers of apoptosis mentioned above, the Fas/FasL-interaction, perforin/granzyme mechanism, TNF_α, as well as oxygen radicals and some transcription factors (c-myc, c-fos, and wild type of p53) have been implicated in rheumatoid arthritis. The genes *bcl-2* and *ras* as well as the soluble Fas that compete with Fas of the cell surface in binding with FasL are seen as anti-apoptotic factors. The regulation of apoptosis in fibroblast-like synoviocytes and T-cells is outlined. Therapeutic strategies including gene therapy based on induction of apoptosis are suggested.

The chapter of M. E. Nuttall, M. Gowen, and M. W. Lark "Apoptosis and inflammatory disease: osteoarthritis" discusses the phenomenon of apoptosis in chondrocytes *in vitro* and *in vivo* as well as transgenic models that provide support for the implicit role of apoptosis in maintenance of homeostasis in cartilage tissue. The authors consider the interplay between apoptosis in chondrocytes and degradation of cartilage matrix in osteoarthritis. They conclude that blocking chondrocyte apoptosis while retaining general apoptosis that is required for cartilage homeostasis might be therapeutic strategy for osteoarthritis.

The chapter of G. G. Song, M. Fleck, J. Wu, H.-C. Hsu, and J. D. Mountz "Lupus and lupus-like syndromes" discusses genetic defects that result in defective apoptosis of inflammatory tissue cells in systemic lupus erythromatosis or lupus-like autoimmune syndromes such as autoimmune-lymphoproliferative syndrome disease. The authors focus on the *Fas* and *FasL* genes as well as the genes of proteins associated with Fas such as TNFR1 (tumor necrosis factor receptor type 1) that contain a death domain or FLICE (interleukin-1_β-converting enzyme). The mutations in genes of bcl-2 and soluble Fas also receive some attention.

Evidence concerning other genetic factors that influence apoptosis in immune system cells (especially in lupus) are presented. Data on autoimmune antibodies that are raised in response to UV radiation, viral infections, etc. and serve as apoptosis initiation signals are summarized in the chapter. The schematic pathways of apoptosis both under normal conditions and in autoimmune diseases such as systemic lupus erythromatosis are shown.

The chapter of C. A. Raskin "Psoriasis and apoptosis: a fundamental analysis of the psoriatic phenotype with clinical and therapeutic correlations" describes clinical manifestations of this disease and evidence on genetic predisposition to the disease along with a triggering role of some environmental factors such as stresses and infections. The author considers that the histological data point to altered keratinocyte maturation during their transformation into corneocytes. The changes are induced by some distortions in programmed cell death, especially by a discrepancy between expression of inhibitor of endogenous endonucleases and keratinocyte differentiation. Among the changes, accelerated proliferation of keratinocytes in psoriasis are highlighted, this leading to changes in differentiation, pushing upwards though the epidermis of individual keratinocytes, elimination of the granular layer, and hyperplasia of psoriasis plaques. Explanations are provided how the hyperexpression of EGF (epidermal growth factor) and TGF (transforming growth factor) receptors as well as aberrant expression of integrins in the suprabasal layer lead to protection of keratinocytes from apoptosis. The integrins act through induction of hyperexpression of *bcl-*x_L that to the *bcl-2* family is an inhibitor of apoptosis and is normally expressed *in vivo* in the basal layer. It is noted that in psoriasis altered localization of expression of IGFBP-3 (insulin-like growth factor binding protein-3) that has intrinsic growth inhibiting properties and leads to terminal differentiation of cells and could result in the observed hyperplasia of skin growths. It has been noted that psoriatic keratinocytes appear to be resistant to IFN_γ (interferon γ) that could act through expression of TGF and ICAM-1 (intracellular molecules of cell adhesion). The production of TNF_α in psoriasis is indicated through all epidermal layers while in health this factor is produced only in the basal layer. The therapeutic effects of UV radiation, cyclosporin A, derivatives of vitamin D, and glucocorticoids in psoriasis are discussed in connection with regulatory influences of these factors on apoptosis in keratinocytes and other epidermal cells including lymphocytes.

The chapter of V. Y. Wong, S. M. Ali, and D. P. Brooks "Apoptosis in renal disease" summarizes evidence concerning the role of changes in apoptosis in such renal diseases as PKD (polycystic kidney disease), acute tubular necrosis, glomerulonephritis, glomerulosclerosis, and human immunodeficiency virus associated nephropathy (HIVAN). The authors have presented some morphological and genetic characteristics of PKD and noted abnormal proliferation of epithelium and altered regulation of apoptosis including abnormal expression of *c-mic* and *bcl-2*. In acute tubular necrosis, the authors indicate altered expression of *c-mic* along with the altered expression of *Fas*. Histological evidence for altered apoptosis in endothelial cells was found in glomerulonephritis and glomerulosclerosis of different etiologies. Increased apoptosis in tubules of patients with HIVAN was observed. This evidence is discussed in relation to induction of apoptosis by the virus envelope protein gp160 via inhibition of *bcl-2* expression.

P. V. Gulak