Molecular Exploitation of Apoptosis Pathways in Prostate Cancer

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MOLECULAR EXPLOITATION OF APOPTOSIS PATHWAYS
IN PROSTATE CANCER

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For all the men fighting prostate cancer
and
in memory of those who lost the battle

- 21 αἱ μὲν περιρρηγξίαι ταχεῖαι, αἱ δὲ τῶν ὀστέων **ἀποπτώ-**
σις, ἣ ἂν τὰ θρία τῆς ψιλώσιος ἦ, ταύτη ἀποπίπτουσι,³⁷⁸
 βραδύτερον δέ.* χρόν δὲ τὰ κατωτέρω τοῦ τρώματος
 καὶ τοῦ σώματος τοῦ ὑγιέος προσαφαιρεῖν — προ-
 θνήσκει γὰρ — φυλασσόμενον ὀδύνῃν· ἅμα γὰρ λει-
 ποθυμῇ θνήσκουσι. μηροῦ ὀστέον ἐκ τοιούτου ἀπε-
 λύθη ὀγδοηκοσταῖον, ἡ δὲ κνήμη ἀφηρέθη εἰκοσταίῃ,

Copy of the original text in Chapter 35 of *ΜΟΧΛΙΚΟΝ* (378–376 BCE), a book attributed to Hippocrates that deals with the instruments for the reduction of fractures and dislocations, according to the transcription of Kuehlewein (see Hippocrates, 1928). The word corresponding to *apoptosis* — in the plural case — is boxed. In the translation below, this word is given in italics [*identifies the end of the translation]. “In cases of fractured bones, lines of demarcation form quickly, and the *falling off* of the bones occurs, where the limits of the denudation may happen so that the bones are falling off, but more slowly.”

Preface

As we witness the end of the first decade of the 21st century, the questions we cancer researchers are most frequently asked are: when we are going to find the cure for cancer; and why we have not found it yet? At national and international conferences we see that data are interpreted at a more assertive rhythm and answers at the genetic and cellular level are generated at a similar pace, moving basic research forward into the oncology clinics and cancer centers globally. Recognized by the major funding agencies in the United States, Europe, Australia, and Japan as a top priority focus, cancer research drives translational applications from the bench to the clinic at a phenomenal rate, impacting therapeutic outcomes and affecting the lives of millions around the world. Yet, we still cannot declare with any degree of confidence to the scientific community that we have found the cure for cancer. The task is most challenging, the expectations are high, and the patience for clinically meaningful answers is running thin. These notions are translated by the public into a belief that powerful technology-driven research and long-term investment in the most talented scientific minds have yet to deliver cures, improve diagnosis, and increase patient survival. There is a general assumption that the complexity of cancer — both as a biological phenomenon and as a life-threatening disease — presents major obstacles in the fight to deliver an effective cure and maximally impact patient survival and quality of life after cancer; nevertheless there have been tremendous strides in research that lead to new treatments. An understanding that uncontrolled tumor growth is due not only to aberrant cell proliferation, but also to an imbalance between cell proliferation and programmed cell death, opened many exciting avenues for therapeutic investigations by selectively targeting apoptosis among the tumor cells.

Apoptosis, identified as a biological process vital to the well-being of an organism and defined as a genetically programmed phenomenon less than forty years ago, holds tremendous promise for the treatment of cancer in its molecular

core. The characteristic analogy that gained popular use in the 1980s and early 1990s was the description of the “falling of the leaves from the trees in the autumn” (from the Greek for “falling from”: *apo ptosis*). When I joined the John Isaacs laboratory at Johns Hopkins Oncology Center in 1986, the genetically regulated phenomenon of programmed cell death was being investigated at the mechanistic level in thymocytes after γ -irradiation or glucocorticoid treatment, by a pioneer Russian scientist, Dr Umansky (Umansky, Korol and Lelipovich, 1981; Umansky, 1982). This was distinctly different from the non-specific, randomly occurring process of necrosis that was not activated by any death stimulus but rather reflected the “collapse” of the cell in a non-programmed manner. The only measure of activation of programmed cell death was the fragmentation of DNA into nucleosomal-sized fragments. My research task was to determine whether androgen deprivation of the normal and malignant prostate leads to activation of programmed cell death and tissue involution. It was the beginning of a most exciting journey: the exposure to an intellectually rich environment, working with a brilliant mentor, to find ways to kill cancer cells and to promote the development of therapeutic regimes to treat patients with prostate cancer. More than two decades later, those inaugural experiences in activating cell-suicidal mechanisms for anti-tumor action in human cancers gave rise to molecular advances in the field of apoptosis, licensing investigators to explore beyond the boundaries of the current understanding of cancer development and clinical management of this life-threatening disease. Prostate cancer is a significant burden on men’s health. It is a major cause of mortality in American men and a major contributor to all male cancer mortality in the United States and Western countries. Although patients with localized prostate cancer can survive for a long period, a large percentage of prostate cancer patients are diagnosed with advanced metastatic disease, or develop skeletal metastases. Prostate cancer metastasis to the skeleton and bone dramatically lowers the patient’s routine activities and lifestyle and severely threatens his life. Castration-resistant prostate cancer (CRPC) (formerly known as androgen-independent prostate cancer) is the lethal stage of the disease and responsible for 30,000 deaths each year in the United States. This monograph was written in the hope and anticipation of translating current understanding of the molecular regulation of programmed mechanisms of cell death into a discovery platform, to allow pharmacologic exploitation of effective therapeutic modalities to conquer metastatic, castration-resistant prostate cancer.

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