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Apoptosis Versus Necrosis: Which Should Be the Aim of Cancer Therapy? (44388)

HIPPOKRATIS KIARIS AND ANDREW V. SCHALLY[1]

Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center and Section of Experimental Medicine, Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70112

Since the discovery of apoptosis (1) and its potential implications for the treatment of cancer, various investigators have devoted their efforts to the development of novel, apoptosis-based, therapeutic strategies. Among various approaches being tried is the synthesis of chemotherapeutic agents (cytotoxic or noncytotoxic) capable of inducing apoptosis in apoptosis-susceptible tumor cells. Other advances aimed at overcoming the presence of apoptosis-resistant cells are based on the manipulation of the genetic material of the cancer cells (gene therapy). This approach could theoretically ensure the stimulation of the programmed cell death pathway in response to the appropriate signals (irradiation, cytotoxic drugs, etc.). Thus, tumor cells that showed resistance to certain apoptosis-inducing agents before the treatment, can become sensitive to these agents after the introduction of the normal alleles of genes that control major apoptotic pathways. Although these procedures are generally successful in the usual laboratory assays, certain disadvantages are apparent considering the mechanism of action of various drugs and their capacity to kill human tumor cells *in vivo*.

Compared to normal cells, cancer cells are characterized by an elevated endogenous mutation rate (2), which frequently increases further after treatment with certain cytotoxic drugs, such as DNA-damaging agents. Thus, the development of drug resistance is predictable and certainly clinically demonstrable. In certain cases this is accompanied by the acquisition of a mutator phenotype as indicated by the microsatellite instability exhibited by drug-resistant cells (3). In addition to the increased mutation rate, primary tumors are also characterized by genetic heterogeneity that increases the possibilities for the selection of drug-resistant clones. Apoptosis is a complex process requiring an orchestrated cascade of multiple biochemical transduction events, and nearly every gene involved is a potential target for conferring drug resistance because of the increased incidence of DNA damage and, consequently, the mutation rate. Within this context, tumors resistant to anticancer treatment actually result from selected cells that are defective in major apoptotic pathways (4, 5). Mutations in specific genetic loci are selected on the basis of their capacity to confer an apoptosis-resistant phenotype (4, 5), or simply such anticancer treatments fail because selected cells are resistant to apoptosis. Thus, such strategies, even if they succeed in bypassing the initial cell-cycle arrest, may result in only a temporary decrease in the rate of the tumor growth instead of a cure.

In contrast to apoptosis, a rapid induction of necrosis may provide a more efficacious approach for the development of novel therapeutic strategies for the treatment of cancer. Necrosis is not an active cell process and does not require energy. Theoretically, the necrotic process can better fend off the development of resistance due to its rapid and vigorous nature, although its cascade remains transductionally undefined. Such a hypothesis can be tested: Agents that induce necrosis or apoptosis, when administered at doses that cause comparable effects on the viability of the cells, as evidenced by the inhibition of cell growth or the colony formation *in vitro*, should display dramatic differences in the rate of development of resistant cell clones. Furthermore, agents that induce necrosis should exhibit a wider spectrum of action, in various cell models, regardless of the genetic status of particular genes that control the cell

[1] To whom requests for reprints should be addressed at Endocrine, Polypeptide and Cancer Institute, VA Medical Center, 1601 Perdido Street, New Orleans, LA 70112–1262.

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cycle check-points and which determine the efficacy of the apoptosis-associated cancer therapies (4, 5). It is well-known that, in the case of the same drug, the induction of necrosis usually requires higher doses than those that are needed for apoptotic death. Many drugs that produce apoptosis, such as antitumor peptides, are receptor-dependent and are used in doses that do not cause toxicity like necrotic cell death (6). Necrosis-inducing drugs exhibit a higher toxicity; however, a targeted delivery of these drugs directly to tumors may overcome or at least substantially diminish such disadvantages (7–12). Our own work on brain tumors and lung cancer suggests that 2-pyrrolinodoxorubicin (7), a superactive derivative of doxorubicin, induces necrosis rather than apoptosis, regardless of the genetic status of the tumor cells, and exhibits stronger antitumor action than doxorubicin, which is known to induce apoptosis (Kiaris and Schally, in preparation).

Our views regarding the therapeutic efficacy of necrosis- versus apoptosis-inducing agents are supported by the observations of Cope and Tomei on the differential kinetics of nuclear versus cytoplasmic effects in the induction of apoptosis (13, 14). These investigations demonstrated the potential for differential rates of mutations affecting apoptotic and necrotic pathways (13, 14). In addition, they also showed that although the induction of necrosis is not directly linked to apoptosis, it is a process that shares a cascade of events with apoptosis (13, 14).

Presently, many fundamental differences between apoptosis and necrosis remain unknown, but future research should re-evaluate the potential of necrosis in cancer treatment and provide appropriate clinical settings for chemotherapy targeted to tumors.

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