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Mini Review

Cell death pathology: Perspective for human diseases

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ABSTRACT

Apoptosis, a genetically regulated form of cell death with distinct biochemical and morphological features, plays a relevant physiological and pathological role in the organism, being pivotal in the maintenance of tissue development and homeostasis in the adult as well as in the regulation of immune responses. Deregulation of this process causes several human disorders including cancer, autoimmune and neurodegenerative diseases. Thus, modulation of the apoptotic process and of cell death in general, is a potential therapeutic approach for the treatment of several human pathologies.

1. Introduction

Since 1965, when the first description of programmed cell death was independently made by Richard Lockshin and John Kerr, searching for the term apoptosis on PubMed yields 206,244 papers. Indeed, during the last year, nearly 20,000 papers have been published using the same search term, indicating that apoptosis remains a major interest in science, accounting for over 3% of all scientific publications. This is what John Kerr [1,2] originally wrote, suggesting the involvement of apoptosis at both physiological and pathological levels:

> "Apoptosis seems to be involved in cell turnover in many healthy adult tissues and is responsible for focal elimination of cells during normal embryonic development. It occurs spontaneously in untreated malignant neoplasms, and participates in at least some types of therapeutically induced tumour regression. It is implicated in both physiological involution and atrophy of various tissues and organs. It can also be triggered by noxious agents, both in the embryo and adult animal."

At the present time, a long list of pathologies is associated with deregulation of apoptosis, including cancer (carcinoma, sarcoma, leukemia, lymphoma, and myeloma), autoimmune diseases (systemic lupus erythematosus, immune-mediated thrombocytopenia, autoimmune neutropenia, glomerulonephritis, rheumatoid arthritis, Hashimoto's thyroiditis, insulin dependent diabetes mellitus, and multiple sclerosis) and viral infections (Poxvirus, Adenovirus, and Herpesvirus). In contrast, excessive apoptosis has been associated, for example, with neurodegenerative disorders (Parkinson's, Alzheimer's, Huntington's [3], amyotrophic lateral sclerosis, cerebellar degeneration, status epilepticus [4], prion disease [5], glaucoma [6,7], diabetic retinophaty [8], retinitis pigmentosa [9], and spinal muscular atrophy), AIDS, liver disease, haematological diseases and ischemic injury (hypoxia-ischemia [10], stroke [11], and myocardial infarction). In 45 years of research on cell death, we have also learned that modulation of apoptosis could be useful in the treatment of these different pathologies. Indeed, control of cancer through the induction of apoptosis is the main therapeutic approach in the clinic [12–15]. Correspondingly, the prevention or delay of apoptosis would seem appropriate in diseases where excessive cell death is present, such as neurodegenerative disorders [16,17].

2. Is cell death finished?

For the first time in the last 25 years, the number of publications in cell death has not increased. Does this decline mean the beginning of the end for the cell death field? In fact, the number of papers on, *sensu strictu*, the basic molecular mechanisms of cell death is decreasing. The real reason for this apparent decline is the

Abbreviations: AIDS, acquired immune deficiency syndrome; TIAF1, TGFβ-induced anti-apoptotic factor 1; TGFβ, transforming growth factor beta; AD, Alzheimer disease; APP, amyloid precursor protein; PD, Parkinson's disease; NSC, neural stem cells; AICD, activation induced cell death; HIV, human immunodeficiency virus.

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Table 1
Apoptosis-based clinical trials.

Target	Reagent	Principle	Company	Effects	Trial status
TRAIL	HGS-ETR1	Agonist TRAIL-R1 mAb	HGS	Apoptosis induction	Phase II Completed Carcinoma Non-Small-Cell Lung Lymphoma
	HGS-ETR2	Agonist TRAIL-R2 mAb	HGS	Apoptosis induction	Phase I Kidney Cancer Lymphoma Neuroblastoma
	PRO1762	Soluble human Apo2L/TRAIL	Amgen	Apoptosis induction	Phase I Solid Tumor Non-Hodgkin Lymphoma
	TRA-8	Agonist TRAIL-R2 mAb		Apoptosis induction	Phase II Ovarian Cancer
CD95	CD95-Fc	Humanized CD95 Fc-decoy construct	ApoGenix	Inhibition of CD95 signaling	Phase II Glioblastoma Phase I GvDH
SMAC	AT-406	XIAP-Smac mimetic	Ascenta Therapeutics	Tumor suppression	Phase I Solid Tumor Lymphoma
	AEG35156	XIAP antisense oligonucleotide	Ascenta Therapeutics	Antitumor activity	Phase I/II Terminated Human mammary Carcinoma Phase I Terminated Advanced cancer
	Low MW SMAC mimetc (LBW247)	Inhibitors of XIAP, cIAP-1 and 2			Phase Ib Clinical trials
SURVIVIN	LY2181308	Survivin antisense	Eli Lilly	Antitumor activity	Phase II Completed, In combination therapy in AML Phase I/II withdrawn Hepatocellular Carcinoma
MPT	Lonidamine	Dichlorinated indazole-3-carboxil acid derivate	Threshold Pharmaceuticals	Permeabilize mitochondria	Phase II/III Terminated Beningn Prostatic Hyperplasia
	Cladribine (Litak)	2-chloro-2′ dexyadenosine		Apoptosis induction	Approved for Hairy-cell leukemia
	Verterporfin	Porphyrin photosensitizer		Triggering of cytochrome c release	Phase II/III Photodynamic therapy, Advanced Pancreatic Cancer
	Betulinic acid	Pentacyclic triterpenoid		Inducer of apoptosis	Phase I/II Dysplastic Nevus Syndrome
ANTI-APOPTOTIC Bcl2 MEMBERS	Genasense	Bcl-2 antisense oligonucleotides	Genta		Phase III Advanced Melanoma CLL Phase II Non-Hodgkin Lymphoma
p53	INGN201	p53-expressing adenovirus	Introgen Therapeutics	Apoptosis Induction	Phase III Completed In combination therapy in Breast Cancer
	SCH58500	p53-expressing adenovirus	Schering-Plough	Apoptosis Induction	Phase I Completed Ovarian Cancer Phase III completed, In combination therapy in Ovarian Cancer
	ONYX-015	p53 delivery adenovirus	Onyx	Antitumor activity	Withdrawn
	Amifostine	Restoration of p53	AstraZeneca	Restores function of mutant p53	Phase II/IV Completed, Colorectal Head and Neck, Lung Cancer
Proteasome inhibitors	Epoxomicin	Streptomyces epoxyketone	Onyx	Apoptotic effect	Carfilzomib analog of epoxomocin Phase I/II Multiple Myeloma

Example of clinical trials on cell death targets, approved by US NIH (http://clinicaltrials.gov/).

reduced number of basic articles on caspases, on the molecular mechanisms of the Bcl2 family, on IAPs and so on. Conversely, publication on the translational aspects of cell death, such as cardiovascular diseases, neurodegenerative pathology and applied oncology, is in fact increasing. Therefore there is a shift from the basic mechanisms towards its translational aspects. Consequently a large number of publications are no longer classified in the apoptosis category, but fall under categories such as cardiology, immunology, oncology and neurodegeneration. At the same time there is a significant effort to develop pharmacological regulators of cell death in these different pathologies, based on particular mechanisms such as inhibitors of Bcl2, IAPs, caspases, p53 and mitochondrial permeabilization [18–20]. Table 1 shows a simplified highlight of some of the clinical trials using regulators of the cell death pathways.

However, the main mechanisms of cell death have not been fully clarified at the molecular level. For example, the mechanism of action of Bcl2 is far from clear; so is the function of Bax and Bak. Consequently, many questions remain open not only on the Bcl2 family but also on death receptor signaling, IAPs and several caspases. The impression that we know all about cell death should be compared to the late XX century, early XIX century physics, before Albert Einstein and Richard Feynman. So, several crucial mechanistic points await clarification and possibly pharmacological exploitation.

Last but not least, an incremental understanding has occurred in alternative regulatory mechanisms. Autophagy has exploded with a revival of flourishing molecular details [21–28]. And a similar expansion is occurring in less known death pathways such as for example pyroptosis, necroptosis or the Wallerian degeneration.

The consequence of this clinical trend of the cell death field is that it becomes more diffuse and less focused, resulting in less "cell death" meetings and more sessions in all specialist medical meetings. It is however pivotal to maintain a central focus for discussions of distinct pathways, pharmaceutical exploitation and pathological applications.

One thing is definitely clear. The fashion of cell death has ended, and, as expected, the cover page has been temporarily been taken by stem cells and a molecular revival of cancer metabolism. But is not this positive?

Hence, the question "is cell death finished?" is erroneously proposed. The more appropriate formulation should be "how is cell death evolving?", or "has cell death become translational?"

3. Apoptosis in cancer

If we ask a student an example of pathology that is associated with defective cell death, the most frequent answer would be cancer. Indeed, evasion of apoptosis is one of the basic features of cancer [29]. A large number of papers have described the underlying molecular mechanisms [30–32]. According to the histological National Cancer Institute classification, cancer can be classified in five major categories: carcinoma, sarcoma, myeloma, leukemia and lymphoma. Focusing only on 2010, apoptosis is present in all cancer types, being predominant in carcinoma [33–37] and leukemia [38–40] (Fig. 1A). Thus, despite the fact that leukemia accounts for just 3% of all cancer cases [41], it is the second most investigated cancer from the apoptotic point of view. Looking at carcinomas, that accounts for about 80% of all cancer cases; the number of publications in 2010 in each cancer hallmark (evading apoptosis, tissue invasion and metastasis, angiogenesis and increased proliferation) is shown in Fig. 1B. We would like to think that this picture could help us understand the state of the art in this field and its future direction. A primary role, in our experience, is within the p53 family [42–47].

Table 1 shows some example of ongoing clinical trials based on regulators of cell death. Killing malignant cells is the main target of cancer therapy, but this could be done not just by inducing apoptosis, but also through the modulation of other cancer hallmarks.

4. Apotosis in neurodegenerative disorders

Neurodegeneration includes pathology that results in loss of neurons and is manifest as a broad group of neurological disorders. Genetic [48,49] and environmental factors [50–53] are the main causes of neurodegenerative diseases. In general, we can consider cell death (neuronal death) as the mechanism underlying these conditions and understanding the pathways that regulate cell death could help to find the road leading to the development of therapy [54–56].

In Alzheimer disease (AD), the extracellular accumulation of fibrillar amyloid β and the intracellular deposition of neurofibrillary tangles are the main features [57,58]. Recently, alteration of TGF-β signaling has been proposed as a further mechanism that could regulate amyloid-β aggregation and plaque formation and Lee et al. have found aggregates of TGFβ-induced anti-apoptotic factor 1 (TIAF1 in the hippocampus of AD patients) [59]. Activation

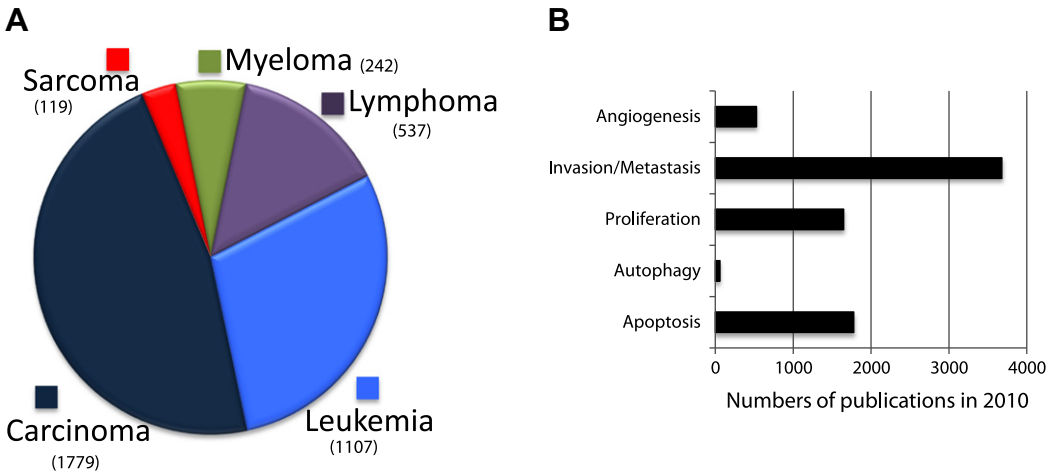

Fig. 1. Current trend of cancer related papers on cell death. (A) Numbers of publications in 2010 on apoptosis in different type of cancers. The search was performed as following: apoptosis or "cell death" with the specific histological type, according to the NCI classification (http://training.seer.cancer.gov/disease/categories/classification.html). (B) Numbers of carcinoma-related scientific papers published in 2010 focused on the selective mechanisms.

of the caspase machinery precedes tangle formation [60] and capsase-6 as well as caspase-3 [61] have been implicated in AD pathology. Indeed, the neuritic beading induced by amyloid precursor protein (APP) is dependent on caspase-6, since it is inhibited by z-VEID-fmk (a specific caspase-6 inhibitor) or by overexpressing a caspase-6 dominant negative [62]. Plaque formation is also secondary to the accumulation and activation of microglia in the CA1 area of hippocampus in a mouse model of AD [63].

Parkinson's disease (PD) is the second most common pathology affecting the central nervous system. A pivotal role in the pathogenesis of PD is played by the α-synuclein protein, and the gene encoding α-synuclein has been found mutated [64,65] or amplified (triplication) [66] in at least some cases of PD. Moreover, ectopic expression of α-synuclein leads to cell death through a mechanism that remains poorly understood [67]. Experimental evidence suggests that the 14-3-3 proteins, negative regulators of cell death, are deregulated and co-aggregated with α-synuclein Lewy bodies in PD [68]. In a recent paper, Yacoubian et al. using two different models of PD, confirm a strong neuroprotective effect of 14-3-3 proteins, in particular of 14-3-3θ, −ε and −γ isoforms [69]. Because PPAR-γ ligands can induce 14-3-3 expression [70], they could therefore be used as neuroprotective agents in PD therapy.

Several observations indicate that adult neurogenesis is impaired in neurodegenerative disorders, suggesting that the postmitotic neuron is not the only target affected by these disorders [71]. Indeed, the proliferation and differentiation of neural stem cells (NSC) into mature neurons is reduced by amyloid-β in human AD. The p73 gene [72,73], a member of p53 family, is implicated in the pathogenesis of AD [74–77]. In 2010, several reports identified p73 as a positive regulator of self-renewal with essential roles both in the maintenance of embryonic and adult neurogenesis, and by inhibiting premature senescence of NSC [78–81]. Moreover, this positive regulation of self-renewal of NCS by p73 is independent of p53.

5. Apoptosis in immune diseases

Physiologically, the immune system is one of the largest users of apoptosis, both in terms of the generation of mature immunologically active cells and in limiting the extent of an immune response [82]. Thus, apoptosis plays a role in both positive and negative selection of immune cells in the thymus, for example by eliminating autoreactive cells, thereby establishing tolerance to self-tissues. Indeed, it has been estimated that 90% of immature thymocytes are eliminated by apoptosis during thymic education. Moreover, the clonal expansion of cells during an immune response is curtailed by apoptosis (Activation Induced Cell Death; AICD) once the response has eliminated its stimulus. In addition, cytotoxic T and NK cells kill virus-infected or transformed target cells by inducing apoptotic cell death.

Defective cell death in the immune system can result in autoimmune disorders. For example, the CD95/CD95L system is a potent inducer of apoptosis on activated T lymphocytes and it has been demonstrated that alteration in Fas-mediated apoptosis is the basic pathology underlying the autoimmune disease systemic lupus erythematosus [83]. In apoptosis mediated by CD95, both extrinsic and intrinsic pathways are activated, depending on the cell context [84–86]. A layer of complexity in this system has been added by the observations that, in some cellular contexts, caspase cleavage of Golgi proteins is required for CD95/CD95L mediated apoptosis [87,88].

Acquired immunodeficiency syndrome (AIDS) as a consequence of human immunodeficiency virus (HIV) infection is the most dramatic example of immune system pathology linked to excessive cell death [89]. An update on the current understanding of the role and mechanisms of accelerated apoptosis of T cells in the immunopathogenesis of HIV infection has now been provided by Cummins et al. and may be a useful stimulus to revisit our concepts of treatment for this devastating disease [90].

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