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Cell death signaling and anticancer therapy

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For a long time, it was commonly believed that efficient anticancer regimens would either trigger the apoptotic demise of tumor cells or induce a permanent arrest in the G_1 phase of the cell cycle, i.e., senescence. The recent discovery that necrosis can occur in a regulated fashion and the increasingly more precise characterization of the underlying molecular mechanisms have raised great interest, as non-apoptotic pathways might be instrumental to circumvent the resistance of cancer cells to conventional, pro-apoptotic therapeutic regimens. Moreover, it has been shown that some anticancer regimens engage lethal signaling cascades that can ignite multiple oncosuppressive mechanisms, including apoptosis, necrosis, and senescence. Among these signaling pathways is mitotic catastrophe, whose role as a *bona fide* cell death mechanism has recently been reconsidered. Thus, anticancer regimens get ever more sophisticated, and often distinct strategies are combined to maximize efficacy and minimize side effects. In this review, we will discuss the importance of apoptosis, necrosis, and mitotic catastrophe in the response of tumor cells to the most common clinically employed and experimental anticancer agents.

Keywords: caspases, lysosomal membrane permeabilization, mitochondrial membrane permeabilization, necrosome, oncosis, phosphatidylserine, RIP1, reactive oxygen species

INTRODUCTION

For a long time, cell death was considered as a mere "consequence" of cellular life and neglected. Then, starting in the mid-nineteenth century, the demise of cells begun to attract the attention of some biologists, who compiled the first morphological descriptions of cell death. Nevertheless, the notion that cell death can occur in a programmed fashion was not explicitly formulated until as late as 1964, thanks to the seminal work of Richard Lockshin (Lockshin and Williams, 1964). A few years later, John Kerr, Alastair Currie, and Sir Andrew Wyllie, who were studying ischemic injury in the rat liver, described for the first time a form of mammalian cell death that manifests with peculiar morphological features and named it "apoptosis," a term of Greek derivation that translates the "dropping off" of petals or leaves from plants or trees (Kerr, 1965; Kerr et al., 1972). As suggested by its stereotyped nature, apoptosis constitutes a genetically regulated cell death subroutine, a concept that was consolidated in 1980–1990 thanks to the work of Robert Horvitz in *Caenorhabditis elegans* (Lettre and Hengartner, 2006). Along with the discovery of apoptosis, attempts were made to classify cell death modes based on morphological features. One of such classifications was proposed by Schweichel and Merker in 1973, who exposed rat embryos to toxicants and observed "type I cell death" associated with heterophagy, "type II cell death" associated with autophagy and "type III cell death," which was not associated with any type of digestion (Schweichel and Merker, 1973). Today, type I and type III cell death would be referred to as apoptosis and necrosis, respectively, whereas the existence of bona fide "autophagic cell death" remains a matter of controversy, as in most instances the inhibition of autophagy accelerates, rather than inhibits, cell death (Kroemer and Levine, 2008).

Following the discovery of the signaling pathways that initiate the cellular demise, of the biochemical mechanisms that execute it, and of its consequences at the organismal level, several additional criteria have been used to classify cell death. For instance, at a biochemical level, cell death sometimes, but not always, requires the activation of a specific class of cysteine proteases, namely caspases, leading to the discrimination between caspase-dependent and caspase-independent cell death. From an immunological standpoint, immunogenic cell death (ICD) has been opposed to cell death that is unable to activate the immune system (silent), or even actively represses it (tolerogenic). Finally, functional aspects have been used to discriminate between accidental and programmed cell death (PCD), or between physiological and pathological cell death (Galluzzi et al., 2007).

Along with an ever more precise mechanistic characterization of the cellular demise, in the last decade several neologisms have been coined to indicate presumably novel cell death subroutines that exhibit peculiar morphological, biochemical or functional features (Kroemer et al., 2009). The terms "anoikis," "paraptosis," "pyroptosis," and "pyronecrosis" are a few examples that exemplify this tendency. However, in most cases, these catabolic pathways do not constitute *bona fide* cell death mechanisms, but rather signaling cascades that engage the apoptotic or necrotic

machinery (Kepp et al., 2010). Similarly, it seems that "mitotic catastrophe," which in the past has been defined as a cell death instance occurring during or shortly after an aberrant mitosis (Vakifahmetoglu et al., 2008), cannot be considered as a cell death subroutine on its own but rather as an oncosuppressive mechanism that can trigger apoptosis, necrosis, or senescence. Importantly, whereas necrosis has been regarded for a long time as a purely accidental cell death mode, it has recently been shown that it can also occur in a regulated fashion (Vandenabeele et al., 2010).

Before this revolutionary change of perspective occurred, it was believed that efficient anticancer regimens would either kill tumor cells by engaging the apoptotic machinery or permanently arrest them in the G_1 phase of the cell cycle, thus inducing senescence. Now, it has become evident that there is a wide array of clinically employed and experimental anticancer agents that function by triggering neither "classical" apoptosis nor senescence. Some of these regimens, which are beyond the scope of this review, work by engaging tumor-extrinsic signaling cascades (e.g., they stimulate an antitumor immune response, they inhibit angiogenesis, etc.). Others may induce programmed necrosis or mitotic catastrophe-engaged apoptosis. These notions have generated considerable interest. On one hand, regimens that kill tumor cells by inducing necrosis might be instrumental to circumvent the elevated incidence among tumors of mechanisms for the evasion of apoptotic cell death. On the other hand, it seems that cancer cells (which are often genomically instable) are much more sensitive to the induction of mitotic catastrophe than their normal counterparts, resulting in a more comfortable therapeutic window (Eom et al., 2005).

In this review, we will summarize the main morphological, biochemical, and immunological features of apoptosis, necrosis and mitotic catastrophe and we will discuss the significance of these lethal biochemical cascades in anticancer therapy.

CASPASE-DEPENDENT AND -INDEPENDENT APOPTOSIS

The morphological features that define the most-studied modality of cell death, apoptosis, include (i) rounding-up of the cell; (ii) retraction of pseudopodes; (iii) reduction of cellular volume; (pyknosis), (iv) chromatin condensation starting from the nuclear periphery (marginalization), followed by overall nuclear shrinkage and breakdown (karyorrhexis); (v) little or no ultrastructural modifications of cytoplasmic organelles; (vi) plasma membrane blebbing (but maintenance of its integrity until the latest stages of the process); (vii) shedding of vacuoles containing cytoplasmic portions and apparently unchanged organelles (known as apoptotic bodies); and (viii) engulfment of apoptotic bodies by resident phagocytes (*in vivo*) (Galluzzi et al., 2007). When the phagocytic system is absent (e.g., in cell cultures) or inefficient, apoptotic bodies progressively break down and their content spills into the extracellular milieu (secondary necrosis).

According to accepted models, two distinct routes to apoptosis exist, which are ignited by extracellular and intracellular stress signals, respectively. "Extrinsic apoptosis" is predominantly mediated by so-called death receptors (e.g., CD95/FAS), which deliver a lethal signal upon ligand binding, resulting in the intracellular activation of initiator caspase-8 and executioner caspase-3 and -6 (Wajant, 2002). On the other hand, "intrinsic apoptosis" responds to a wide array of intracellular stress conditions (e.g., DNA damage, oxidative damage) and is controlled by mitochondria, whose permeabilization constitutes a point-of-no-return in the signaling pathway that leads to the activation of the caspase-9-caspase-3 cascade as well as of multiple caspase-independent cell death effectors (e.g., apoptosis-inducing factor, AIF; endonuclease G) (Kroemer et al., 2007). Thus, several biochemical markers have been associated with the execution of apoptotic cell death including: (i) the massive activation of caspases, in particular caspase-3, -6, -8, and -9; (ii) mitochondrial membrane permeabilization and (iii) the internucleosomal cleavage of DNA (Kroemer et al., 2007; **Table 1**).

However, none of the morphological features and processes that have been linked to apoptosis can be used alone as a *bona fide* indicator of this cell death subroutine (Kroemer et al., 2009), for several reasons. First, taken singularly, some of these morphological traits can manifest (and most of these biochemical events can occur) during non-apoptotic instances of cell death (Vandenabeele et al., 2010). For instance, MMP reportedly takes place during apoptosis and programmed necrosis (Kroemer et al., 2007; Vandenabeele et al., 2010). Second, not all of these (morphological and functional) characteristics manifest in all instances of apoptosis. As a major example, apoptosis can occur independently of caspases (Chipuk and Green, 2005). Third, it has recently become evident that most, if not all, the players that mediate PCD also have cell death-unrelated functions (Galluzzi et al., 2008). Thus, the activation of the apoptotic executioner caspase-3 and MMP have been implicated in the differentiation of hematopoietic cells (Zermati et al., 2001; De Botton et al., 2002). Similarly, the caspase-independent cell death effector AIF, which mediates large scale DNA degradation once released from mitochondria (Joza et al., 2001; Kroemer et al., 2007), regulates the assembly/stability of the respiratory complex I from its physiological localization, i.e., within the mitochondrial intermembrane space (Joza et al., 2005).

Apoptotic cells produce several well-known "find-me" (e.g., soluble lysophosphatidylcholine, LPC; ATP) (Lauber et al., 2003; Elliott et al., 2009) and "eat-me" (e.g., surface-exposed and oxidized phosphatidylserine) (Martin et al., 1995) signals, which allow them to interact with macrophages and to be recruited into tight-fitting phagosomes through a zipper-like mechanism (Krysko et al., 2006). Often, phagocytic cells that take up apoptotic bodies do not activate inflammatory or immunogenic reactions. Thus, for a long time it was thought that developmental and pathological PCD would occur only via apoptosis, as this would not elicit any kind of immune response, in contrast to the well-known inflammatory potential of necrosis (see below) (Galluzzi et al., 2007; Green et al., 2009). This oversimplified view has been definitively invalidated in 2007, when Obeid et al. (2007) demonstrated that some anticancer agents such as anthracyclins and γ irradiation are able to kill cancer cells by apoptosis while rendering them able to stimulate a tumor-specific immune response. Since then, great efforts have been directed to the discovery of the molecular mechanisms underlying ICD and it has turned out that ICD depends on the activation of a multi-module

Table 1 | Main morphological, biochemical, and inflammatory/immunological features of apoptosis, necrosis, and mitotic catastrophe.

	Morphological features	Biochemical features	Inflammatory/immune features
Apoptosis	Rounding-up	Caspase activation	Generation of soluble find-me signals (ATP, LPC)
	Pseudopode retraction	MMP/LMP	Uptake via tight-fitting phagosomes
	Cytoplasmic pyknosis	$\Delta\psi_m$ dissipation	Often anti-inflammatory and silent/tolerogenic
	Chromatin condensation Karyorrhexis	Release of IMS proteins PS exposure	In some instances, eliciting an immune response that depends on CRT exposure
	Little alterations of organelles	Internucleosomal DNA cleavage	
	PM blebbing	ROS overgeneration	
	Apoptotic bodies	ATP depletion	
	Phagocytosis	Activation of calpains/cathepsins	
Necrosis	Increasingly translucent cytoplasm	RIP1/RIP3 activation Increased glutamino- and glycogenolysis	Uptake by macrophages via micropinocytosis
	Swollen organelles	ROS overgeneration	Most often, pro-inflammatory
	Dilatation of the nuclear membrane	Sphingosine and ceramide overproduction	In some cases, anti-inflammatory
	Chromatin condensation in small irregular patches	MMP/LMP Cytosolic Ca^{2+} waves	
	Absent karyorrhexis	Activation of calpains/cathepsins	
	Oncosis	cPLA2 activation	
	PM breakdown	PARP1 hyperactivation	
		ANT inhibition	
		ATP and NAD^+ depletion	
		Impaired LIP homeostasis	
		Sometimes, PS exposure	
Mitotic catastrophe	Micronucleation	Activation of caspase-2	Poorly determined
	Multinucleation	Prolonged SAC signaling	Most likely, dependent on the executioner mechanism engaged (i.e., apoptosis, necrosis or senescence)
	Apoptotic and/or necrotic features	TP53 activation Aberrant levels of cyclin B1 and signaling via CDK1	

Abbreviations: ANT, adenine nucleotide translocase; CDK1, cyclin-dependent kinase 1; cPLA2, cytosolic phospholipase A2; CRT, calreticulin; $\Delta\psi_m$, mitochondrial transmembrane potential; IMS, mitochondrial intermembrane space; LIP, labile iron pool; LMP, lysosomal membrane permeabilization; LPC, lysophosphatidylcholine MMP, mitochondrial membrane permeabilization; PARP1, poly(ADP-ribose) polymerase 1; PM, plasma membrane; RIP, receptor-interacting protein kinase; ROS, reactive oxygen species; SAC, spindle-assembly checkpoint.

signaling pathway that eventually results in the exposure at the cell surface of the endoplasmic reticulum (ER) chaperones calreticulin (CRT) and ERp57 (Panaretakis et al., 2009). The ecto-CRT/ERp57 complex acts as an "eat-me" signal and functions by binding to a yet-to-be-identified receptor on the surface of dendritic cells (DCs), stimulating the uptake of tumor antigens by DCs and the DC-mediated cross-priming of tumor-specific T lymphocytes (Obeid et al., 2007; Panaretakis et al., 2009).

Numerous clinically used and experimental anticancer agents trigger apoptosis (**Table 2**). These range from DNA-damaging agents including cisplatin (Schwerdt et al., 2005), ionizing radiations (Mi et al., 2009), and mitomycin c (Pirnia et al., 2002) to proteasome inhibitors such as bortezomib (Bonvini et al., 2007; Shi et al., 2008), from corticosteroids like prednisone (Casale et al., 2003) to inhibitors of histone deacetylases (HDACs) such as vorinostat (Koyama et al., 2010), from topoisomerase I inhibitors like camptothecin (Sanchez-Alcazar et al., 2003), etoposide (Cosse et al., 2007), and mitoxantrone (Cao et al., 2009) to a large number of monoclonal antibodies including bevacizumab (Wedam et al., 2006), cetuximab (Niu et al., 2010), and trastuzumab (Hudis, 2007), just to mention a few examples.

PROGRAMMED NECROSIS

Similar to their apoptotic counterparts, necrotic cells exhibit peculiar morphological features, though these have been disregarded for decades, along with the conception of necrosis as a totally uncontrollable and accidental phenomenon (**Table 1**). Initially, necrotic cells were classified in a negative fashion, i.e., dying cells that neither showed morphological traits of apoptotic nor massive autophagic vacuolization (which was considered a sign of autophagic cell death). Now, it has become evident that cells succumbing to necrosis display (i) an increasingly translucent cytoplasm; (ii) swollen organelles; (iii) little ultrastructural modifications of the nucleus including the dilatation of the nuclear membrane and the condensation of chromatin into circumscribed, asymmetrical patches; and (iv) increased cell volume (oncosis), which culminates in the breakdown of the plasma membrane (Vandenabeele et al., 2010).

Table 2 | Examples of anticancer agents that operate via apoptosis.

Class	Agent	Main indication(s)	Reference
CLINICALLY EMPLOYED			
Angiogenesis inhibitors	Thalidomide	Multiple myeloma	Mitsiades et al. (2002), Gockel et al. (2004)
Anthracyclins	Daunorubicin	AML	Palucka et al. (1999), Laurent and Jaffrezou (2001)
		ALL	
	Doxorubicin	Breast cancer	Wang et al. (2004), Casares et al. (2005), Ji et al. (2010)
		Bladder cancer	
		Gastric cancer	
		HL	
		Leukemia	
		Lung cancer	
		Multiple myeloma	
		Soft tissue sarcoma	
		Ovarian cancer	
		Thyroid cancer	
	Epirubicin	Breast cancer	Kandioler-Eckersberger et al. (2000), Lo et al. (2008)
	Idarubicin	ALL	Ketley et al. (1997), Majsterek et al. (2005)
		AML	
		CML	
		MDS	
Antimetabolites	6-Mercaptopurine	Leukemia	da Silva et al. (1996), Hortelano and Bosca (1997)
		NHL	
	Capecitabine	Breast cancer (metastatic)	Ciccolini et al. (2002), Wisniewska-Jarosinska et al. (2011)
		Colorectal cancer	
	Cytarabine	AML	Guchelaar et al. (1998), Iacobini et al. (2001)
		Acute non-lymphoblastic leukemia	
		CML	
		NHL	
	Fludarabine	AML	Vrana et al. (1999), Nishioka et al. (2007)
		CLL	
		NHL	
	Fluorouracil	Breast cancer	Hwang et al. (2001), Rigas et al. (2002)
		Colorectal cancer	
		Gastric adenocarcinoma	
		HNSCC	
		Pancreatic cancer	
	Methotrexate	ALL	da Silva et al. (1996), Huang et al. (2011)
	Pralatrexate (Folotyn®)	Leukemia	Marneros et al. (2009), Marchi et al. (2010)
		PTCL	
Aromatase inhibitors	Anastrozole (Arimidex®)	Breast cancer	Thiantanawat et al. (2003), Howell (2005)
	Letrozole (Femara®)	Breast cancer	Thiantanawat et al. (2003), Lisztwan et al. (2008)
Chimeric antibodies	Rituximab (Rituxan®)	B-cell NHL	Cartron et al. (2004), Marignani et al. (2009)
		CLL	
Corticosteroids	Prednisone	ALL	Lanza et al. (1996), (Casale et al., 2003)
		CLL	
		HL	
		Multiple myeloma NHL	
		Prostate cancer	
		Thymoma	
		Thymic carcinoma	

(Continued)

Table 2 | Continued

Class	Agent	Main indication(s)	Reference
DNA-damaging agents	Carboplatin	NSCLC Ovarian cancer	Girnun et al. (2008), Vidot et al. (2010)
	Chlorambucil	CLL	Begleiter et al. (1994), Thomas et al. (2000)
	Cisplatin	Breast cancer Colorectal cancer Germ cell tumor Lymphoma NSCLC Ovarian cancer Pancreatic cancer Sarcoma	Barry et al. (1990), Gonzalez et al. (2001), Schwerdt et al. (2005)
	Cyclophosphamide	Breast cancer Leukemia Lymphoma Ovarian cancer	Kandioler-Eckersberger et al. (2000), Schiavoni et al. (2011)
	Ionizing radiations	Breast cancer CLL Gastric cancer Lung cancer Multiple myeloma Skin cancer Thyroid cancer	Watters (1999), Mi et al. (2009)
	Mitomycin C	Bladder cancer Breast cancer Rectal cancer Upper gastrointestinal cancer	Park et al. (2000), Kelly et al. (2000), Pirnia et al. (2002)
	Oxaliplatin	Colorectal cancer	Gourdier et al. (2004), Tesniere et al. (2010)
Glucocorticoids	Dexamethasone	Brain cancer Multiple myeloma	Brown et al. (1993), Sharma and Lichtenstein (2008)
HDAC inhibitors	Vorinostat (Zolinza®)	Cutaneous T-cell lymphoma	Fantin and Richon (2007), Koyama et al. (2010)
Immunomodulatory agents	Lenalidomide (Revlimid®)	Multiple myeloma	Wu et al. (2008), Chauhan et al. (2010)
Macrolides	Rapamycin (Syrolimus®)	Multiple hematopoietic and solid tumors	Castedo et al. (2002), Huang et al. (2004)
Monoclonal antibodies	Alemtuzumab (Campath®)	B-cell CLL	Nuckel et al. (2005), Jaglowski et al. (2010)
	Bevacizumab (Avastin®)	Breast cancer Colorectal cancer (metastatic) Glioblastoma SCLC	Wedam et al. (2006)
	Cetuximab (Erbitux®)	Colorectal cancer HNSCC	Van Cutsem et al. (2009), Niu et al. (2010)
	Ofatumumab (Arzerra®)	CLL	Cheson (2010)
	Panitumumab (Vectibix®)	Colorectal cancer (metastatic)	Hoy and Wagstaff (2006), Van Cutsem et al. (2007), Dubois and Cohen (2009)
	Tositumomab and 131I-tositumomab (Bexxar®)	B-cell NHL Follicular lymphoma	Shan et al. (2001), Cardarelli et al. (2002)
	Trastuzumab (Herceptin®)	Breast cancer	Mohsin et al. (2005), Hudis (2007)
mTOR inhibitors	Everolimus (Afinitor®)	ALL Subependymal giant cell astrocytoma Renal cell carcinoma	Beuvink et al. (2005), Motzer et al. (2008), Crazzolara et al. (2009)
	Temsirolimus (Torisel®)	Renal cell carcinoma	Hudes et al. (2007), Mahalingam et al. (2010)

(Continued)

Table 2 | Continued

Class	Agent	Main indication(s)	Reference
Proteasome inhibitors	Bortezomib (Velcade®)	Mantle cell lymphoma Multiple myeloma	Bonvini et al. (2007), Shi et al. (2008)
Retinoids	Alitretinoin (Panretin®)	Kaposi's sarcoma	Fujimura et al. (1998), Dezube (2000)
	Bexarotene (Targretin®)	Cutaneous T-cell lymphoma	Budgin et al. (2005), Wagner et al. (2009)
	Tretinoin (Vesanoid®)	APL	Warrell et al. (1991), Sakoe et al. (2010)
Selective estrogen receptor modulators	Fulvestrant (Faslodex®)	Breast cancer	Bundred and Howell (2002), Riggins et al. (2005)
	Raloxifene (Evista®)	Breast cancer	Obrero et al. (2002), Mori-Abe et al. (2003)
	Tamoxifen (Nolvadex®)	Breast cancer	Nazarewicz et al. (2007), Howell et al. (2005)
Topoisomerase I inhibitors	Camptothecin	Lung cancer Lymphoma Ovarian cancer	Traganos et al. (1996), Sanchez-Alcazar et al. (2003)
	Irinotecan	Colorectal cancer	Xu and Villalona-Calero (2002), Li et al. (2009)
	Topotecan	Cervical cancer Ovarian cancer SCLC	Caserini et al. (1997), Nakashio et al. (2000)
Topoisomerase II inhibitors	Etoposide	Ewing's sarcoma Glioblastoma multiforme Lung cancer Lymphoma Non-lymphocytic leukemia Testicular cancer	Karpinich et al. (2002), Cosse et al. (2007)
	Mitoxantrone	AML Breast cancer (metastatic) NHL	Bhalla et al. (1993), Cao et al. (2009)
Tyrosine kinase inhibitors	Dasatinib (Sprycel®)	ALL CML Prostate cancer	Talpaz et al. (2006), Guerrouahen et al. (2010)
	Erlotinib (Tarceva®)	NSCLC Pancreatic cancer	Ling et al. (2008), Felip et al. (2008)
	Gefitinib (Iressa®)	NSCLC	Tracy et al. (2004), Mok et al. (2009)
	Imatinib mesylate (Gleevec®)	CML GIST Ewing's sarcoma MDS Melanoma	Vigneri and Wang (2001), Schiffer (2007)
	Lapatinib (Tykerb®)	Breast cancer	Geyer et al. (2006), Olaussen et al. (2009)
	Pazopanib (Votrient®)	Renal cell carcinoma	Olaussen et al. (2009), Paesler et al. (2010)
	Sorafenib (Nexavar®)	GIST Hepatocellular carcinoma Renal cell carcinoma (metastatic)	Escudier et al. (2007), Llobet et al. (2010)
	Sunitinib malate (Sutent®)	GIST Renal cell carcinoma	Gore et al. (2009), Xin et al. (2009)
IN CLINICAL DEVELOPMENT			
Alkylating agents	Mafosfamide	CNS cancer (Phase 1) Meningeal neoplasms (Phase 1)	Pette et al. (1995), Goldstein et al. (2008)
Corticosteroids	Prednisolone	ALL (Phase 4)	da Silva et al. (1996), Boor et al. (2006)
Flavonoids	Alvocidib (Flavopiridol)	CLL (Phase 1–3) Rhabdoid tumors (Phase 1–3)	Byrd et al. (1998), Billard et al. (2003)

(Continued)

Table 2 | Continued

Class	Agent	Main indication(s)	Reference
Immunomodulatory agents	Lenalidomide (Revlimid)	CLL (Phase 2) HL (Phase 2) MDS (Phase 2) NHL (Phase 2)	Wu et al. (2008), Chauhan et al. (2010)
Macrolides	Rapamycin (Syrolimus)	Multiple hematopoietic and solid tumors (Phase 1–3)	Castedo et al. (2002), Huang et al. (2004)
Monoclonal antibodies	Dacetuzumab (SGN-40®)	Multiple myeloma (Phase 2)	Law et al. (2005)[1]
	Epratuzumab	ALL (Phase 1–3) NHL (Phase 1–3)	Stein et al. (2004), Carnahan et al. (2007)
	GA101	B-cell lymphoma (Phase 1) NHL (Phase 1)	Dalle et al. (2011)[1]
	Galiximab	B-cell lymphoma (Phase 3)	Bello and Sotomayor (2007)
	Ofatumumab (Arzerra®)	B-cell CLL (Phase 3) Follicular NHL (Phase 3)	Cheson (2010)[1]
	Veltuzumab	NHL (Phase 2)	Stein et al. (2004), Rossi et al. (2008)
mTOR inhibitors	Everolimus (Afinitor®)	Large B-cell lymphoma (Phase 3)	Beuvink et al. (2005), Motzer et al. (2008), Crazzolara et al. (2009)
Proteasome inhibitors	Bortezomib (Velcade®)	Large B-cell lymphoma (Phase 3)	Bonvini et al. (2007), Shi et al. (2008)
Topoisomerase I inhibitors	Camptothecin	Multiple solid tumors (Phase 1–3)	Traganos et al. (1996), Sanchez-Alcazar et al. (2003)

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CNS, central nervous system; GIST, gastrointestinal stromal tumor; HDAC, histone deacetylase; HL, Hodgkin's lymphoma; HNSCC, head and neck squamous cell carcinoma; MDS, myelodysplastic syndrome; mTOR, mammalian target of rapamycin; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; PTCL, peripheral T-cell lymphoma; SCLC, small cell lung cancer.
[1]*http://www.clinicaltrials.gov*

Necrosis does not result in the formation of discrete entities that would be similar to apoptotic bodies. Moreover, the nuclei of necrotic cells do not fragment similar to those of their apoptotic counterparts and have indeed been reported to accumulate in necrotic tissues, *in vivo*. It should be kept in mind that whereas the signaling pathways and biochemical mechanisms the underlie programmed, accidental, and secondary necrosis are distinct, these phenomena manifest with highly overlapping end-stage morphological features. It is therefore impossible to discriminate among these three processes by relying on single end-point morphological determinations (Galluzzi et al., 2009).

The biochemical processes that ignite and execute programmed necrosis have only recently begun to be unveiled. These include, but are not limited to: (i) the activation of receptor-interacting protein kinases 1 and 3 (RIP1 and RIP3, respectively), which have recently been shown to play a critical role in several instances or programmed necrosis, and in particular in tumor necrosis factor receptor 1 (TNFR1)-elicited necroptosis (Hitomi et al., 2008; Cho et al., 2009; He et al., 2009; Zhang et al., 2009); (ii) a metabolic burst involving the glycogenolytic and glutamynolytic cascades (Goossens et al., 1996; Zhang et al., 2009); (iii) the overgeneration of reactive oxygen species (ROS) by mitochondrial and extra-mitochondrial sources (Goossens et al., 1995, 1999; Kim et al., 2007); (iv) the overproduction of membrane-destabilizing lipids such as sphingosine and ceramide (Thon et al., 2005; Won and Singh, 2006), promoting lysosomal membrane permeabilization (LMP) and the consequent release of toxic hydrolases into the cytosol (Boya and Kroemer, 2008); (v) the generation of cytosolic Ca^{2+} waves, driving the activation on one hand of Ca^{2+}-dependent non-caspase proteases of the calpain family that favor LMP (Yamashima et al., 2003; Yamashima, 2004; Yamashima and Oikawa, 2009), and, on the other hand, of the cytosolic phospholipase A2 (cPLA2), which catalyzes the first step in the conversion of phospholipids into membranotoxic lipid peroxides (Jayadev et al., 1997; Shinzawa and Tsujimoto, 2003); (vi) the hyperactivation (possibly induced by ROS-triggered DNA damage) of the ATP- and NAD^+-dependent nuclear enzyme poly(ADP-ribose) polymerase 1 (PARP1), favoring ATP and NAD^+ depletion as well as the mitochondrial release of AIF via a calpain-mediated mechanism (Yu et al., 2002; Zong et al., 2004; Moubarak et al., 2007); (vii) the inhibition of the ATP/ADP exchanger of the inner mitochondrial membrane adenine nucleotide translocase (ANT), contributing to ATP depletion (Temkin et al., 2006); and (viii) the generation of a c-JUN N-terminal kinase (JNK)-transduced signal affecting the homeostasis of the redox-active labile iron pool (LIP), further promoting oxidative stress (Antosiewicz et al., 2007). Most likely this list is not exhaustive and additional processes that are involved in the necrotic disintegration of cells will be discovered in the forthcoming years.

Similar to their apoptotic counterparts, necrotic cells sometimes externalize phosphatidylserine before plasma membrane permeabilization (Krysko et al., 2004), promoting their recognition and uptake by phagocytes (Hirt and Leist, 2003; Brouckaert et al.,

2004). However, full-blown necrosis results in the recruitment of macrophages that internalize necrotic cells via spacious macropinosomes (Krysko et al., 2003), a phenomenon that involves the sorting of fluid-phase macromolecules, as demonstrated by the co-localization of fluid-phase tracers (Krysko et al., 2006). Thus, apoptotic and necrotic cells are handled by the immune system in a radically different fashion. Nevertheless, the phlogistic and immunological consequences of these cell death subroutines cannot be summarized by the old belief that apoptosis always inhibits, while necrosis always stimulates, inflammation and immunity. On one hand, immunogenic instances of apoptosis have been reported (see above). On the other hand, in some cases, necrotic cells can suppress inflammatory reactions (Hirt and Leist, 2003; Brouckaert et al., 2004). These observations suggest that the complexity of the mutual crosstalk between dying cells and the immune system has not been clearly understood yet.

Some clinically employed anticancer regimens (e.g., photodynamic therapy) have been associated with the necrotic regression of tumors (Bown et al., 2002; Lou et al., 2004; Moore et al., 2009), but in most cases it remains to be determined whether such a therapeutic response truly reflects the induction of programmed necrosis. Nevertheless, along with the increasingly more refined understanding of the molecular cascades that underlie regulated necrosis, several compounds are being investigated at pre-clinical and clinical levels for their ability to kill cancer cells by inducing necrosis. Notable examples include DNA alkylating agents, which may trigger cancer cell necrosis via PARP1 hyperactivation (Zong et al., 2004); inhibitors of the cellular inhibitor of apoptosis (cIAP) protein family such as SMAC mimetics, which (at least *in vitro*) promote necroptosis by facilitating the deubiquitination of RIP1 (Dineen et al., 2010; Vandenabeele et al., 2010; Vanlangenakker et al., 2011); and shikonin, whose promising pro-necrotic activity has not yet been precisely characterized (Han et al., 2007) (**Table 3**).

MITOTIC CATASTROPHE

In the last decade, the term "mitotic catastrophe" has been extensively employed to describe a form of cell death affecting higher eukaryotes and has been defined in several fashions, for instance as a case of cell death occurring either during or shortly after aberrant mitosis (Vakifahmetoglu et al., 2008). Nevertheless, the current literature is devoid of a clear-cut definition of this process. The present tendency is to consider mitotic catastrophe as an oncosuppressive signaling cascade that precedes the cellular demise (or senescence) rather than a *bona fide* cell death executioner mechanism (Vakifahmetoglu et al., 2008; Vitale et al., 2011). Thus, based on functional considerations, mitotic catastrophe can be viewed as a signaling pathway that is activated by perturbations of the mitotic apparatus (including chromosomes and the machinery that ensure their faithful segregation) that are sensed during mitosis and that lead first to (at least some extent of) mitotic arrest and then to cell death of senescence.

In spite of (or even along with) this change of perspective, the interest in mitotic catastrophe as a target for anticancer regimens continues to be high, for at least two reasons. First, a sizeable proportion of cancer cells are tetraploid or aneuploid, which renders them intrinsically more prone to mitotic aberrations and hence particularly sensitive to the induction of mitotic catastrophe (Vitale et al., 2011). Second, multiple chemotherapeutic agents that are now employed at relatively high doses to trigger cell cycle-independent cell death are very efficient at inducing mitotic catastrophe at lower doses (Eom et al., 2005).

The most prominent morphological features of mitotic catastrophe are (i) micronucleation and (ii) multinucleation. Micronuclei often derive from chromosomes and/or chromosome fragments that have not been distributed evenly between daughter nuclei, whereas two or more nuclei with similar or heterogeneous sizes can be generated upon an aberrant karyokinesis (Vakifahmetoglu et al., 2008). Once mitotic catastrophe proceeds and engages apoptosis, necrosis, or cell senescence, cells acquire at least some of the morphological traits that characterize these processes, resulting in a spectrum of morphotypes that are difficult to classify.

The biochemical events that accompany mitotic catastrophe have not yet been precisely characterized, and there seems to be a high degree of variability in the molecular cascades that are activated in distinct instances of mitotic catastrophe (Gascoigne and Taylor, 2008). Thus, most of the processes that so far have been linked to mitotic catastrophe are required for this lethal cascade in some, but not all, experimental settings. These include (i) the activation of the DNA damage-responsive caspase-2, which reportedly can operate both upstream and downstream MMP (Krumschnabel et al., 2009; Vakifahmetoglu-Norberg and Zhivotovsky, 2010); (ii) the protracted activation of the spindle-assembly checkpoint (SAC), which prevents anaphase (and hence chromosome missegregation) in cells with spindle defects or misattached chromosomes (Musacchio and Salmon, 2007); (iii) the activity of the tumor suppressor protein TP53 (Castedo et al., 2006; Vitale et al., 2007; Huang et al., 2009); and (iv) aberrantly high levels of cyclin B1, leading to prolonged activation of the cyclin-dependent kinase 1 (CDK1) (Harley et al., 2010; Terrano et al., 2010).

Although a role for pro- and anti-apoptotic proteins from the BCL-2 family, for TP53 and for several SAC-related and -unrelated kinases has been demonstrated (Puthalakath et al., 1999, 2001; Castedo et al., 2006; Musacchio and Salmon, 2007; Harley et al., 2010; Terrano et al., 2010), it remains to be clarified how mitotic catastrophe signals to the molecular machineries of apoptosis, necrosis or senescence, and which factors determine the choice among these three oncosuppressive mechanisms. A detailed analysis of the crosstalk between mitotic catastrophe and the inflammatory and immune systems is also missing. With regards to this, it is tempting to speculate that the reaction of the inflammatory/immune system to cells undergoing mitotic catastrophe might be deeply influenced (if not entirely dictated) by the cell fate, be it apoptosis, necrosis, or senescence. Future work will confirm or invalidate this hypothesis.

Irrespective of these incognita, an entire class of clinically employed anticancer agents, i.e., microtubular poisons, operate by inducing mitotic catastrophe. These include taxanes, which disrupt microtubular functions by stabilizing polymerized tubulin; vinca alkaloids, which acts as tubulin depolymerizers; as well as recently developed compounds such as epothilones, which mimic the activity of taxanes yet bind to a distinct binding site on tubulin (Dumontet and Jordan, 2010). In addition, there are several inducers of mitotic catastrophe that are currently being evaluated in pre-clinical and clinical settings, including inhibitors of Aurora kinases (Perez Fidalgo et al., 2009; Lens et al., 2010), of checkpoint

Table 3 | Examples of anticancer agents that ignite programmed necrosis or mitotic catastrophe.

Class	Agent	Main indication(s)	Reference
CLINICALLY EMPLOYED			
DNA alkylating agents	Cyclophosphamide	Breast cancer Leukemia Lymphoma Ovarian cancer	Kandioler-Eckersberger et al. (2000), Zong et al. (2004)
Epothilones	Ixabepilone	Breast cancer	Lee and Swain (2008)
Estrogens	Estramustine	Prostate cancer	Panda et al. (1997), Dumontet and Jordan (2010)
HDAC inhibitors	Romidepsin (Istodax®)	Cutaneous T cell lymphoma	Peart et al. (2003), Woo et al. (2009), Whittaker et al. (2010)
Photodynamic therapy	Temoporfin	HNSCC Pancreatic cancer Prostate cancer	Bown et al. (2002), Lou et al. (2004), Moore et al. (2009)
Taxanes	Cabazitaxel	HRPC (metastatic)	Galsky et al. (2010)
	Docetaxel (Taxotere®)	Breast cancer Gastric adenocarcinoma NHSCC HRPC NSCLC	Perez (2009)
	Paclitaxel (Abraxane®) (ABI-007®)	Breast cancer Kaposi's sarcoma NSCLC Ovarian cancer	Nyman et al. (2005), Perez (2009), Miele et al. (2009), Dumontet and Jordan (2010)
Vinca alkaloids	Vinblastine (Velban®)	Multiple hematopoietic and solid tumors	Dumontet and Jordan (2010)
	Vincristine (Oncovin®)	Multiple hematopoietic and solid tumors	Dumontet and Jordan (2010)
	Vindesine	ALL Lymphoma NSCLC	Dancey and Steward (1995), Joel (1996)
	Vinflunine	Bladder cancer	Frampton and Moen (2010)
	Vinorelbine	Breast cancer NSCLC	Aapro et al. (2007), Gralla et al. (2007)
IN PRECLINICAL/CLINICAL DEVELOPMENT			
AURKs inhibitors	AS703569	Multiple hematopoietic and solid tumors (Phase 1)	McLaughlin et al. (2009)[1]
	AT9283	Leukemia (Phase 1–2) Multiple myeloma (Phase 2)	Cheung et al. (2009)[1]
	AZD1152	AML (Phase 1–3) Solid tumors (advanced) (Phase 1)	Wilkinson et al. (2007)[1]
	MK-0457 (VX-680)	Leukemia (Phase 2) NSCLC (Phase 2) Solid tumors (advanced) (Phase 1)	Harrington et al. (2004), Dar et al. (2010)
	MLN8054	Solid tumors (advanced) (Phase 1)	Hoar et al. (2007), Kitzen et al. (2010)
	MLN8237	AML (advanced) (Phase 2) MDS (Phase 2) Solid tumors (advanced) (Phase 1)	Kitzen et al. (2010), Huck et al. (2010)
	PF-03814735	Solid tumors (advanced) (Phase 1)	Kitzen et al. (2010), Jani et al. (2010)
	PHA-739358	CML (Phase 2) Multiple myeloma (Phase 2) HRPC (metastatic) (Phase 2)	Carpinelli et al. (2007)[1]
	SNS-314	Solid tumors (advanced) (Phase 1)	Cheung et al. (2009), VanderPorten et al. (2009)
cIAPs inhibitors	SMAC/DIABLO mimetics	Preclinical development	Foster et al. (2009), He et al. (2009), Awasthi et al. (2011)

(Continued)

Table 3 | Continued

Class	Agent	Main indication(s)	Reference
CENP-E inhibitors	GSK923295	Solid tumors (Phase 1)	Wood et al. (2010)
CHEK1 inhibitors	AZD7762	Solid tumors (advanced) (Phase 1)	Zabludoff et al. (2008), Dai and Grant (2010)
	PF-00477736	Solid tumors (advanced) (Phase 1)	Blasina et al. (2008), Ma et al. (2011)
	SCH900776	Acute leukemia (Phase 1) Lymphoma (Phase 1) Solid tumors (Phase 1)	Dai and Grant (2010)[1]
	UCN-01	Multiple hematopoietic and solid tumors (Phase 1–2)	Busby et al. (2000), Ma et al. (2011)[1]
Combretastatins	CA4P (Fosbretabulin®)	Anaplastic thyroid cancer (Phase 3) HNSCC (Phase 2) Solid tumors (Phase 1)	Kanthou and Tozer (2007), Mooney et al. (2009)
Epothilones	Dehydelone (KoS-1584)	NSCLC (Phase 2)	Perez (2009)[1]
	Ixabepilone	Solid tumors (Phase 1–3)	Rivera et al. (2008), De Geest et al. (2010)
	Patupilone	Solid tumors (Phase 1–3)	O'Reilly et al. (2008), Perez (2009)
	Sagopilone	Solid tumors (Phase 1–3)	Hoffmann et al. (2008), Galmarini (2009)
HDAC inhibitors	Romidepsin (Istodax®)	Multiple myeloma (Phase 2)	Niesvizky et al. (2011)[1]
KRP inhibitors	ARRY-520	AML (Phase 1–2) Multiple myeloma (Phase 1–2) Solid tumors (Phase 1)	Huszar et al. (2009), Woessner et al. (2009)
	AZD4877	AML (Phase 1) Bladder cancer (Phase 2) Solid tumors (Phase 1)	Huszar et al. (2009)[1]
	LY2523355	Acute leukemia (Phase 2) Solid tumors (Phase 1)	Huszar et al. (2009)[1]
	SB-715992 (Ispinesib®)	Breast cancer (Phase 2) Colorectal cancer (Phase 2) Hepatic cancer (Phase 2) HNSCC (Phase 2) NSCLC (Phase 2) Ovarian cancer (Phase 2) Prostate cancer (Phase 2) Renal cell carcinoma (Phase 2)	Lad et al. (2008), Sarli and Giannis (2008)[1]
	SB-743921	NHL (Phase 1–2) Solid tumors (Phase 1)	Huszar et al. (2009)[1]
Macrocyclic ketons	Eribulin mesylate (Haraven®)	Breast cancer (Phase 3) NSCLC (Phase 2) Solid tumors (advanced) (Phase 1)	Twelves et al. (2010), Gradishar (2011)
Natural compounds	Shikonin	Preclinical development	Han et al. (2007), Hu and Xuan (2008)
Noscapinoids	Noscapine	Multiple myeloma (Phase 1–2) NHL (Phase 1–2)	Ye et al. (1998)[1]
PLK1 inhibitors	BI 2536	AML (Phase 2) NSCLC (Phase 2) Pancreatic cancer (Phase 2) Prostate cancer (Phase 2) SCLC (Phase 2)	Steegmaier et al. (2007), Degenhardt and Lampkin (2010), Lens et al. (2010)
	BI 6727	AML (Phase 2) NSCLC (Phase 2) Solid tumors (Phase 1)	Rudolph et al. (2009), Lens et al. (2010)[1]
	GSK431634A	NHL (Phase 1)	Gilmartin et al. (2009), Degenhardt and Lampkin (2010)
	ON01910.Na	AML (Phase 1–2) MDS (Phase 3) Ovarian cancer (Phase 2) Solid tumors (Phase 1)	Gumireddy et al. (2005)[1]

(Continued)

Table 3 | Continued

Class	Agent	Main indication(s)	Reference
Survivin inhibitors	LY2181308	AML (Phase 2) HRPC (Phase 2) NSCLC (Phase 2)	Carrasco et al. (2011)[1]
	Peptide vaccine	Breast cancer (Phase 1) Cervical cancer (Phase 1–2) Colorectal cancer (Phase 1–2) Melanoma (Phase 1–2) Pancreatic cancer (Phase 1–2)	Ryan et al. (2009)[1]
	Terameprocol	Leukemia (Phase 1) Solid tumors (Phase 1)	Smolewski (2008), Ryan et al. (2009)
	YM155	HRPC (Phase 2) Large B cell lymphoma (Phase 2) Melanoma (Phase 2) NSCLC (Phase 2)	Nakahara et al. (2011)[1]
Taxanes	Docetaxel	Various solid tumors (Phase 3)	Dumontet and Jordan (2010)[1]
	Larotaxel	Pancreatic cancer (Phase 3)	Metzger-Filho et al. (2009)[1]
	Milataxel (MAC321)	Mesothelioma (Phase 2) Solid tumors (Phase 1)	Sampath et al. (2003)[1]
	Paclitaxel	Various solid tumors (Phase 3)	Dumontet and Jordan (2010)[1]
Topoisomerase I inhibitors	β-lapachone	HNSCC (Phase 2) Solid tumors (Phase 1)	Sun et al. (2006)[1]
TTK inhibitors	AZ3146	Preclinical development	Hewitt et al. (2010)
	Mps1-IN-1/2	Preclinical development	Kwiatkowski et al. (2010)
	NMS-P715	Preclinical development	Colombo et al. (2010)
	Reversine	Preclinical development	Santaguida et al. (2010)
	SP600125	Preclinical development	Schmidt et al. (2005)
Vinca alkaloids	Vinblastine (Velban®)	Various solid tumors (Phase 1–3)	Dumontet and Jordan (2010)[1]
	Vincristine (Oncovin®)	Various solid tumors (Phase 1–3)	Dumontet and Jordan (2010)[1]
	Vindesine	Various solid tumors (Phase 1–3)	Dumontet and Jordan (2010)[1]
	Vinorelbine	Various solid tumors (Phase 1–3)	Dumontet and Jordan (2010)[1]

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AURKs, Aurora kinases; CA4P, combretastatin A-4 phosphate; CENP-E, centromere protein E; CHEK1, checkpoint kinase 1; cIAPs, cellular inhibitor of apoptosis proteins; CML, chronic myeloid leukemia; DIABLO, direct IAP-binding protein with low pI; HNSCC, head and neck squamous cell carcinoma; HRPC, hormone-refractory prostate cancer; KRPs, kinesin-related proteins; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; PLK1, Polo-like kinase 1; SCLC, small cell lung cancer; SMAC, second mitochondria-derived activator of caspases.
[1]*http://www.clinicaltrials.gov*

kinase 1 (CHEK1) (Dai and Grant, 2010; Ma et al., 2011), of Polo-like kinases (PLKs) (Degenhardt and Lampkin, 2010; Lens et al., 2010), of survivin (Ryan et al., 2009), and of kinesin-related proteins (Huszar et al., 2009), just to mention a few examples (**Table 3**).

CONCLUDING REMARKS

So far, two major biochemical cascades that execute cell death have been characterized, i.e., apoptosis and necrosis. While the cytocidal potential of autophagy remains rather controversial, mitotic catastrophe appears to be an oncosuppressive mechanism that operates upstream of the molecular machinery for cell death and cell senescence. As we have discussed above, the vast majority of clinically used and experimental anticancer regimens work by triggering the apoptotic demise of tumor cells, programmed necrosis and mitotic catastrophe being much less employed as therapeutic targets. Nevertheless, since most, if not all, cancer cells exhibit or acquire increased resistance against pro-apoptotic agents, the future of anticancer therapy also relies on the exploitation of non- and pre-apoptotic signaling cascades. The concept of programmed necrosis has gained consensus only a few years ago, along with the idea of circumventing apoptosis resistance by triggering necrosis. Mitotic catastrophe can result in the activation of three distinct oncosuppressive mechanisms, i.e., apoptosis, necrosis and senescence, and cancer cells appear to be intrinsically more sensitive to succumb to this type of death than their normal counterparts. Thus, programmed necrosis and mitotic catastrophe hold great promises for anticancer therapy. It will be really interesting to see how the recent knowledge that has been generated around these oncosuppressive mechanisms will be translated into a clinical reality.

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