

# Evaluating the Remote Control of Programmed Cell Death, with or without a Compensatory Cell Proliferation

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## Abstract

Organisms and their different component levels, whether organelle, cellular or other, come by birth and go by death, and the deaths are often balanced by new births. Evolution on the one hand has built demise program(s) in cells of organisms but on the other hand has established external controls on the program(s). For instance, evolution has established death program(s) in animal cells so that the cells can, when it is needed, commit apoptosis or senescent death (SD) in physiological situations and stress-induced cell death (SICD) in pathological situations. However, these programmed cell deaths are not predominantly regulated by the cells that do the dying but, instead, are controlled externally and remotely by the cells' superior(s), i.e. their host tissue or organ or even the animal's body. Currently, it is still unclear whether a cell has only one death program or has several programs respectively controlling SD, apoptosis and SICD. In animals, apoptosis exterminates, in a physiological manner, healthy but no-longer needed cells to avoid cell redundancy, whereas suicidal SD and SICD, like homicidal necrosis, terminate ill but useful cells, which may be followed by regeneration of the live cells and by scar formation to heal the damaged organ or tissue. Therefore, "who dies" clearly differentiates apoptosis from SD, SICD and necrosis. In animals, apoptosis can occur only in those cell types that retain a lifelong ability of proliferation and never occurs in those cell types that can no longer replicate in adulthood. In cancer cells, SICD is strengthened, apoptosis is dramatically weakened while SD has been lost. Most published studies professed to be about apoptosis are actually about SICD, which has four basic and well-articulated pathways involving caspases or involving pathological alterations in the mitochondria, endoplasmic reticula, or lysosomes.

Key words: Apoptosis, Stress-induced cell death, Senescent death, Necrosis, Cancer, Evolution, Regeneration

## Introduction

In the culture of China and quite a few other east Asian countries, "Yin" (meaning negative, female,

etc.) and "Yang" (meaning positive, male, etc.) are often used to describe two opposite extremes or

situations, like black *vs* white, night *vs* day, life *vs* death, etc. This Yin-Yang contrast has, in the recent decades, been borrowed to describe different balances between two extremes in the biomedical sphere, with exemplary references cited here [1-5]. For instance, in an animal's body, cells may die via a predetermined procedure, which are coined as programmed cell deaths, with ensuing proliferation of the live cells to compensate for the cell loss [6], together constituting a Yin-Yang balance. Cells can die via a predetermined procedure because evolution has built death program(s) in the genome of each animal species. However, in the meantime evolution has also built mechanisms to allow the cells' host tissue, organ and even the entire body of the animal to control the death program(s) for the animal's ultimate interest, although this systemic regulation has not been sufficiently addressed in the literature. Because of the evolutionary establishment of this systemic control, both the programmed cell death and the death-and-birth balance are not predominantly regulated by the cells themselves, but are mainly regulated by the cells' superior(s), i.e. the host organ or tissue or even the animal's body [7-9]. Actually, this superior and external control of deaths and death-birth balances is a common rule of the earth's ecosystem and occurs at all levels of life, in our opinion. We infer that, because the death program(s) are controlled superiorly, an individual at any level has to be loyal to its superior as a condition for its survival, with organismal species controlled by the earth's ecosystem, which is the paramount "superior" and consists of the earth's environment and the interactions among different organismal species. In this essay we describe our musings on the control and coordination of cell deaths and births by host tissues or organs, and in turn by the animal's body, in physiological and pathological situations, as these external and superior regulations of different modes of programmed cell death have not been sufficiently addressed in the literature.

### **Birth-and-death balance at all levels of life is regulated externally and from above**

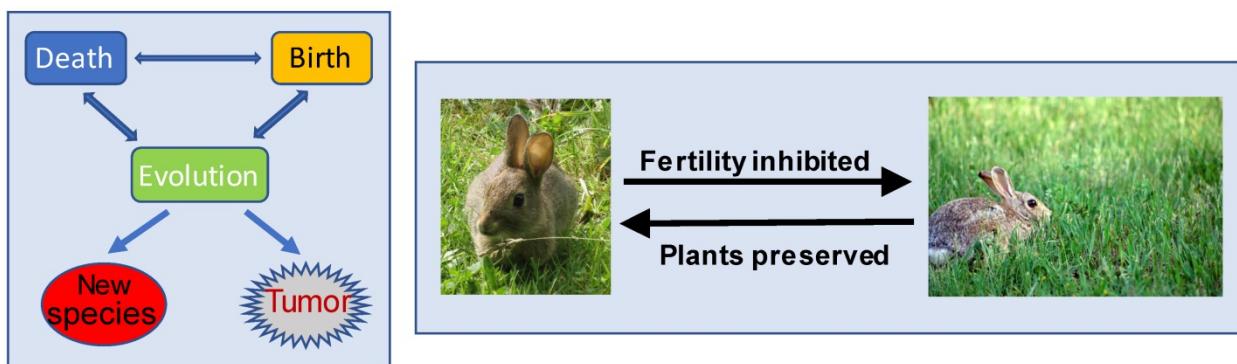
Organisms of all kinds constantly come by birth and go by death. Actually, here on earth, the birth-and-death relationship overarches, and is the pivot of, life at all levels, i.e. at the levels of organelle, cell, organ/tissue, organism, and species, as stratified and adumbrated below:

- Many organismal species have reached extinction or are becoming extinct [10-13]. The ecocide does not occur as the wish of the extinct

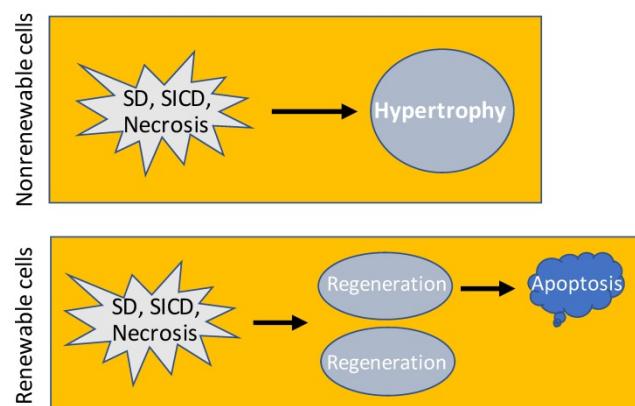
species themselves but, instead, is largely due to environmental changes [12, 14-19]. For instance, the dinosaur's extinction was not due to collective suicide of the dinosaurs but was because the environment had changed to a situation that was no longer suitable for their survival. In the meantime, environmental change also prods organisms into adaptation that leads to evolution either to new species (Fig 1) or to the development of new mechanisms for the organisms to survive in the new environment. As an example of the latter case, throughout evolution, a variety of microbes have equipped themselves with an ability to produce antibiotics, such as ampicillin, to kill their foes [20-25]. Similarly, many plants have also evolutionarily established ability to produce certain chemicals to fend off their enemies [26-33]. For example, many plants have evolutionarily equipped themselves with a mechanism to produce phytoestrogens that can interfere with animals' reproductive function [34-38]. We speculate that this can be a self-defensive mechanism, as those animals who eat too much of the plants will have their fertility inhibited and thus their population decreased, leading to the preservation of the plants (Fig 1).

- Within each species, individual organisms will die when they reach the end of their lifespans [39-41], but the species as a whole will survive via reproduction. The eventual death of individuals is a condition of the earth's ecosystem to allow the species to continue to exist, as the ecosystem would not allow any species to limitless expand its population to dominate the earth. To warrant this control by the ecosystem, aging-caused death of organisms is evolutionarily programmed in the genome of the species to make its individuals allegiant to, and controlled by, the species itself [39, 42-45]. In our opinion, this built-in program is a condition of the earth's ecosystem to allow the species to survive and, in turn, is a condition of the species to allow its individuals to survive, which again shows an ecosystem's basic rule that an individual has the built-in death program but its superior has the "remote control" of the program. In addition, because many species of plants and animals often die from various natural reasons, such as predation by their enemies, we surmise that evolution has also balanced their fecundity against their deaths caused by natural causes. Cannibalism is another mechanism evolutionarily conferred on many animal species, which allows these animal species to regulate their

- populations, to survive certain adverse situations, or to gain other advantages [46-48].
- Within an individual with multiple organs, such as a human being, some organs or tissues “die” after a certain embryonic stage or certain age, such as the disappearance of the pronephroi and then the mesonephroi during the embryonic development [49-54], and the regression of the thymus after puberty [55-59]. On the other hand, some other tissue structures “are born” after a certain embryonic stage or certain age, such as the appearance of the mesonephroi and then the permanent kidneys during the embryonic development [49-54]. The development of the mammary glands during the pregnant and lactating periods in women is another example of “new tissue birth” (women before pregnancy only have the breasts but not the mammary glands) [60-62]. Although usually considered as a disease, degeneration as a manifestation of aging is a natural event we all will experience sooner or later, which in most cases is due to cell demise in those cell types that can no longer regenerate in adulthood [63, 64], and sometimes is associated with the “birth” of new histological structures. For instance, some new histological entities may appear in the brains of certain neurodegenerative patients, such as the senile plaques and neurofibrillary tangles in the patients with Alzheimer’s Disease [65, 66] and the Lewy bodies in the patients with Parkinson’s Disease [67, 68].
  - Cells of an animal may be killed by external hazards such as infectious bacteria. Sometimes, external hazards may activate a death program of the cells, as explained before [6] and later in this essay. Even if without encountering an external hazard, cells will still die of aging when they reach the end of their lifespans [69-74]. Cells in a multi-cellular animal can be dichotomized based on whether they are renewable, i.e. whether they still retain a regenerative ability when they come to a certain age [75]. One group, exemplified by the cardiac myocytes [76-79] and neurons [75, 80], experiences proliferation during the periods of development and growth but loses the replicative ability in the adulthood [64]. When this nonrenewable group of cells experiences a massive death, such as from a bacterial infection or lack of blood supply, the remaining cells will undergo hypertrophy, i.e. increase in their cellular size, with the purpose of restoring the function of the organ or tissue (Fig 2), as often seen in cardiac myocytes [81-84], although hypertrophy appears in neurons only occasionally for unaddressed reasons [85-91]. The other group, such as white blood cells and epidermal keratinocytes, retains a lifelong ability to proliferate, although some cell types actually do not replicate themselves but are derived from another cell type, like most white blood cells that are constantly derived from the bone marrow. This renewable group not only has a short lifespan but also is often requested by the animal’s body to defend the nonrenewable group, and in turn the body itself, by fighting against various external hazards, often causing the cells to die quickly and massively in adverse situations. For example, white blood cells are required to fight against infectious bacteria and are often killed by the bacteria. Therefore, this renewable group of cells usually has a teeming loss but, in the meantime, also regenerates robustly, ending with a high rate of cell turnover. In either of the two cell groups, when cell death abounds, the connective tissue may step in to form a granulation and an ensuing scar as new tissues to help in healing the damaged tissue or organ [92-94]. For instance, a myocardial infarction may cause the death of many cardiac myocytes with ensuing fibrosis in the affected areas of the heart [95, 96], and a chronic infection by hepatitis viruses may cause constant death of hepatocytes followed by the development of liver fibrosis and cirrhosis [97, 98]. The death-and-hypertrophy balance or the death-and-regeneration balance, with or without formation of granulation and scar as new tissues, is controlled, or, more correctly, coordinated, by the animal’s body.
  - Within individual cells, various organelles are often increased or decreased in their number or size in various situations, often discerned in the mitochondria [99], lysosomes [100] and endoplasmic reticula (ER) [101-103], for example. Skeletal muscle cells even have many nuclei and may gain more with additional muscle growth [104]. In a stressful situation, organelles may be requested to “die” so that the cell as a whole can survive, which is often manifested as autophagy that can be regarded as cannibalism at the organelle level or as self-cannibalism [6, 105]. In our opinion, neither the increase nor the decrease of these organelles is their own wish, but rather is willed and controlled by their superior, i.e. the cell.



**Figure 1.** Interrelationships among the death, birth and evolution of organisms. **Left panel:** The death and birth of organisms are balanced by the ecosystem, so that the earth will not be over-crowded by organisms and that there will not be any particular species dominating the earth. Deaths often occur when the environment is changed, whereas individual species, organisms, organs, etc., are not willing to die and will find ways to survive, resulting in evolution to new species and, sometimes, also to neoplasms that can be considered as “new species” at the tissue/organ level. **Right panel:** Phytoestrogens are, hypothetically, developed during evolution as a mechanism for plants to protect themselves from animals: The more an animal (such as a rabbit) eats a phytoestrogen-containing plant (such as a sort of grass), the more severely its reproductive function will be interfered with by the phytoestrogens. The plant is thus preserved by the decrease in the fertility of the animals.



**Figure 2.** Consequence of SD, SICD and necrosis. In nonrenewable cell types, SD, SICD or necrosis may cause hypertrophy of the remaining cells to restore the cell-death-caused functional loss. In renewable cell types, SD, SICD or necrosis triggers regeneration that usually results in over regeneration and ensuing apoptosis of the over-regenerated cells, which is a one-way procedure because apoptosis will not trigger regeneration.

## Individuals at different levels of life are also egocentric, which drives evolution

As stratified above, individual deaths happen constantly at the levels of the organelle, cell, organ/tissue, organism, and species. Many of the deaths are evolutionarily programmed events, but the deaths are not actual suicides. Instead, the deaths are controlled by the superior, such as the animal’s body, the species or the earth’s ecosystem, and this control is the superior’s condition to allow the individual to exist. This is, in our opinion, because evolution has built death program(s) inside a cell’s genome but has handed the control of the program to their superior, e.g. the organ or tissue, the animal’s body, up to the earth’s ecosystem, to force individuals at all levels to be loyal to their superior and to obey its “orders”. However, individuals are also egocentric and, once they are endangered, their egoism will push them to

look for ways to survive [8, 9, 106-109]. “Try to survive” is an impetus for organismal evolution that leads to the development of new species via mutations [107-109]. We are all familiar with the question “which comes first, the chicken or the egg?” The correct evolutionary answer for it is that neither one comes first. The first chicken evolved from a species that genetically is not chicken but is very close to chicken, with mutations occurring in the egg or the bird leading to its transformation, i.e. evolution, to the chicken.

Within an animal species, individuals also fight against each other to live better and longer, with cannibalism as an extreme phenomenon of this fight and filial cannibalism as an even more extreme example [110-113]. Similarly, within individual organs or tissues of an animal, individual cells fight against their fellow cells to live better or longer, which is commonly coined as “cell competition” [114-118]. We infer, with trepidation, that some cells may win the competition by mutating certain gene(s) to gain competence, and some of the mutations may convert the cells to a neoplastic version. This conjecture, which has not been explored and thus has so far not received material evidence, actually states that tumorigenesis can occur via an active mechanism, as it occurs due to a motivation of the parental normal cell to live longer or better. Of course, there are two additional possible mechanisms for neoplastic transformation [119]. One is that environmental change imposes survival pressure onto normal cells, such as when the cells encounter irradiation, genotoxic chemicals, etc. The cells need to evolve via efficacious mutations to survive the stressful situation, and some of the mutations beget neoplastic transformation [119]. This mechanism has received a rich vein of clinical evidence that chemo- or

radio-therapy of tumors, which can cause mutations, increases the incidence of a second primary tumor [120-125]. As another mechanism, DNA replication during routine proliferation of normal cells may mistakenly result in mutations, and some of the mutations may be irreparable and lead to neoplastic transformation [126]. In this latter case, neoplasms as a sort of "new organism" are fortuitously developed without specific motivation, i.e. neither because the parental cells want to live longer or better nor because they want to survive in a stressful situation.

### Animal cells have three programmed death modes

As abovementioned, all cells in an animal have a lifespan and have, beginning at birth, started their journey of aging towards death [41, 127, 128], but the lifespans of different cell types vary drastically. We define cell death via aging as "senescent death" (SD) [6], because aging and senescence are highly interrelated [129-137], although senescence itself is often defined as permanent growth arrest that does not necessarily lead to the death of the cell [131, 135-138]. Obviously, SD has been programmed in the cells [39], likely in the nuclear genome although it remains possible that part of the program is allocated to the mitochondrial genome [139, 140]. The fact that all cells of an animal have the same genome but may differ greatly in lifespan insinuates that the same SD program may be regulated quite differently in different cell types. A longer lifespan not only connotes a weaker SD ability, i.e. having more difficulty in dying of SD, but also is associated with a weaker regenerative ability, and vice versa, in our opinion [6]. For instance, cardiac myocytes and neurons have the longest lifespan but have the weakest SD mechanism and the weakest regenerative ability [64, 75, 76, 78, 80, 141-146], whereas the epidermal keratinocytes show the opposite properties [147, 148].

Any cell in an animal may encounter a host of stressors in its lifetime. A stressor may be an external one such as a toxic chemical or an infection by micropathogens. A stressor may also be an internal one such as a genetic mutation occurring spontaneously during DNA replication, but often an internal stressor may initially be created by an external one. For example, a genotoxic chemical often causes DNA mutations, and a change in the microenvironmental temperature (such as a fever) can alter the cellular metabolic rate and in turn the cellular pH. A very severe stress will directly kill the cell, which is dubbed as "necrosis" [6, 149]. However, when a stress is not severe enough to kill instantly, it may elicit cell death via the cell's own demise

program, which is coined by us as "stress-induced cell death", or "SICD" [6, 7, 149, 150]. For instance, when a cell cannot repair a mutation, caused by irradiation or a genotoxic chemical for example, it will likely turn on a death program to commit suicide, so that the mutation will not be passed to the filial cells during cell replication and become inherited [6, 7, 149]. Actually, causing mutation-driven SICD has become a major mechanism for irradiation and many chemotherapeutic agents in eliciting their therapeutic effects on cancer cells [119, 149, 151, 152], although this mechanism is widely misconstrued as apoptosis [149, 151, 152], as discussed below. As another commonly seen example, when white blood cells are infected by bacteria or viruses but cannot kill the micropathogens, the cells may also commit suicide by turning on a demise program, so that they will not carry the micropathogens to other body sites and spread the infection [153-157]. These exemplary cell deaths are the iron will of the animal's body for its ultimate interest [6, 149].

In animals, many cells will no longer be useful and thus need to be eliminated after certain developmental or physiological stages or certain ages [158, 159]. Examples include digit individualization during the human embryonic development which is associated with the death of the interdigital cells to avoid hand-webbing [131, 160], thymus regression after puberty which is actually a cell dooming procedure [55-59], post-partum involution of the uterus [161-164] and post-weaning involution of the mammary glands [165-168] featuring massive cell death, and atrophy of the gonads in older men and women which is also associated with death of certain gonadal cells [169-174]. These physiological deaths occur in part because each organ or tissue has a physiological total number of the described cells, and, to keep the cell number within the physiological range, jettison of the excessive cells is a must [175]. In the exemplary physiological situations mentioned above, the jettisoned cells are those no-longer needed or, in Savill's word [176-180], "unwanted", by the animal's body, thus being redundant and useless, and the dooming procedure has been evolutionarily programmed inside the cells. This program needs to ensure 1) that the decease remains physiological without eliciting immune reactions that damage the host organ or tissue, and 2) that the decease occurs in a cannibalistic manner so that the materials of the dead cell can be recycled. These two requirements are met by a swift engulfment of the dooming or doomed cell by a macrophage or another phagocytic cell [6, 7, 149, 150, 181]. Since the engulfment functions as the scavenging of the cell corpse [177-180, 182], these cells are collectively tagged by us as "scavengers" [6, 7,

149, 150]. Because of the requirement of scavengers, this dooming mechanism becomes well established only when an animal's lymphatic and blood circulation systems have been evolutionarily developed to allow macrophages to travel distantly to the apoptotic cells [6, 7, 149, 150, 181]. We define this particular death program that aims at purging away useless and redundant cells from a tissue or organ as "apoptosis", as we construe that this is the cell death mode described by Kerr et al in their seminal study in which the word "apoptosis" was created [183]. As summarized by Savill [176], Kerr et al and a professor of ancient Greek created the word "apoptosis" to liken the cell death to "the dropping off as of leaves from a tree", which emphasizes that the death is physiological, occurs to individual cells (or leaves) via an endogenous program, and can be triggered through a program regulated by external stimuli (or autumn). We emphasize the "external regulation" of this "endogenous program" because it is insufficiently addressed in the literature.

If we are familiar with how some companies are so wary of causing themselves troubles when they want to get rid of their redundant employees, we will be able to fathom why and how evolution equips animal cells with an apoptotic mechanism for the animal's body to expunge its redundant cells, in a manner not only harmless but also wholesome, in order to lower the total cell number of each tissue or organ to the physiological range. As a caveat that needs to be given, although probably all of us describe apoptosis as a suicidal event, this is only partially correct. On the one hand we can indeed regard it as a suicide because the cell dies via a program contained in itself. However, on the other hand we can also consider the death as a homicide, not only because it is not the cell's own wish but also because there is a killer, who is the cell's host, and the killing has a motivation, which is that the host wants to get rid of no-longer needed cells. Restated, the death is remotely controlled.

### **Apoptosis is irrelevant to nonrenewable cell types**

During the developmental and growth stages, all cell types, including the nonrenewable ones like cardiac myocytes and neurons, proliferate to meet the body's growth needs, but this growth is not regeneration. After cessation of the body growth, nonrenewable cell types become well-differentiated and post-mitotic, and thus can no longer proliferate [64]. These facts lead us to a conclusion that in the whole lifespan the body never has excessive cells of a nonrenewable type to scrap via apoptosis. In other words, nonrenewable cell types do not have a chance

to undergo apoptosis, if apoptosis is defined as a physiological mechanism to remove excessive cells. However, nonrenewable cell types may die of SD, SICD or necrosis. Actually, if these cells experience a massive SICD or necrosis during the developmental or growth period, such as when the cells are severely infected by bacteria, regeneration may still occur in these early stages of the life. Therefore, although apoptosis, a form of cell death, and regeneration, a form of cell birth, have a Yin-Yang contract, they share a property, i.e. being skipped by nonrenewable cell types. This property has never been pointed out before in the literature, to our knowledge.

### **Cancer cells may lack SD and have strengthened SICD but weakened apoptosis**

It has been known to all pathologists for a century that cancer cells are weaker and have a higher death toll than their normal counterparts [119, 149, 152]. As the Nobel laureate Peyton Rous had pointed out in 1941, "that cancer cells are often sick cells and die young is known to every pathologist" [184]. In our opinion, these myriad deaths occur via necrosis and SICD, but not apoptosis. We opine that the SICD program in cancer cells has been strengthened, compared to that in their parental normal cells (Table 1), which justifies the use of SICD-causing irradiation or genotoxic chemicals to treat cancer. In contrast, the apoptotic mechanism may have been weakened or even lost in cancer cells (Table 1), since a neoplasm is autonomous and thus is generally acknowledged as a "new organism" [149, 185-188], somewhat similar to a new bacterial strain, because both of them are maintained by constant replication of their cells and have no predetermined physiological total number of cells and thus no redundant cells [149]. Indeed, tumor lumps continue enlarging their sizes, proving their lack of cell redundancy. This conjecture that the apoptotic mechanism in cancer cells has been greatly weakened still lacks substantiation but deserves testing, as it nixes the popular strategy of cancer therapy by enhancing cancer cells' apoptosis [189-192], although in most cases this so-called "apoptosis" is actually SICD, as discussed before [6] and further enlarged below.

In our opinion, cancer cells cannot undergo aging and thus will not die of SD (Table 1), because cancer cells by their definition in all pathology textbooks are immortal, making cancers somewhat resemble bacterial strains as abovementioned. The concept of "cancer cell senescence" and its enhancement as cancer therapy, which has recently become popular [193-197], is unfathomable to us, as it hints slyly that "immortal cells still undergo aging

and die of it", and thus is illogical [6]. Those cells that can undergo aging and die of SD should not be called neoplastic, no matter how their morphology and/or behavior resembles that of neoplastic cells, if we all agree to stick with the definition of neoplasm in pathology textbooks that put immortality as an indispensable criterion for neoplastic cells, including the benign ones. However, a caveat that needs to be given is that certain treatments may be able to induce differentiation of certain, but probably not all, types of cancer, and thus reestablish an SD mechanism. This reestablished SD via induction of differentiation (probably, re-differentiation) is actually a "reprogramming of a reprogrammed program" and thus is not the same thing as a simple enhancement of an existing SD mechanism.

An enchanting question that has thus far not been answered is whether SD, apoptosis and SICD, or any two of the three (such as apoptosis and SD), share the same death program. Reiterated, it remains unknown whether animal cells have only one suicidal program or, instead, have two or three different suicidal programs responsible for apoptosis, SD and/or SICD. Since building more programs will likely enlarge the genome and become extravagant, we intend to believe that evolution has likely followed a more efficient path and built only one single program in a cell but allows it to be regulated differently to control SD, apoptosis or SICD. Despite that cancer cells may have lost SD and even apoptosis, the fact that irradiation and many chemotherapeutic agents can cause SICD of cancer cells, as described above, evinces that these immortal cells still retain a suicidal program (Table 1). One possibility is that normal cells have three different death programs controlling apoptosis, SD and SICD, respectively, and their immortalization deletes the one for SD and weakens the one for apoptosis but leaves the one for SICD intact. Alternatively, normal cells have only one single but flexible death program that can be directed to apoptosis, SD or SICD in different situations, and immortalization blocks the pathway to SD and dramatically neutralizes that to apoptosis without affecting that to SICD. Although neither of these two possibilities has hitherto been supported by material evidence, it is clear that the death program(s) in cancer cells differ, in one way or another, from the one(s) in their parental normal cells.

**Table 1.** Differences between normal cells and cancer cells in the four cell death modes

	Apoptosis	SD	SICD	Necrosis
Normal	+	+	+	+
Cancer	-	-	++	++

Note: "++" means more severe than "+", and "-" means lacking or weakened.

## Most studies professed to be on apoptosis are actually on SICD

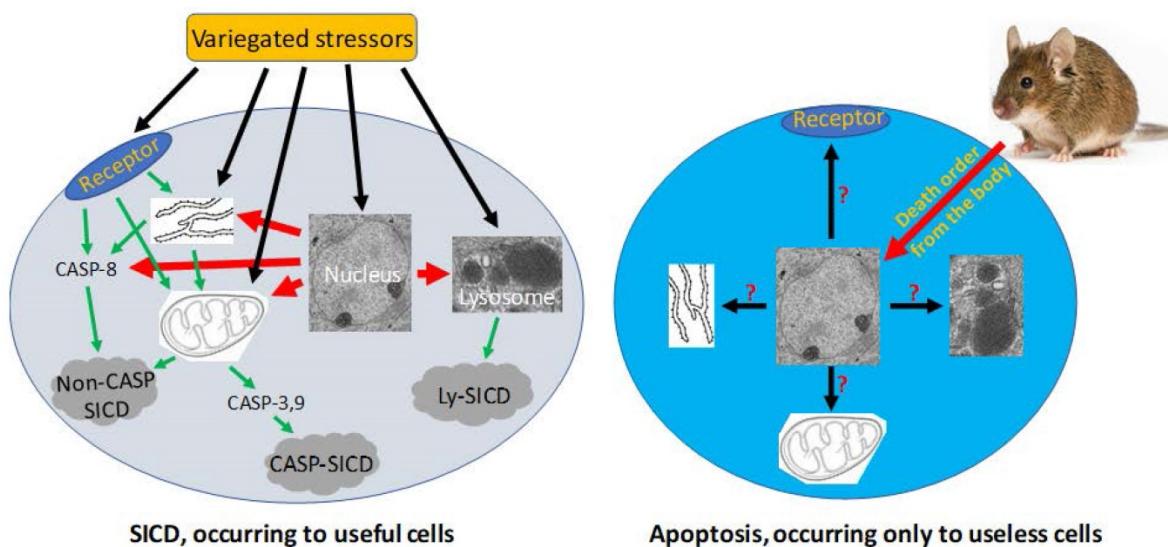
As we have repeatedly pointed out before [6, 7, 149, 198], SICD has been extensively studied under the name of apoptosis, whereas authentic apoptosis has hitherto received insufficient attention. In case readers do not want to leaf through our previous perspective articles, herein we adumbrate our rationales for why most relevant studies have misconstrued SICD as apoptosis: First, in apoptosis, it is those healthy but no longer needed cells that die [176-179], which is a black-white demarcation distinguishing apoptosis from SD, SICD and necrosis wherein it is those ill but useful cells that die [6, 7, 149]. Therefore, apoptosis does not trigger regeneration, because the animal's body will not annihilate redundant cells via apoptosis and simultaneously produces more cells to increase the redundancy [6, 7, 149]. In contrast, SD, SICD or necrosis of renewable cells triggers regeneration to restore the physiological cell number. The other way around may be correct, i.e. a regeneration triggered by SD, SICD or necrosis usually produces more cells than what is needed, and thus apoptosis usually ensues to eliminate the over-regenerated cells. Indeed, fresh granulations and scars usually experience such over regeneration and thus usually shrink (regress) later via apoptosis of the over-regenerated cells (Fig 2) [199-202]. Second, almost all studies claimed to be on apoptosis involve a stressor, such as a chemotherapeutic agent, to trigger the death, making it pathological and homicidal with the stressor as the killer, whereas apoptosis is a physiological event initiated by the animal's body and not by an external agent [6, 7, 150, 176, 178]. Indeed, in most of these studies, the stressor causes damage to the mitochondria and/or lysosomes, typically increasing the permeability of their membranes, which then results in leakage of their proteins into the cytoplasm [203-211] and thus is unadulteratedly pathological. Third, most studies professed to be on apoptosis involve cell lines in cell culture systems, making the studies irrelevant to apoptosis for at least three reasons [6, 7]: 1) Cell lines are immortalized with their apoptotic mechanism drastically weakened or even lost, as we have expounded above for immortal cancer cells. Even if they still retain an apoptotic program, it is reprogrammed from, and thus is not the same as, the program in their normal parental cells, whereas our purpose in studying apoptosis is to know the original death program, but not the reprogrammed program. In other words, we are dealing with two different programs, i.e. the original, intact one and its altered version, and we should only name one of the

two as apoptosis. 2) Unlike their normal counterparts in animals, immortal cell lines growing in culture dishes no longer have a physiological total number and cannot be split into the “useful” and “useless” categories, although they may behave differently and may die when their growth becomes confluent [212-218]. Therefore, in a culture dish there is no way of deciding how many cells, and which ones, should be extinguished. Actually, no cell within the dish has any interest in, and qualifications for, making these decisions. 3) Apoptosis requires two players, i.e. a scavenger cell, the predator, and the dying or dead cell, the prey [178, 179]. The later part of the apoptotic procedure occurs inside, and is performed by, the scavenger cell [177-180, 182]. This means that apoptosis also involves proteins, mostly lysosomal enzymes, of the scavenger origin [6, 7]. In contrast, in most cell culture studies there is only one player, i.e. the dying cell itself, with the whole procedure occurring inside it only and involving its proteins only; therefore, the cell deaths have no way of being a true apoptosis [6, 7]. There are other iconic features of authentic apoptosis that differ from SD, SICD and necrosis and have been detailed by us before [6, 7, 149, 198].

### There are four basic SICD pathways that have been well delineated

Since SICD has been extensively studied under the name of apoptosis, we can search its mechanisms in the literature simply by changing the keyword from apoptosis to SICD. Because stressors are

variegated, SICD has numerous circumstances and thus multitudinous ad hoc modes [6]. A stressor, no matter whether it is an external one like a chemotherapeutic agent or an internal one like a change in the cellular pH, may trigger SICD via one of four basic pathways (Fig 3), as summarized from a rich vein of the literature that is actually overbearing [203-211, 219-223]: 1) The stressor may bind to a death receptor on the cell membrane, in turn activating caspase-8 and then the so-called “extrinsic apoptosis pathway”, which does not involve mitochondria [209, 224-231] and, in our opinion, should be renamed as “mitochondria-independent SICD” as it is not apoptosis at all. 2) The stressor may occur within, or directly act on, the mitochondria, resulting in its leakage of cytochrome c and other proteins to the cytoplasm and then the activation of the so-called “caspase-dependent apoptosis” or “caspase-independent apoptosis” [204, 207, 224, 232, 233], which in our opinion should be redefined as “caspase-dependent or -independent SICD”. We remain the only ones who are intrepid enough to remind peers that the permeability change of the mitochondrial membrane is caused by a stressor, is an unadulteratedly pathological event, and thus cannot be part of physiological apoptosis [6, 198]. 3) The stressor may occur within, or directly act on, the ER [234], in turn triggering a mitochondria-independent death via caspase-8 [229, 230] or triggering a mitochondria-dependent death that may be caspase-dependent or -independent [206, 229, 230, 235-238], as described above. 4) The stressor may



**Figure 3. Pathological SICD vs physiological apoptosis.** **Left-panel:** SICD occurs to useful cells and is often caused by an external stress directly or indirectly via causing an internal stress (such as a genomic DNA damage). The external or internal stressor acts on a death receptor at the cell membrane, the endoplasmic reticulum (ER), the mitochondria, or the lysosomes, executing a suicidal procedure via a caspase-dependent (CASP-SICD) or -independent (Non-CASP SICD) pathway or via a lysosome (Ly) mediated pathway. **Right-panel:** Apoptosis occurs as an order from the animal's body to eliminate no-longer useful (thus redundant) cells. Because few *in vivo* studies on authentic apoptosis without involving a stressor as the death inducer have been documented, we really know little about apoptosis, but it cannot be ruled out, or ruled in, that the apoptotic mechanism is the same as, or similar to, that used in SD and/or SICD.

occur within, or act directly on, lysosomes, leading to the leakage of its enzymes into the cytoplasm to kill the cells by hydrolysis of various cellular components [219-223]. Obviously, the lysosomal damage is also pathological. In addition, a stressor may also directly occur within or act on the nuclear genome (Fig 3), such as a lethal mutation occurring spontaneously, which may elicit an SICD via a pathway involving mitochondria and caspases described above.

The fact that mitochondria, lysosomes and ER play roles in programmed cell death, besides their primary functions in physiological situations, reflects another fact that most, if not all, components and genes in our cells have dual functions, i.e. can be good or bad to the cells [239]. Indeed, our genes and organelles often function oppositely in physiological and pathological situations [239]. What function a gene or an organelle should elicit depends on our body's decision regarding its ultimate interest in that particular situation, which usually is an attempt to convert a pathological situation to a normal one [127, 239]. For instance, mitochondria normally power the cell but kill the cell in many pathological situations [240], as described above. Cytochrome c normally serves as the most potent oncoprotein as it sustains our cells' life by powering them, but, once released from the mitochondria to the cytoplasm, it serves as the most potent tumor suppressor to kill our cells via SICD [6, 198, 241]. Somewhat oppositely, the P53 protein normally arrests progression of the cell cycle to gain time for the cell to repair mutations and in turn to return to its normal life trajectory [242-245], for which it should not be considered as a tumor suppressor, in our opinion [239, 246]. However, if the mutations are irreparable, P53 goads the cell into SICD and thus functions as a tumor suppressor [131, 239].

## Concluding remarks

There has been a prodigious amount of research on animal cell death modes. However, most of these studies have been focused on the death procedures and on the underlying mechanisms within the dying cell only, with insufficient attention on how the animal's body regulates the death and coordinates it with the responses of the live cells in the involved organ or tissue and in other body sites, including cells of the connective tissue that form granulations and scars. We sort cell demise modes into four basic types, i.e. physiological SD and apoptosis as well as pathological SICD and necrosis [6, 149]. SD, apoptosis and SICD are programmed events, with the program(s) evolutionarily built into the cells that do the dying, but largely with the animal's body maintaining remote control of the program(s).

Apoptosis expunges those useless yet normal cells while SD and SICD, like necrosis, exterminate those useful but ill cells, warning us that uselessness is always fatal and illness is dangerous in many cases. In cancer cells, SICD may have been strengthened while SD has been lost and apoptosis has been dramatically weakened. Apoptosis involves phagocytosis of the dooming or doomed cell by a macrophage or another scavenger-type cell, with the later part of the procedure occurring inside, and performed by, the scavenger cell. This insinuates that apoptosis has a cannibalistic property at the cellular level. SICD as a programmed pathological event resides between, and overlaps with, apoptosis and necrosis [6, 149]. This unique trait makes it often misconstrued as apoptosis or necrosis. Admixing a physiological death, like apoptosis, with a pathological one, like SICD involving a stressor and at least mitochondrial or lysosomal damage, is a major source of confusion in the literature. Because stressors are multifarious, SICD has a sheer number of ad hoc modes that in the literature are categorized into four basic pathways that involve death receptors on the cell membrane or involve pathologically altered mitochondria, ER or lysosomes, with some of the pathways using caspases as downstream effectors. Although these SICD pathways have been well articulated, they are often mistakenly put under the umbrella of apoptosis.

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## Competing Interests

The authors have declared that no competing interest exists.

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