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Does the Cytochrome C-Caspase Pathway of Cell Death Occur Physiologically in Animals?

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Introduction

There have been numerous published studies on the mechanisms of cell death, so far having established tens of different modes of cell death in the literature. A small number of these reported cell death modes are listed here as examples: necrosis, apoptosis, aponecrosis [1], netosis [2], necroptosis [2,3], parthanatos [4], entosis [5,6], methuosis [7], oncosis [8], paraptosis [9], anoikis [10], pyroptosis [11], ferroptosis [12], phagoptosis [13], caspase-independent apoptosis [14,15], cell death independent of caspases [16], and excite toxicity [17,18]. Some of these reported cell death modes manifest features of programming, usually coined as "programmed cell death", whereas others do not. Of these modes, apoptosis is the one best-studied of the programmed cell death type, and is considered to use a cascade of cytochrome c (CYTc) and caspases as the overarching pathway or mechanism.

Actually, some other modes of cell death that are considered to be non-apoptosis or not typical apoptosis but show features of programming involve CYTc and caspases as well. Although these CYTc-caspase-involved death modes may have certain differences from one another, in general they are triggered by a form of stress that induces mitochondrial outer membrane permeabilization (MOMP). MOMP leads to loss of mitochondrial functions, including the loss of inner trans membrane potential, which in turn results in release of inter membrane proteins CYTc and Apaf-1 into the cytoplasm, wherein the CYTc and Apaf-1 form a complex to activate initiator caspases, such as caspase 9.Once activated, initiator caspases will cleave (activate) effect or caspases, such as caspases 3 and 7, leading to death of the cell [19-21].

The above-described features of the CYTc-caspase cascade indicate that CYTc has dual functions [21]: at its normal, i.e. physiological, sub cellular location, CYTc participates in ATP production to power the cell, thus resembling an on co protein that sustains the cell's life. However, when it relocates from its normal sub cellular habitat to an abnormal one, i.e. to a pathological sub cellular location, it binds to some death-causing proteins to initiate death of the cell, thus functioning as a tumor suppressor protein. Therefore, the CYTc-caspase-involved cell death is a purely pathological procedure with increased permeability of the mitochondrial membrane and other sub cellular pathological alterations as its early events. Besides CYTc, our cells actually have many other proteins that have similar dual functions and are thus compartmented in (or confined to) a type of organelle as well. Good examples include lysosomal enzymes, which will digest the cell and kill it once being leaked from the lysosome to the cytoplasm. In fact, most genes and their protein products in human cells have dual or multiple functions, with some functions different from or even opposite to the others, which may be one of the reasons why the human genome encodes only slightly over 20,000 protein-coding genes [22-25] but controls the greatly diversified traits of human beings, as we have delineated before [26-28].

For different genes, their functional variation may be regulated at different levels and by different mechanisms, including single nucleotide polymorphism or point mutation of the DNA, variation of the RNA sequence due to alternative initiation or termination of transcription or due to alternative splicing, variation at post-translational modification such as phosphorylation at different sites of a protein, variation at different sub cellular locations of RNAs or proteins, etc [26,28]. For example, the longer RNA splice form of the Bcl-x gene, i.e. Bcl-xL, encodes an on co protein, whereas the shorter RNA splice form of this gene, i.e. Bcl-xS, encodes a tumor suppressor protein. The wild type form of the

P53 protein functions mainly as a tumor suppressor but some of the P53 mutants may be oncogenic [27,29]. However, different functions of different P53 proteins are not mainly determined by their sub cellular habitats; whereas CYTc, lysosomal enzymes, and other compartmented proteins manifest different functions when they appear at different sub cellular locations, with one sub cellular habitat being physiological while another being pathological.

Although apoptosis is generally accepted by the cell death research fraternity to be "a mechanism of programmed cell death", in the literature many different modes of cell death with innate programming features are actually described as "apoptosis" or "apoptotic death". For instance, on the one hand, those cell deaths of the involution type, such as those during digit individualization in the human embryo, postpartum involution of the uterus, post-lactating (post-weaning) involution of mammary glands, post-pubertal involution of the thymus, etc, are programmed cell deaths occurring in a physiological situation and are described by us as authentic apoptosis [30-32]. On the other hand, in cancer research, almost all cell deaths caused by irradiation, chemo drugs or chemo preventive agents, either in culture dishes or in animals, are described as "apoptosis" as well, albeit all these forms of radiation as well as these chemo drugs or chemo preventive agents are quite different forms of stress to the cells and have quite different physical or chemical properties. It seems that "apoptosis" or "apoptotic death" is quite convenient, at least for cancer researchers, to use without any worry of being questioned. This reality in the literature of cell death research, which is that many different types of cell death in vitro and in vivo are all put under the umbrella of "apoptosis", clearly indicates that either 1) "apoptosis" has not yet obtained a pellucid definition that is accepted by most peers, or 2) "apoptosis" does have a strict definition but most peers do not follow it, or 3) "apoptosis" has a very broad definition that covers many different modes of cell death with some traits of programming. In our opinion, many, probably most, cancer researchers love the word "apoptosis" and use it at their convenience to describe the cell deaths in their systems that involve CYTc and caspases, such as the deaths caused by their chemo drugs. In other words, the relationship between apoptosis and CYTc-caspases has been upended: Initially, peers studied the mechanism of apoptosis and identified the CYTc-caspase cascade as its overarching pathway, but then peers use the involvement of CYTc-caspases as the criterion to define apoptosis, meaning that it is apoptosis as long as CYTc-caspases are involved.

Cell deaths involving the CYTc-caspase pathway have two common features:

a) It is usually, if not absolutely, triggered by a form of stress to the cell, such as a chemo drug.

b) It requires MOMP that leads to the leak of CYTc from the mitochondrion to the cytoplasm to activate caspases.

These two features clearly indicate that cell death via this path way is a purely pathological event. If this pathological procedure is defined as apoptosis, as it has actually been in numerous studies, a question is thus raised as to whether apoptosis can really occur in animals in a physiological situation. As a more specific example, there is a question of whether the cell deaths during the aforementioned involutions in animals should still be considered as apoptosis, since the death procedure is pre-programmed and is purely physiological in the host animals. A fact that needs to be realized is that, apoptosis initially evolves as a programmed procedure for animals to purge away those cells that are no longer useful for them, in a way without being detrimental to the bodies of the host animals, i.e. in a physiological manner [30-32], whereas most data that establish the CYTc-caspase pathway as an overarching mechanism of apoptosis are derived from studies with pathological systems that involve a sort of stress. Few data are derived from studies on the aforementioned involution type of cell death in animals without an exogenous stress involved. In other words, we need to have more studies on cell deaths with those animal models of involution to determine whether CYTc can still initiate cell death

A. When there is no stress involved, such as no irradiation.

B. When the permeability of the mitochondrial membrane remains normal, or

C. When CYTc still remains at its normal location in mitochondrion without being leaked out to the cytoplasm.

There is some evidence that caspases may not be involved in the massive cell death during post-weaning involution of mouse mammary glands [33], although in our opinion caspases and probably also lysosomal enzymes of macrophages or whatever cells that engulf the dying or dead cells may still be involved to dispose of the cell corpses [32,34]. Therefore, we surmise that the CYTc-caspase cascade may not really be involved in authentic apoptosis occurring in such situations that are physiological to the host animals, exemplified by the aforementioned involution type of cell death [32]. If we agree that apoptosis is initially developed during evolution of the animal kingdom as a physiological mechanism to eliminate obsolete cells, such as those no-longer useful mammary epithelial cells after weaning, we need to reconsider whether cell deaths in pathological situations, mainly those elicited by the CYTc-caspase cascade, should be defined as apoptosis. In our opinion, "apoptosis" should be used to define those cell deaths occurring physiologically in animals without involving any exogenous form of stress, with the abovementioned involution type of cell death as good examples, whereas any of those cell deaths involving a sort of stress should be redefined as "stress-induced cell death", or SICD, but not as apoptosis [30-32]. Most, if not all, forms of SICD utilize the CYTc-caspase cascade as the overarching mechanism, with cells killed by chemotherapy or radiotherapy as good examples, as has been shown by numerous published studies. The physiological apoptosis and the pathological SICD are irreconcilable to each

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other, albeit both of them are programmed events and share many similarities, as we have expounded before [31].

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