"Programmed Cell Death: A Process of Death for Survival" – How Far Terminology Pertinent for Cell Death in Unicellular Organisms

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ABSTRACT: Programmed cell death (PCD) is genetically regulated phenomenon of selective elimination of target cells that are either under pathological conditions or unwanted for organism's normal growth and development due to other reasons. The process although being genetically controlled is physiological in nature that renders some hallmarks like blebs in the cell membrane, lobe formation in nuclear membrane, DNA nicks resulting to DNA ladder of 200 bp, and downstream activation of caspases. Moreover, as the process refers to the death of "targeted cell", the term is exclusively suitable for multicellular organisms. Number of reports advocate similar type of cell death process in unicellular organisms. As cell death in unicellular organisms is also reflected by the signature of PCD obtained in metazoans, such cell death has been grouped under the broad category of PCD. It is pertinent to mention that by definition a unicellular organism is made of a single cell wherein it carries out all of its life processes. Using the term "Programmed Cell Death" with a preset "survival strategy of the organism" for unicellular organisms looks misnomer. Therefore, this correspondence argues and requests recommendation committee on cell death to revisit for the nomenclature of the cell death process in the unicellular organisms.

KEYWORDS: Programmed Cell Death, Unicellular organism, multicellular organsim, Regulated Cell Death, nomenclature

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Introduction

Cell death is a process that occurs ubiquitously in all organisms and is mediated by termination of normal cellular metabolism which leads to extinction of normal cell activities. Cell death may be executed by controlled mode called as programmed cell death (PCD) and/or uncontrolled mode. Apoptosis and autophagy is described under PCD; however, necrosis is generally considered as an uncontrolled mode of cell death mediated by external factors such as infection and injury. PCD is genetically regulated phenomenon of selective elimination of target cells that are either under pathological conditions or unwanted for organism's normal growth and development due to other reasons. The process although being genetically controlled is physiological in nature that renders some hallmarks like blebs in the cell membrane, loab formation in nuclear membrane, DNA nicks resulting to DNA ladder of 200 bp, and downstream activation of caspases. Moreover, as the process refers to the death of "targeted cell", the term is exclusively suitable for multicellular organisms.

Apoptosis and PCD are not synonyms because PCD may be non-apoptotic also.[1–3] Apoptosis is a best studied form of PCD and in principle, a kind of cell death induced by mitochondria via release of cytochrome *c* and driven by caspases and apoptosomes.[4–8] Programmed nature of apoptosis has been well defined during the developmental fate of *Caenorhabditis elegans*, a nematode that has been shown to be an excellent model organism to study the mechanisms of PCD because of its transparency, knowledge of its cell lineage, and the ability to study cell death with single-cell resolution.[9–12] Autophagy is a fatal destruction of a cell that includes degradation of cytoplasmic materials using cellular lysosomal machinery, formation of autophagic vacuoles, dilation of the mitochondria and endoplasmic reticulum, and slight enlargement of the Golgi.

A recently coined term "Regulated cell death" (RCD) that intends to describe all modes of cell death regulated by a cellular mechanism has been defined specifically for yeast, as a failing response of a yeast cell upon exposure to mild microenvironmental conditions.[13] It was suggested that RCD encompasses PCD and other instances of cell death that depend on a molecular machinery and is mediated by regulated necrosis or apoptosis and can exhibit a spectrum of morphologies, resulting from multiple signaling pathways.[13]

Number of reports advocate similar types of cell death processes in unicellular organisms. As cell death in unicellular organisms is also reflected by the signature of PCD obtained in metazoans, such cell death has been grouped under the broad category of PCD. It is pertinent to mention that by definition a unicellular organism is made of a single cell wherein it carries out all of its life processes. Using the term "Programmed Cell Death" with a preset "survival strategy of the organism" for

unicellular organisms looks like a misnomer. Therefore, this correspondence argues and requests recommendation committee on cell death to revisit the nomenclature of cell death processes in the unicellular organisms.

Rationale Behind PCD

Every organism surviving on this planet is identified by its shape that accommodates certain fixed number of the cells that in-turn gives the visual identity of the organism.[14] Best known and well worked example of cellular sculpting is free digit formation from the elimination of the inter-digital tissue by apoptosis. Suzanne and Steller[14] have compared cellular sculpting with a stone sculptor who gives a shape to stone by clipping off small fragment in a precise manner from a crude block. Here, the major purpose of apoptosis is to remove excessive cells in an ordered fashion to give a new shape in the tissue/organ. Analogous to digit formation, developmental leaf remodeling in higher plants is another example of visible identity of organism involving PCD.[15] Apart from its involvement in visible identity of tissue/organ, PCD has been reported to be involved in elimination of the cells that are not properly functional or are generated in excess (as in case of immune system)[16,17] and not required for a system or required transiently (as in case of nervous system).[18] Such cells may be harmful for the system, although other cells within the same organism are sufficient to complete the required function, under such conditions the non functional or excessively formed cells route through PCD. For example, PCD in tail of the tadpole in which cells that lose their function become superfluous during metamorphosis of a tadpole into a frog. As a tadpole changes into a frog, the cells in the tadpole's tail are induced to undergo apoptosis; as a consequence, the tail is lost.[19] Another example in the developing human brain where there is cellular competition. Many more neurons are generated in developing brain than the needed to make a functional brain. Many neurons do not make a functional connection/wiring route toward PCD.[20,21] The liver is kept at a constant size through the regulation of both the cell death rate and the cell birth rate via PCD.[22]

In plants, PCD is involved in different processes on demand at different spatial niches in plant body during the course of plant development.[23–25] Some of the examples include abortion of the primordia of female flowers in unisexual flowers,[26] and death of tapetum and stomium cells during anther development.[27] PCD in xylem cells for water conduction and mechanical support during xylem development[28,29] and falling of leaves in deciduous trees during winter to survive within limited photosynthesis.[30] In addition, in a plant exposed to a moderate abiotic stress, removal of selective and susceptible cells through PCD has been reported.[31–33] Similarly, to limit the infection in a plant challenged by a non-host pathogen, hypersensitive response (HR) is produced by PCD-mediated selective killing of cells around the infected area to prevent spread of infection.[34]

Existence of the PCD in Unicellular Eukaryotes

Number of reports depicts the involvement of PCD in single-celled organism. PCD in unicellular chlorophyte *Chlamydomonas reinhardtii* benefits others of the same species, and also develops an inhibitory effect on the growth of other species.[35] It was observed that heat-induced PCD in *C. reinhardtii* is associated with positive fitness effects on neighbors, and this is called as species-specific fitness effects. It was suggested that the fitness effects of programmed death in unicells can depend upon the genetic relatedness between individuals.[35]

Involvement of PCD is revealed in *Trypanosoma cruzi*, a protozoan unicellular parasite during the in vitro differentiation of proliferating epimastigote stage into the G0/G1 arrested trypomastigote stage and shows the cytoplasmic and nuclear morphological features and DNA fragmentation pattern of apoptosis.[36] *Trypanosoma brucei* rhodesiense treated with concanavalin A also showed key features associated with apoptosis such as activation of an endogenous nuclease resulting DNA fragmentation, surface membrane vesiculation and migration of chromatin to the periphery of the nuclear membrane, however, cell membranes and mitochondria remained intact.[37]

PCD is also reported in unicellular protozoan parasites *Plasmodium*,[38] *Escherichia coli*[39] and *Leishmania*.[40] PCD in these organisms follows a number of morphological features with PCD in multicellular organisms. Bioinformatics analysis showed that PCD mechanisms in protozoan parasites have diverged during their evolution, and that some apoptosis factors are shared across taxa while others have been replaced by specific proteins with similar functions, for example, metacaspase replaces caspase.[41,42]

It was observed that the unicellular microalga *Dunaliella viridis* undergoes PCD process when it is subjected to several environmental stresses and matches classical and unambiguous apoptotic-like characteristics such as chromatin condensation, DNA fragmentation, intact organelles, and blebbing of the cell membrane.[43]

Justification of the Process in Multi-cellular Eukaryotes

As discussed above, PCD is an intrinsically instituted cellular process that requires following steps in sequence: decision, execution, and dismantle processes. More importantly as it is in operation during different stages of development as well as during stress and pathological conditions, it is a process of survival of the organism and technically if such an organism is surviving by disposing some of its cells it must be a multicellular organism. Thus, the term fits very well with metazoans.

Programmed cell process observed in unicellular systems does follow almost all the hallmarks of cell death that is reported in metazoans but in almost all the cases process has been justified in terms of population level[44] or species-specific fitness effects[35] at community level. There are certain examples

of PCD wherein cell death had been explained at organismic level. Best example is *Dictyostelium discoideum,* a soil living amoebae commonly called slime mold. *D. discoideum* is a unicellular form during normal course of its life and shows PCD to escape from unfavorable environmental conditions.[45] Although *D. discoideum* spend most of their lives as unicellular amoebae, during starvation the individual cells aggregate into a distinct "slug" and form a fungus like structure consisting of both a stalk and spores. The spores from the fruiting structure disperse for a better hospitable environment, whereas the stalk cells undergo PCD.[46,47] *Dictyostelium* is the critical example of support for the requirement of multicellularity for PCD to occur and as being related to class Protista, it has aspects of both unicellularity and facultative multicellularity, and PCD has been observed only when individual amoebae interact with each other to form multicellular stalk.

In *Heterosigma akashiwo*, unicellular microalga belonging to the Raphidophyceae, PCD and possibly "cannibalism" was described as a possible method to recover nitrogen nutrients in a situation where other source in the medium were not available.[48] This type of PCD, linked to population advantages should not be considered real PCD, since populations cannot be considered organisms. Use of "Induced cell death (ICD)" will be more appropriate terminology in the case of *H. akashiwo*. It is common to use the term "Developmental PCD" to indicate a PCD of cells in relation to develop a new organ or a change in shape or function of the organ, however in unicellular organism PCD is not a part of normal developmental stage rather it is induced by unfavorable environmental conditions; hence, the term Developmental PCD should not be used. Ubiquitous involvement of apoptosome and caspase activation/execution in animal apoptotic death differentiate apoptosis PCD from unicellular PCD; therefore, many scholars feel that the PCD of a unicellular organism shouldn't be called apoptosis.[49] In an excellent review, Skulachev[50] discussed PCD in bacterial system for the proteins that monitors DNA damage and postulated that "a massive apoptosis that targets organism in question and that is a member of a community of other individuals, such altruistic death of target individual may be useful for a supra-organismal level as a mechanism to adapt to changing environment". Skulachev coined the term "Phenoptosis" for such types of death. Recently introduced terminology RCD includes both types of cell death, that is, apoptosis and regulated necrosis; therefore, it should not be used for unicellular organisms. Though appropriate for the intended context, this seems to add extra layer of already existing conundrum with respect to pertinent unambiguous terminology adoption for discriminating different PCD processes to each other or self-explanatory terminologies that could decrease the existing confusion over the appropriate usage of terminologies. The aspect of intended beneficiary from the process in case of original PCD definition needs to be extended to cover communities of single-celled organisms where the members communicate with each other and for the overall benefit of the member cells (acting as an organism) sacrifice few members something akin to what happens in the multicellular organisms where the inter cellular communication is more pronounced and better understood. Authors like to suggest modification in existing PCD terminology involving its bifurcation as variations into "Population-PCD" (P-PCD) and "Organismal-PCD" (O-PCD) to differentiate between the processes which are controlled or triggered by the survival fitness need of the population, and the whole organism itself, respectively. Additionally, the "P" could mean to be involved in purging(pragmatic disposal) of the members from population for its overall survival as a group, while "O" could mean to orient/organize the body in case of multicellular organism where group of cells are more integrated and dependent on each other for their survival for the most part of the life.

Examples discussed above incline authors to believe that PCD is a process of cell death for organism survival thus it is strictly linked to multicellularity. Authors do not deny the process of cell death in single-celled organisms that also works at same motive, that is, for the maintenance at population level. As technically, a population cannot be compared with a organism, therefore nomenclature of cell death in unicellular organism needs a revisit.

Author Contributions

BST generated the idea. BST and SSP wrote the paper, CMP and SS provided supporting documents for writing the manuscript.

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