

Appendix G: Programmed cell death in the light of the OGT

Programmed cell death (PCD) is an active, energetically costly and genetically controlled cellular self-destruction driven by complex biochemical and specialized cell processes (Berman-Frank et al. 2004). The seminal work on PCD (Lockshin and Williams 1965) was followed by another that coined the term apoptosis (Kerr et al. 1972). These early works showed this “cell suicide” in animal tissues. For decades, the terms PCD and apoptosis have been used interchangeably, although apoptosis is now considered a form of PCD with a particular morphology and process within the more than a dozen differentiated PCDs that are currently recognized (Kopeina and Zhivotovsky 2022, Kulkarni and Kardwick 2023).

For decades now, PCD has been considered functional to multicellular organisms for at least three physiological reasons: for the normal development of the organism from the embryo, for adult homeostasis, and as a defensive mechanism against some type of cellular damage, stress, or pathogen (Vaux 1994). Importantly, from the perspective of the cells involved, it was argued that it had a clear evolutionary meaning as extreme altruism of somatic cells by and for the good of the multicellular organism, precisely selected because it is a functional process for the organism (Vaux 1994, Ameisen 2002, Koonin 2016). It has been theorized that the evolution towards organic multicellularity comes from PCD mechanisms (Koonin 2016) and models have been developed in which apoptosis-like mechanisms or PCD are part of the mechanisms that, hand in hand with cooperation, lead to higher levels of individuality (Iranzo et al. 2014, Moreno and Ofria 2019), such as the Major Transition in Evolution (MTE) (Durand et al. 2019), which we have also referenced from our OGT scheme. Nevertheless, in these models PCD may be limited by the entry of cheaters (individuals who take advantage of the benefit of not committing suicide) (Bourke 2016).

From the logic of natural selection, the adaptive-functional view of PCD in multicellular organisms, led in turn to the prediction that it would probably not occur in unicellular organisms (Vaux 1994, Zwilling 1992, Oberley et al. 1980, Vomastek and Franek 1993), since a trait that implied the non-survival of the individual subject to natural selection could not be selected.

It was this theoretical paradigm that probably led to the fact that PCD mechanisms were not recognized in unicellular organisms until the second half of the 1990s, despite the existence of strong experimental evidence even before the terms PCD and apoptosis were named in multicellular organisms (Ameisen 2002) and even though observational work affirming this had appeared (Davis et al. 1991), which included the bacterium *E. coli* (Trgovčević et al. 1981). After the “rediscovery” of PCD in unicellular parasites in 1995, it was speculated that it must be a later mechanism, picked up, perhaps by horizontal gene transfer, from multicellular organisms, that is, a rare and unstable phenomenon in the evolutionary history of life on our planet (Ameisen 2002).

To explain the ecological and evolutionary origin and maintenance of PCD in unicellular organisms, one must turn to selection at higher levels than the individual that commits suicide. Okasha (2006) shows that evolution by selection occurs at multiple levels of organization, and when levels of organization cooperate and coordinate into a new organic individuality, as in MTEs, natural selection ceases to operate directly on lower levels (de Castro and McShea 2022), which facilitates the extreme cooperation or altruism that PCD entails.

This behavior, apparently contrary to the classical vision applied to multicellular organisms (e.g. Konin 2016, Kasuba et al. 2015, Johnson and Karzsuch, 2022, Tanouchi et al. 2012, Duran

and Ramsey 2023), has been described as paradoxical, puzzling, ironic or improbable, which is why it has required ad hoc hypotheses or speculations, some quite complex, to apply them to unicellular organisms (Kasuba et al. 2015, Ameisen 2002). Reviews and works from the last decade continue to conclude that “a broad understanding of the ecological function of PCD in microbial communities is missing” (Ndhlovu et al. 2020, pp. 2) and that “currently, there seem no convincing arguments about the evolutionary significance of such a death pathway of unicellular organisms” (Kasuba et al. 2015, abstract).

The extreme altruism of cells that commit suicide so that other cells in the same organism can function properly can also be seen in our language as cooperation at the cellular level with bottom-up consequences and coordination from the top-down view of the organism. This principle, which operates in the MTEs and in the PCD of current multicellular organisms, was assumed to not be at work in unicellular organisms (Kooning 2016, Taylor-Brown and Hurd 2013). Conversely, the OGT would predict the occurrence of programmed cell death in unicellular organisms because it considers them cells of a much larger multicellular organism. In fact, this hypothesis is already made in previous works on the organic Gaia (de Castro 2020(2008), de Castro 2013, de Castro 2019), where some of the predictions that we will develop in the following are also noted.

The OGT asserts that Gaia becomes an evolving organism composed of a hierarchy of structures originating from bacteria and incorporating all other “organisms” as Gaia’s “cells” (and the biosphere as Gaia’s technological product or “house” or “extended phenotype”). In the logic described in the OGT, all of her “cells” must transfer most of their functions, goals, or purposes to the “organism,” even to the point of “sacrificing” themselves for Gaia, for example, to maintain her large-scale biogeochemical cycles. In biology and physiology, it is argued that the cells of a multicellular organism work more for the organism than for themselves, performing “illogical” actions in terms of their “survival,” such as the phenomenon of PCD as an extreme example of altruism shows. PCD in pluricellular organisms is also an example where Prigogine's trinomial applies with its top-down feedback: it is the organism that dictates the behavior, even suicidal behavior, of its cells when they cease to function for the organism or can harm it. From the OGT we say that cells transfer their functions to the larger structure, which must be organic to make full sense (the sacrifice of a cell or organism must be for the “greater good”—the good in the functional sense of that “greater” entity, not for a structural system that does not even reach the level of an organism).

The leap to the OGT and its application to PCD on this topic is obvious and direct:

We should expect programmed cell death to be a widespread property of Gaia's “cells,” as ancient as Gaia itself. PCD serves the benefit of structures beyond the population of individuals committing suicide and serves to control these “cellular” populations, precisely because otherwise they could become analogous to cancer, as would happen if this disorder occurred in a multicellular organism. PCD would serve Gaia to prevent the entry of free riders or cheaters into the “system” that otherwise could break Gaia functionalities. The planetary regulation that other Gaia theories try to explain, frequently use “Daisyworld-like” models. These models could have problems with the appearance of this type of cheaters that can break homeostasis and cause the system to collapse –losing planetary habitability (Rubin and de Castro 2021). For the case of Daisyworld-like models, Rubin and de Castro (2021) have developed models that, inspired by the organic Gaia paradigm and Bidle’s (2004) observation of the huge extension of PCD in phytoplankton, develop better temperature regulation than other models, when programming an analogous to PCD or altruistic behaviour in daisies.

In short, PCD is a physiological process of Gaia and could be studied as it has been studied in animal and plant tissues and physiology for decades.

Therefore, we explicitly make the following predictions about programmed cell death at the light of our OGT:

1. It must be common and widespread in all living kingdoms, including single-cell organisms (eukaryotes and prokaryotes) and is very likely implied in evolutionary transitions like the FECA (first eukaryote common ancestor) and other later symbiotic additions such as plant plastids, and all the transitions to multicellular organisms which are believed to have been performed dozens of times more or less independently.
2. It must be very ancient in the geological record. Gaia, as an organism, has existed since the genetic networks that govern PCD were complexified and irreversibly fixed.
3. It must be one of the primary mechanisms of death and population control in rapidly growing cellular organisms.
4. PCD must operate at spatial and temporal levels over local communities and related taxa, where standard group selection theories have been applied. PCD would help the formation of structures by closing the coupled Prigogine trinomials, i.e., must operate even among ecosystems, implying global biogeochemical cycles and global RAMO properties, serving, for instance, the cycling of the elements between different ecosystems (equivalents to tissues of Gaia). It is possible that in some cases entire communities of micro-organisms “commit suicide” by this and other related mechanisms in the event that they serve other communities that are distant in space and time.

All four predictions are testable, and in fact, they have passed the observational test as studies have progressed since the phenomenon was discovered in multicellular organisms up to the present:

1. It has been found in all kingdoms, including bacteria and has been implied in evolutionary transition (Durand et al. 2019) with parallels to eusociality emergence in insects (Romi et al. 2016).
2. It appears to be a very ancient mechanism, as it has been found conserved and with a diversity of PCD mechanisms with circuitry of more than 20 genes in phylogenies of phytoplankton bacteria, which suggests a date back more than 2.8 billion years (Bidle 2016, Ameisen 2002, Kasuba 2015).
3. To the authors' knowledge (also Ndhlovu et al. 2020), no taxa of fast-growing unicellular species—more easily capable of deregulating with dysfunctional growth—has been found to exist. This suggests that programmed cell death is indeed a primary mechanism by which Gaia regulates its cellular populations. Bidle's work on oceanic microplankton (2004, 2016) supports this view, showing that more than 50% of observed deaths in these communities result from apoptosis, while the remainder are attributable to accidents, starvation, radiation and other physical insults, viral infection, grazing or predation. Notably, viruses appear to play a significant role, even in PCD (Ameisen 2002), which, from a Gaian perspective, can be interpreted as an additional regulatory tool serving functional purposes within the larger system—constituting another prediction of the theory. But if apoptosis is the main cause of death in those communities important for global biogeochemical cycles, then the theory that PCD emerges as defense against the extension of a viral infection, is not the present main

cause of their conservation during eons, because the death toll by suicide is enormous, and larger than the death toll through virus “attacks”.

4. Examples have been observed where a population of one taxa benefits from the PCD of another unrelated taxa in hypersaline communities (Orellana et al. 2013), which has helped to launch the hypothesis that PCD is a possible mechanism of the “black queen hypothesis” if this hypothesis generalizes to altruistic processes above and beyond the genetically similar community (Ndhlovu et al. 2020). Kojic and Miliasajevic (2020) show that PCD facilitates nutrient recycling and has recently been implicated in large-scale biological cycles (Bidle 2016, Kuhlisch et al. 2024), where the cycling of major nutrients in the oceans is affected by large-scale phytoplankton blooms, which are hot spots of microbial life. Phytoplankton feed the entire marine food web and not only are they under the control of various mortality agents such as grazing and viral lysis, but also, the cell-to-cell communication mechanisms that elicit PCD, which synchronizes bloom demise, amplify the nutrient release to other ecological zones (Kuhlisch et al. 2024).

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