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Commentary
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Programmed Cell Death Vs Death by Suicide; A Functional Comparison

Prasanna N. de Silva*
Monkwearmouth Hospital, Sunderland, UK

***Corresponding author:** Prasanna N. de Silva, Monkwearmouth Hospital, Sunderland, UK

ABSTRACT

This article reviews the physiology of programmed cell death (PCD); commonly known as cell suicide. The 3 main processes of PCD; apoptosis, necroptosis and pyroptosis are described, including external and internal signalling precipitating cell death. These are then compared with behavioural phenotypes of planned suicide, associated with toxic relationships, 'anomie' (disconnection from the contemporary social network), 'learned helplessness' (the main model for depression), social media reporting of suicides and political indoctrination leading to suicide bombings. Ethical arguments for and against active medical assistance in completing suicide by people with progressive neuropsychiatric disorders (such as dementias) and those with long standing severe mental illness (such as anorexia and personality disorder) are discussed. Emerging therapeutic prospects of 'stalling' PCD and using inflamatory interleukin patterns to predict overwhelming PCD and dramatic suicides are highlighted.

Keywords

Apoptosis
Pyroptosis
Necroptosis
Anomie
Lithium
social media
assisted suicide

LEARNING OBJECTIVES

- Understanding the physiology and classification of Programmed Cell Death (PCD), including the potential to generate systemic inflammation.
- Comprehending models describing behavioural phonotypy of suicide, including learnt helplessness and characteristics of anomie
- Be aware of emerging therapeutic prospects of 'stalling' PCD in order to protect neuronal cells in early dementia utilising MEG 3 blockade, and in long term protection from suicide utilising Lithium.
- Be aware of patterns of inflammatory interleukins (High IL6 and *IL1*-β, low IL2) which could be biomarkers for dramatic (violent) completed suicide and predicting the likelihood of overwhelming cytokine storms secondary to pyroptosis

PROGRAMMED CELL DEATH

Programmed Cell Death (PCD) involves processes multicellular organisms use to destroy individual cells deemed irreversibly damaged or senescent [1], divided in to intrinsic and extrinsic processes. The 3 main processes are Apoptosis, Pyroptosis and Necroptosis. Apoptosis (intrinsic PCD) is initiated by the individual cell utilising a cascade of proteolytic enzymes collectively termed Caspases [2] to disassemble intracellular contents. Pyroptosis and Necroptosis (extrinsic PCD**)** involves the innate immune system utilising natural killer T cells to perforate cell membrane and expose cell contents [3], so that macrophages can ingest intracellular organelles to extract usable amino acids. Compared to Intrinsic PCD, the extrinsic alternative generates significant inflammatory reactions, in order to alert the innate immune system of potential damage to surrounding tissue.

In embryonic development, Apoptosis is used to clear webs between digits and to remove T and B cells which have the potential to attack healthy tissue, risking autoimmune disease [4]. During apoptosis, interferon gamma (IF δ) is expressed by the dying cell to warn surrounding cells of imminent self-destruction. Furthermore, cell membranes incorporate 'death receptors' such as Fas/FasL [5] which commence apoptosis when 'death ligands', for example Tumour Necrosis Factor alpha (TNFα), lock onto them.

PCD processes are also divided into lytic and non-lytic processes [6]. Lytic processes (pyroptosis and necroptosis predominantly) occur when the cell is damaged by anoxia [7].

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They include pyroptosis and necroptosis, when cell contents are exposed to surrounding interstitial fluid stimulating an inflammatory cascade to prime a vigorous immune response. Pyroptosis is the more rapid (and toxic) process, as it releases large quantities of cytokines into the systemic circulation mediated by cellular inflamazones. The recent SARSCov2 infection had the potential to cause widespread cell pyroptosis of macrophages, platelets and respiratory endothelium with the resulting cytokine storm causing acute respiratory distress [8]. Pathophysiology of Necroptosis [9] also results in an inflammatory reaction (for example following neurone, muscle or gut endothelial cell death), albeit following a slower trajectory, leading to for example chronic inflammatory bowel and neurodegenerative disease.

Non-lytic processes are commenced by the cell, usually secondary to senescence or oxidative stress (the accumulation of Reactive Oxygen Species or ROS) leading to mitochondrial failure in producing energy [10]. This mainly involves apoptosis, where the cell undergoes a graduated process of self-destruction within intact cell membranes with partially disassembled contents retained in multiple apoptotic bodies before being discarded without an inflammatory reaction [11]. Of late, there has been rapid advances in using in-vitro modulation of Natural Killer Cells with a tumour specific antigen, which detects lack of 'normal' surface antigens in cancer cells, can provide non-lytic effects without the toxic cytokine storm which typically accompanies current anti-tumour therapies [12]. Alternative tumour reducing approaches include inhibiting blood vessel formation (angiogenesis) in existing and growing tumours, leading to non-Lytic programmed cell death [13].

The alternative to cell death is autophagy, which involves the replacement of unproductive cellular organelles such as ribosomes and mitochondria within intact cellular membranes [14]. The organelles are broken down to amino acids to form new organelles. The commonest precipitants of autophagy are physical exertion and fasting influencing muscle, bone, endothelial and neuronal cellular regeneration [15,16]. However, in some circumstances, persistent or recurrent autophagy can lead to apoptosis for example, when organelle regeneration is inadequate [17]. One of the problems of current anticancer drugs is the secondary build-up of ROS; there are pharmacological agents being designed to reverse this, potentially resulting in less cardiovascular and neurodegenerative side-effects of oncological treatments [18-20].

There are cellular mechanisms for 'stalling' apoptosis, utilising intracellular Beclin 2 (Bcl-2) proteins interacting with the autophagy essential factor Bcl-1 [21]. Similarly, modulating intracellular calcium concentrations can avoid apoptosis and autophagy [22]. Necroptosis of neurones in Alzheimer's disease could be reduced using pharmacological or epigenetic inhibition of neuron specific maternally expressed gene 3 (MEG3) based on recent in-vitro research [23]. Lithium salts appear to assist autophagy by inhibiting inositol monophosphatase [24] and is considered to be neuroprotective through epigenetic alteration of apoptotic-regulatory protein production [25].

DEATH BY SUICIDE

Anomie was a societal condition originally described by Emile Durkheim [26], involving progressive disassociation of an individual from the usual societal norms, alongside breakdown on familial and social networks. Anomie is best described as a presumed environmental (extrinsic) driver of suicide. Other extrinsic precipitants of suicide include persistent bullying and toxic comments generated via social media [27], sometimes including active suggestions to end one's life. On occasion, clusters of suicide occur following death a celebrity, especially when the method of suicide is revealed in the media. Common features leading to anomie include living in high-rise buildings, single occupancy (especially involving middle aged men) and frequent changes in accommodation [28] with associations with both recurrent self-harm and completed suicide [29,30].

Intrinsic suicide is best associated via the concept of 'learned helplessness' advanced by Seligman [31], utilising rodent studies. When electric shocks are delivered to one site, a rodent will jump to another site. However, if unpredictable shocks are delivered to any of the sites, the rodent will cower in one area, despite change in the shock delivery to the previous specific site. This behaviour is seen as being equivalent to development of major depression, which has significant association with completed suicide [32]. Learnt helplessness could also result from inescapable exposure to toxic relationships and to previous experience of childhood trauma [33], unpredictable auditory hallucinations in psychosis, out of control compulsive behaviours (including addiction to alcohol), and intrusive flashbacks associated with post-traumatic stress disorder [34].

Although most suicides take place in private, another variant involves public suicides to gain attention to political issues; for example, suicide bombings or self-immolation [35]. In some instances, incapacitious adults or children are manipulated by influential others to carry out these acts. Perhaps those persuaded to commit suicide (like those influenced by social media) are already in a situation of anomie, with no social network to moderate their beliefs or impulses. Public suicides could be seen as akin to pyroptosis, causing trauma to onlookers, potentially a trigger to post traumatic stress disorder (PTSD) or death by suicide in due course [36]. The equivalent

of necroptosis could be death caused by refusal to eat and drink, as occurs with people suffering terminal malignancy, severe depression or anorexia nervosa.

Similar to a cell signalling of its imminent self-destruction utilising IF **δ**, humans signal their intentions of suicide to others around them, for example through verbal comments, texts on social media, or rehearsing potential actions at a site where scrutiny by others is likely. Some facing progressive neurological disease or senility will plan suicide and / or seek help from medical professionals.

There are units performing euthanasia on request in Switzerland, Belgium, Holland and most recently in Canada as part of the Medical Assistance in Dying (MAID) programme. [37]. This includes clinicians actively asking patients if they wish to seek help in committing suicide. In one Canadian state (Quebec) secondary legislation is being considered to accommodate MAID for people suffering from psychiatric conditions such as personality disorder or PTSD. However, in most countries offering voluntary euthanasia, medical assistance in dying is an alternative to palliation of untreatable medical disease, with psychiatric patients deemed to lack capacity [38].

DISCUSSION

On comparing processes involved in PCD and suicide, there appears to be some broad similarities, for example, on intrinsic and extrinsic precipitants. Apoptosis could be compared to 'quiet' intrinsic suicides including those which are medically assisted. Necroptosis seems similar to a person starving themselves to death. Pyroptosis is akin to public suicides including those of suicide bombers. In terms of precipitants, similar to cells being exposed to toxins or viruses leading to PCD, suicide can be precipitated by exposure to toxic relationships, negative comments on social media or a cluster of successful suicide utilising a specific method as reported in social media. There is evidence of a pattern of cytokines (High IL6 and *IL1*-β, low IL2) appearing to be a harbinger of completed suicide, especially involving dramatic methods; potentially a biomarker to predict suicide risk [39]; similar to IL6 and other inflammatory cytokines being biomarkers for potential necroptosis and pyroptosis.

Similar to vulnerable cells (for example due to progressive accumulation of ROS or nutritional deficiencies), people can be made vulnerable by multiple negative life events and childhood trauma. It is estimated that over 60% of suicide victims have experienced childhood trauma [33]. Intrinsic intracellular processes involving a cascade of various caspases could be compared to negative thinking development in suicidality; moving from ideas that death is preferable, progressing to wishes of suicide, thereafter, consideration of specific plans.

Furthermore, similar to 'stalling' of apoptosis by modulating intracellular Calcium homeostasis, inhibition of Bcl and MEG3, temporary restrictions can be imposed on suicidal actions by utilising Socratic why, what & how questioning [40], admission for observation, restricting access to materials usable for suicide or using Ketamine infusions [41]. Longer term prevention of suicidal behaviour via changes of core beliefs can be accomplished by cognitive behaviour therapy [42]. Creating a social network via social media [43]. is perhaps similar to the anti-apoptotic, pro-autophagic effect of exercise and intermittent fasting. Lithium also has the potential to stall suicidal behaviour amongst mood disordered patients [44], perhaps linked with its potential to epigenetically modify the Brain Derived Neurotropic Factor (BDNF) promotor gene conferring neuroprotection [25].

Comparison of the purposes and consequences of apoptosis and suicide however does not indicate similarities. Apoptosis appears to be beneficial to surrounding tissues via improved innate immune responsiveness, better nutrition and oxygen supply [45]. Human suicide does not necessarily result in improved resources to others around them, especially if the death is of a family breadwinner. The trauma of witnessing the attempt or discovering a body can lead to chronic PTSD or suicide [36].

However, in the context of poorly funded health services, it might be tempting to consider if it is economically more realistic to offer physician assisted suicide where costs of maintaining life in 'terminal' medical conditions or 'unmanageable' psychiatric conditions become increasingly prohibitive in terms of staff resources and finances [46]. This type of reasoning, unfortunately, is reminiscent of eugenic thinking during the 1930's in Weimar Germany [47] where people with learning disability and chronic psychosis were put to death using Potassium Chloride infusions. This was prior to the Nazi government coming to power. The Nazi's made this programme more efficient as the T2 project. The Nazi's described eradicating 'cancerous' populations, using gas chambers to eliminate specific racial groups (Jews and Romany's in particular) from society, resulting in the deaths of many millions of people.

Clearly the Weimar and Nazi projects did not involve assessment of capacity unlike current physician assisted suicide protocols [38]. However, allowing a physician to ask patients if they are interested in medically assisted suicide can be viewed as perceived coercion, especially if family members also favour this suggestion. Consequently, concern has been raised about

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Quebec offering physician assisted suicide for people with psychiatric illnesses, dementia and other neurodegenerative conditions [48]. The debate on assisted suicide has also led to rethinking the clinical goal of 'zero suicide' on grounds of beneficence, non-maleficence, patient autonomy and social justice with a greater emphasis primary prevention, by focussing on tackling deprivation and social isolation [49-52].

CONCLUSIONS

Awareness of pathways and processes leading to PCD and death by suicide can lead to an improved understanding of suicidal behaviours and on pathophysiology of neuronal death in dementias. Patterns of inflamatory interleukins (High IL6 and *IL1*-β, low IL2) could be biomarkers for completed dramatic suicide and for overwhelming Cytokine storms following pyroptosis, as was seen among a minority of people with SARSCov-2. However, current interest in PCD of the non-lytic form (avoiding cytokine storms in cancer treatments) involves immunotherapy using in-vitro engineered Natural Killer cells, techniques which can be extended to other non-oncological conditions.

The recent finding of MEG3 blockade protecting neurones from necroptosis despite the presence of oligomers could be a breakthrough in dementia treatment. Lithium appears to be beneficial in reducing both PCD and suicidality, possibly utilising shared processes leading to neuroprotection. Targeted suicide prevention can also be a beneficiary; for example, in the use of social media to combat isolation, homelessness and debt, whilst restricting toxic posts via legislation. From a psychiatric service viewpoint, the swing away from zero suicide as an objective is (probably) beneficial, although ethical and legal issues relating to medically assisted suicide, especially regards coercion, needs continued vigilance.

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