Essay: Cell death in health and disease

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Introduction

Since the 19th century, cell death has been appreciated but until the 20th century no experimental investigation had taken place. 1 It was later suggested that programmed cell death (PCD) has been a vital mechanism in the survival of multicellular organisms.2 Cell death is an ongoing process in the human body before and after birth. In humans, both physiological and pathological PCD occur to maintain homeostasis. It plays an important role in protecting the body from infections to diseases such as cancer. Cell death is often described as a double edged sword with regards to its beneficial and harmful characteristics. Uncontrolled cell death has been an explanation for many neurodegenerative diseases such as Alzheimer's and Parkinson's. In

contrast inhibition of cell death has often been the cause of developing cancer. This essay will outline plus examine the mechanisms of the different cell deaths which occur in the body before and after birth, discussing the pathway of diseases caused by both excessive and insufficient cell death.

Cell death before birth

PCD is an important mechanism in the formation of limbs during the embryonic development period. Apoptosis is responsible for the death of extra cells which are produced to ensure that there is no shortage during organ and limb development. The cells which make up the extra tissues are broken down in the interdigital regions. This is controlled by signaling proteins. Inhibition of transferring growth factors could lead to anomalies in the limb development and is the explanation for conditions referred to as syndactyly and polydactyly.3 Polydactyly (see figure 1) limb defect emerges from the lack of apoptosis and formation of extra fingers or toes during embryogenesis.3 On the other hand osseous syndactyly is a condition where there is excessive cell death resulting in failure of the digital rays to separate consequently leading to the formation of joined finger or toes (see figure 2) 3. PCD is important in the development of limbs in embryos but it is essential that apoptosis is controlled to benefit the body rather than contributing to disease. This process continues in the body after birth.

Types of Cell Death

Necrosis is a pathological cell death which follows a different mechanism from the PCD (which has evolved to benefit the body). Therefore it is described as a passive and non-hereditary PCD.6 This death mechanism is distinct from the PCD in several ways; from the structural features (necrotic cells are enlarged in comparison to the normal apoptotic cells) the timing of the pathways (occurs over a period of several hours).7 There are many different conditions which can initiate cell death by necrosis. One trigger is the change in the permeability of the ion channels in the cell surface membrane. This leads to the activation of lysosome rupture thus resulting in DNA fragmentation and consequently cell death. It has been suggested that necrotic cell death is a major component in the damage to the nervous system during neurodegeneration.8 Necrosis is a form of cell death which frequently contributes to disease in the human body.

In comparison apoptosis is an evolutionary mechanism for the selective removal of damaged, ageing and unnecessary cells in the body therefore this complex PCD system has many different mechanisms.9 This essay will look at the mitochondrial mediated pathway as the mitochondria is vital to the survival of multicellular organisms. The active central role of mitochondria in PCD had not been evident until the mid 1990s.1 They are thought to be the primary organelles in regulating the apoptotic pathways by responding to stress stimuli including different forms of radiation, environmental factors, genes and DNA damage. These signals to the mitochondria are interpreted by multiple cytosolic or intraorganellar molecules which eventually give rise to adjustments in the outer mitochondrial membrane.1 One of these adjustments could be change in the permeability of the membrane to proteins which would otherwise be present between the inner and the outer mitochondrial membrane.10 These proteins escape the mitochondria and initiate apoptosis by activating caspase-3. 1 This is described as the intrinsic pathway (see figure3)1. The mitochondria can also follow the extrinsic pathway which is initiated by death ligands (see figure3)1. Here death ligands generate signals which can either directly engage the mitochondria through a series of events activating the effector (caspase-3) or promote the cleavage of non-caspase substrates stimulating changes in the outer mitochondrial membrane. This causes the release of apoptogenic factors.1 Apoptosis also has physiological mechanisms and is not possible for the cell to carry out these it will initiate type II PCD (autophagy) as an alternative .1 Overall necrotic and apoptotic cell deaths are relatively different (see figure 3).9

Autophagy is another form of PCD which is induced by stress situations. In this cell death pathway autophagosomes deliver intercellular proteins and organelles to lysosomes for destruction.6 One of the common stress stimuli which can induce autophagy is oxidative stress which results in myocardial infarction. Here autophagy is not a contributor to ischaemic cardiac diseases but is an adaptive response demonstrating

its role in aiding health .6 Although autophagy is viewed as a survival assisting mechanism, just like apoptosis excessive autophagy leads to undesirable cell death. It can be induced by both extracellular and intercellular signals.6 Due to its stress stimuli response, prolonged exposure to the signals will result in the development of diseases. One of the common branches of diseases caused by excessive cell death are the neurodegenerative diseases.

Figure 3. The Mitochondrial Death Pathway; Schematic representation comparing components of the intrinsic and extrinsic apoptotic pathways in C.elegans and mammals.

Neurodegenerative diseases

Neurodegeneration is the central mechanism causing disease in the nervous system responsible for a range of diseases from a small stroke to chronic Parkinson's and Alzheimer's.8 Continued research into cell suicide has revealed greatly on the origins of neurodegenerative diseases suggesting the predominant cause as excessive PCD; a result of mutations in the regulatory gene expressions resulting in the degeneration of healthy cells 1. Repetitive observations of the accumulation of autolysosomes during autophagy in the development of Alzheimer's has questioned the involvement of autophagy in such senarios.8 Thus autophagy has been excessively induced in cells to identify autolysosomal maturation and substrate proteolysis as the disease initiation steps. This defect causes an accumulation of organelles and transport failure giving rise to symptoms such as memory lapses, difficulty in performing spatial tasks etc. Similar observations have been seen in other neurodegenerative diseases.11

Parkinson's is a neurodegenerative movement disorder with common symptoms such as tremor, slow movement and rigidity.12 Neurodegeneration in Parkinson's has been implicated with the degeneration of the mitochondria by autophagy. The protective pathway responsible for defence against mitochondrial damage and dysfunction is disrupted thus resulting in the accumulation of protein complexes which initiate miatophagy.11 There are also implications of oxidative stress and selective dopamine neurone degeneration.11 Excess dopamine can cause oxidative damage initiating the mechanism for cell death. Hyperactivity of cell death mechanisms bring about these degenerative diseases; however some diseases are initiated by insufficient cell death.

Insufficient cell death

Cancers are characterised by their unregulated growth and spread of cells throughout the body.13 In normal cells transcription factors control cell death and growth promotion.14A mutation in the PCD regulation gene results in resistance to multiple cell death mechanisms with uncontrolled cell cycle thus a tumour forms using the nutrients which are available for the growth of healthy cells.15 16 Oncogenic transformation however is not just escape from apoptosis, it is the balance between mitosis and apoptosis that is critical. Interestingly regions in oncogenes which increase susceptibility to apoptosis are similar to those which promote proliferation.17 Thus the role of active p-53 in apoptosis is important as increased p-53 is required to trigger cell death and cells normally express low levels.17 Consequently there is insufficient cell death resulting in the formation of a tumor.

Therapeutic implications

The vital role of cell death in health and disease discussed in the essay and many more have promoted research into curing these diseases by manipulating PCD. Experiments have observed the impact of inhibiting cell death with apoptosis inhibitors. 4'Methoxyflavore a neuroprotective agent which inhibits neuronal cell death is a drug with the potential to manage neurodegenerative diseases.18 Researchers have observed the impact of drugs such as Nilotinib which can aid the function of lysosomes by helping the transportation of the damaged organelles and accumulated proteins as potential rug for Parkinson's.19 On the other hand, the therapeutic potential of cell death in cancer has examined inducing cell death in cancer cells through various

pathways. Targeting mitochondria to induce PCD as well as targeting apoptosis inhibitors involved in the development of cancer have been looked at as important therapeutic strategies.1 Arsenic trioxide (ATO) a chemotherapy drug used in the treatment of acute promyelocytic leukaemia is effective in speeding up death of leukemic cells.20 Tumour Necrosis Factor (TNF) is a protein which induces necrotic cell death of tumour cells and is also one of the existing means of treating cancer.21 Research has identified p53 (a TNF) as a major suppressor of tumour formation.22

Conclusion

Research has established that the evolved mechanism of PCD in humans has played an important role in health and disease. Different mechanisms of cell death have been identified focusing mainly on Apoptosis (the most understood and common forms of PCD), Autophagy and Necrosis. The absence of the inflammatory response in apoptosis is an advantage over necrosis.23 The significance of regulated PCD in the prevention of emerging ailments ranging from neurodegenerative diseases to cancer has been emphasised several times. This knowledge has been used in therapeutic research to try and develop cures for these disorders. To date no such drug has been created which has the primary function to manipulate PCD mechanisms in neurodegenerative diseases therefore the therapy of these diseases confronts significant challenges.24 However in cancer treatment, such approach have been used. The discovery in the role of PCD in aging, disease, growth and several others has introduced many opportunities to potentially cure terminal diseases. Could the future be relieved of 'incurable' diseases?

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