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Neurodegeneration - A Means to an End

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Cell death, a global phenomenon found throughout the animal kingdom, is a mechanism to maintain tissue homeostasis and for adaptation to changes in the environment [1,2]. Millions of cells die in our body daily- they succumb to stress and commit suicide by a mechanism referred to as cell death or apoptosis [2-4]. Under normal conditions cells are continuously replaced by new cells from the stem- or progenitor- cells. For example, an optimum balance in shedding of dead cells from the skin and their replenishment by new ones maintain our health and hygiene. In this context, apoptosis is a mechanism to eliminate cells that are no longer useful. Apoptosis has also emerged as an important player during development when programmed cell death (PCD) is triggered to eliminate extra cells and to sculpt the final form of an organ. PCD is a crucial developmental process for the removal of problematic or unnecessary cells in multi cellular organisms [5,6].

Programmed cell death is also employed for refining the nervous system both in vertebrates as well as invertebrates [7]. In the nervous system the outcome of cell death is not favorable. The basic building blocks of the nervous system are neurons and glial cells. The neurons are post-mitotic cells and unlike the skin cells or the cells of the intestinal lining these cells are not renewed. Therefore, loss of neurons in the central nervous system always has consequences. It has been estimated that there are three billion neurons in the human brain. The hallmark of neurodegenerative disorders is loss of neurons over a period of time. Initially, there is a room to accommodate the loss of some neurons by generation of new neuronal network by generating *de novo* dendritic connections. The loss of neurons beyond a certain threshold can no longer be accommodated. Therefore, the loss of neurons over a period of time compounds the effect and manifest in terms of progressive neurodegenerative disorders. Since this loss of neurons takes place along a time axis therefore it is also referred to as progressive neurodegenerative disorder or age related disease. The hallmark of these disorders is the loss of cognitive functions like learning and memory. All diseases that affect neuronal health have been classified as neurodegenerative disorders. Some of the neurodegenerative disorders are: Alzheimer's disease, Huntington's, Parkinson's, Amyloid lateral Sclerosis (ALS) [8-10]. All these disease have genetic basis which effect various different sub-cellular organelle. Here we take example of the Alzheimer's disease to ascertain the effects:

Alzheimer's disease has been shown to be an outcome of genetic mutations, which may have significant bearing on intracellular mechanisms like protein-degradation pathways, mitochondrial dysfunction, axonal transport and cell death mechanisms [8-10]. The major effect of neurodegeneration in Alzheimer's disease is generation of amyloid-beta 42 (A β 42) oligomers, which due to their hydrophobic nature tend to make plaques [11-14]. These A β 42 are highly toxic and result in triggering neurodegeneration. Another reason for onset of neurodegeneration in AD is called tauopathy [8-11]. The tauopathy is an outcome of degeneration of the microtubule of the neurons into neurofibrillary tangles. Microtubules are important part of the

cytoskeleton of the cells, which are used by motor proteins to transfer the cargo from the cell body of the neuron to the presynaptic membrane of the neuron. Microtubules are a polymer of different isomers of tubulin which join to form the protofilament. These protofilaments are linked together to form the hollow microtubule by proteins called MAPs (microtubule association proteins). In tauopathy mediated neurodegeneration the hyperphosphorylation of MAPs results in disintegration of the neurons, which prevents the transport and as a result causes stress and onset of neurodegeneration.

Death rules our existence. Cell death is a safe mechanism for disposal of malfunctioning, damaged, excess and/or pathogen-infected cells or debris and is crucial to keep us alive and healthy. On the contrary uncontrolled or mislocalized cell death can be deleterious as observed in neurodegenerative disorders.

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