

Apoptosis in Neurodegenerative Disease, Myocardial Infarction and in Cancer

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Editorial

Apoptosis or program cell death is a very important and normal sequential, ordered process through which cells go to death. In case of apoptosis, there is shrinkage of cell and in its nucleus, formation of blebbing, chromatin fragmentation, loss of adhesion to neighboring cells and rapid engulfment by phagocytosis. But there is contrast between apoptosis and necrosis; necrosis is caused by physical trauma or biochemical drastic changes in the cellular environment. In necrosis, leakage of cell contents in the medium and as a result inflammation is occurred.

In 1972, John Kerr et al. proposed the term Apoptosis in their paper where they first time described the events which occur during apoptosis.

Apoptosis is triggered by both internal stimuli such as abnormalities in the DNA and external stimuli such as cytokines [1]. From the literature, it is found that external stimuli activate apoptosis by the extrinsic signaling path way whereas internal stimuli activate intrinsic path way [2]. There is distinction between two signaling path way. Different types of internal stimuli hypoxia, irreversible DNA damage, viral infection, oxidative stress trigger apoptosis by intrinsic pathway. In this pathway, Bax and Bak help to the release of cytochrome-c from mitochondria and can complex with Apaf-1 and Procaspase-9 and trigger the apoptotic response [3]. Apaf-1 helps in the conformational changes in procaspase-9 and activates its catalytic activity. On the other hand, extrinsic signaling pathway is triggered by TNF (tumor necrosis factor), TNF binds with its receptor TNFR-1; the activated receptor then binds with TRADD, FADD and procaspase-8 through the death domain (DD) linker [4]. This multi protein complex activates the procaspase-8 and triggers to the direction of apoptosis i.e. executes to cell death.

Normal level of ordered apoptosis is very important for cell biology to maintain the homeostasis in cellular environment. Over induced apoptosis and less activated apoptosis both are the cause of different types of disease formation. Over induce apoptosis is the cause of neurodegenerative disorder; Alzheimer's disease (AD) and parkinson's disease (PD) are the neurodegenerative disorder caused by the loss of neuronal cells and as a result motor nerves loss their activity. So, the extrinsic signaling pathway (Fas ligand activation) is over activated also with the intrinsic pathway (mitochondrial degeneration; cytochrome-c, Bax and Bak over activation) [5] and triggered uncontrolled-unordered apoptosis and as a result neuronal cell loss is found.

The over-induced apoptosis is also found in myocardial infarction. Myocardial cell death is occurred by excessive apoptosis due to the low oxygen, scarcity of nutrients due to the plaque formation in coronary arteries [6]. In this hypoxic condition caspase is activated and cell death is occurred [7]. From our laboratory we reported that dermcidin isoform-2 (DCN-2), a small protein was able to activate platelet aggregation [8,9] and triggered cell death on myocardium and it was hypothesized that the event was occurred by unordered caspase activation [6]. We also explained that insulin & low dose of aspirin

would inhibit the cell death through the activation Nitric Oxide in the physiological range [6,10]. Insulin also inhibits uncontrolled cell death through the Akt pathway [10,11].

In another way, under-regulated apoptosis is the cause of cancer formation. Apoptosis is inhibited in both extrinsic and intrinsic signaling pathway. In intrinsic pathway, the expression of Bax and Bak are reduced on the other hand, the anti-apoptotic Bcl-2 family proteins (Bcl xL, Bclw) are over expressed and as a result apoptosis of tumor cell is inhibited [12]. Another tumor suppressor protein is P53 which is also reduced in presence of Bcl-2 family protein [13]. The check-points in the cell cycle do not function properly in presence of Bcl-2 and as a consequence cells are unable to control their growth. Therefore the ratio of Bax and Bcl-2 is an important signal from which it can understand that the cell will go in which direction.

So, from this short review it can be concluded that the signaling pathways of apoptosis play the pivotal role in the disease formation and its regulation. Many proteins are already discovered in these signaling pathways but there are many more proteins which are not known yet. That undiscovered protein would play the role of linker proteins which might solve or stop abnormal loss of neural cells in neurodegenerative disorders or could be able to inhibit the cancerous growth. To know the mechanism of proteins in the signaling pathways of apoptosis and anti-apoptosis is one of the main aims of current science.

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