Mini Review

iMedPub Journals
www.imedpub.com

European Journal of Experimental Biology
ISSN 2248-9215

2021
Vol. 11 No. 4: 132

Pathological Inflammation and Various Mechanisms of Apoptosis

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Citation: Chhabra R, Bass S, Parashar N (2021) Pathological Inflammation and Various Mechanisms of Apoptosis. Eur Exp Biol. Vol. 11 No. 4: 132.

Abstract

Inflammation is protective response of mammalian tissue when exposed to infective agents which includes bacteria, viruses and fungi (fungal arthritis which is caused by invasion of fungus in the body and triggers inflammation), chemical toxins like reactive oxygen species (which affect cytochrome P4502E1 by metabolism of chemical to neoantigens triggering immunological reactions), and physical agents like heat, cold or mechanical trauma. In response to etiologic agents (physical and chemical toxins) our immunity triggers inflammation, making it distinct from infection. Infection is invasion of toxins and resultant ill effects whereas inflammation is union of inflammatory response and healing as well. Though this is a protective mechanism it can inflict harm to the body such as pyrexia, arthritis etc.

Enumerated the famous 4 cardinal signs of inflammation so named-rubor (redness), tumor (swelling), calor (heat), dolor (pain) and later on "functio laesa" (loss of function) was added by Virchow. Apoptosis is programmed and coordinated cell death mediated by physiologic or pathologic conditions. The term "apoptosis" was discovered by Kerr Wyllie in 1972 after its discovery a century back by Carl vogt in 1842. Apoptosis can be mediated by physiologic processes include changes in body like involution of thymus in early age leading to cell death whereas pathologic processes include diseased state like in degenerative diseases of CNS (Alzehimer disease) accompanied with various biochemical changes followed by morphological changes like proteolysis of cytoskeletal proteins or fragmentation of chromatin.

Keywords: Inflammation; Inflammatory response; Apoptosis; Mechanism of apoptosis; Programmed cell death; Pathological inflammation; Biology apoptosis; etiology inflammation

Received: May 12, 2021, **Accepted:** May 29, 2021, **Published:** June 11, 2021

Introduction

The term inflammation (Latin word-inflammare) which means to set on fire is in conjunction with two of the 5 cardinal signs that are rubor (redness) and calor (heat). In inflammation, activation of inflammatory signalling pathways and recruitment of inflammatory mediators (like cytokinins by leukocyte chemotaxis) in the tissue by blood. Inflammation can be acute and chronic depending on the severity of the condition and cause of inflammation. Recent research on assessing time course for chronic inflammation showed the anti-inflammatory efficacy of prednisolone and roflumilast when performed on mice which were exposed to HDM (House Dust Mite) which are natural allergens triggering bronchial inflammation and other symptoms depending on the time of exposure. On the other hand apoptosis is programmed cell death mediated by physiologic and pathologic conditions but apoptosis is not linked with inflammatory response but necrosis (localised cell death or degradation of tissues with hydrolytic enzymes liberated from dead cells) which can be caused by various agents such as hypoxia, physical, chemical, microbial agents is linked with the inflammatory response. Morphological features can be seen with the aid of a light microscope in histologic examination. Recent research has shown that the cause of many diseases is due to irregular regulation of apoptotic programs [1].

Pathologic Inflammation and Recent Researches

Inflammation is the body's defence mechanism as its cardinal

signs such as redness, heat, pain and swelling leads to activation of the immune system triggering motion repair mechanisms and eventually accumulation macrophages such as Polymorphonuclear Neutrophils (PMNs) appear on early in acute inflammatory response Inflammation are classified into acute inflammation and chronic inflammation depending upon the duration of response, Immunity of host and severity of condition. Acute inflammation as the name suggests is of short duration and can be repaired quickly and is followed by healing [2].

Main characteristics of acute inflammation are generally accumulation of fluid and plasma on activated site, activation of platelets and Polymorphoneutrophils (PMNs) in vascular area of affected tissue. In the acute inflammation mechanism, it is characterised in two parts that are vascular events and cellular events. Chronic inflammation is characterised by presence of chronic inflammatory cells such as macrophages, plasma cells and lymphocytes. Chemical mediators include vasoactive amines, arachidonic acid, lysosomal components, platelet activating factors, cytokinins, free radicals etc. Although they have distinct mechanisms, both share a common mechanism [3]. First, the cell's surface receptors detect harmful stimuli, then inflammatory pathways are activated and inflammatory cells are released and presented at the site. Inflammation is pathogenesis of most of the chronic diseases like arthritis. Inflammation includes coordinated activation of mediators of inflammation and pathways in the affected area and inflammatory cells accumulation from the blood.

There are pattern recognition receptor activation pathways, in which Pathogen Recognition Receptors (PRRs) which are germline encoded proteins and are expressed in both immune and non-immune cells. Activation of PRR's starts an inflammatory response [4]. There are some endogenous biomolecules which can activate PRRs, those are called Danger Associated Molecular Patterns (DAMPs). DAMPs can initiate the anti-inflammatory response. Releasing of DAMPs can lead to recruitment of inflammatory mediators from the blood in the absence of pathogens. PRR class includes Toll-like Receptors (TLRs) such as Retinoic Acid Inducible Gene (RIG), C-type lectin receptors. TLRs are the most studied and most well-known of the PRRs. PAMPs and DAMPs are activated by Myeloid differentiation factor 88 (MyD88) with TLRs which in turn activates cascade of signals, which in turn translocate nuclear transcription factor such as (AP-1) and (NF-kB) and (IF3). Intracellular stimuli activate inflammatory pathways that activate production of mediators. Stimuli include cytokinins and Interleukins-1b (IL-1b), Interleukin-6 (IL-6) and tumour necrosis factor mediate inflammation by activating toll-like receptors (TLRs). Receptor activation leads to signalling of different pathways so named Mitogen Activated Protein Kinase (MAPK), Nuclear Factor Kappa-B (NF-kB), JAK-STAT pathway etc.

In one of the recent research for determination of time course of chronic inflammation in HDM (House Dust Mite) model showed the efficacy of prednisolone and roflumilast in treating BALB/c mice. In this experiment BALB/c mice were exposed intranasally to HDM, which is an allergen known to activate inflammatory response in lungs. Inflammatory cells were assessed in Bronchoalveolar Lavage Fluid (BALF) [5]. Roflumilast (10 mg/kg) and prednisolone (10 mg/kg) were administered orally twice after week 3. Extending exposure to HDM resulted in peak values of lymphocytes, macrophages, eosinophiles etc following week 1. Mice developed prevascular, peribronchiolar and pre alveolar inflammation and epithelial hyperplasia/hypertrophy in bronchi and bronchioles which got worse due to 5 week exposure to HDM . Though therapeutic treatment with prednisolone and roflumilast decreased the severity which suggests their efficacy in treating inflammation [6].

Apoptosis and Mechanisms

Apoptosis is programmed and coordinated cell death. Apoptosis is distinct from necrosis because in necrosis there is involvement of inflammation and maybe some collateral tissue damage as well. In apoptosis the "cell suicide" or cell death pathway is activated because there is no longer need of the cell. There are physiologic as well as pathologic processes that mediate apoptosis. Some examples of pathologic processes include-cell death by cytotoxic T cells as in graft *vs* host disease and autoimmune reactions or in degenerative disease such as in alzheimer disease, parkinson's disease whereas physiologic processes examples are organised sculpting of tissue as embryo develops or involution of thymus at early age [7].

Morphological features

The histologic characters as viewed under microscope showed that there is involvement of cluster of cells which can be seen distinctly over the background of normal cells, the apoptotic cells are round or oval in shape having eosinophilic cytoplasm having shrunken organelles, pyknosis or karyorrhexis is seen, cell surface can have some invaginations or projections on cell surface, there are spherical bodies around the cell which contain compacted organelles, not like necrosis no sign of inflammation can be seen, phagocytosis of apoptotic body can be fast or slow, there can be much damage or minimum damage to the tissue [8].

Pathways/Mechanisms

There are 2 pathways for apoptosis that are extrinsic and intrinsic pathway, in extrinsic apoptosis, certain plasma membrane receptors are activated by their ligands whereas intrinsic pathway is activated by intracellular stress and has a central role in mitochondria [9].

There are cell surfaces which express some receptors that are responsible for apoptosis. The important example can be Tumour Necrosis Factor-α (TNF-α) binding to receptors of TNF-R family or the recognition of Fas ligand by Fas receptor. Triggering of this cell receptors can be either intracellularly or extracellularly which can be

- Non availability of the signals required for ursula cell survival as in growth factors and cytokinins
- Activation of Fas receptors can lead to triggering of extracellular apoptosis
- Intracellular stimuli include hypoxia, heat, radiation

After its rediscovery in 1972 by Kerr, there have been many advances in the theories of apoptosis, one of them being a breakthrough in research of apoptosis by genetic study of nematode identified to be containing genes regulating apoptosis

which is the first proof that apoptosis is regulated by genetic control and many of the genes have mammalian homologs which their worm counterparts regulate mammalian apoptosis. In nematode three of the genes- ced-3, ced-4, ced-9 are found to be directly involved in the regulation of apoptosis. In these ced-3 and ced-4 are both killing genes which are required to kill the cell whereas ce-9 is for survival of C-elegans cell which is essential for coordinated conduction of cell death [10].

Conclusion

PRR pathways are prominent pathways for inflammation in which PRR, a kind of receptors are responsible which can be activated by endogenous biomolecules such as DAMPs and most well studied of PRRs are TLRs which are activated by inflammatory mediators whereas apoptosis is programmed death of the cells that are no longer in need. Both processes have their own significance and mechanisms. Both topics are prominent in human pathology study. The genetic study showed that mutations or activation by their RNA leads to cell death in C. elegans but still it's a far way to go as we know the CED genes are somehow responsible for cell death but we don't know what express CED genes, those cases are yet to be studied.

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