Mini Review

CLINICAL INVESTIGATION

Various Apoptosis Mechanisms and Pathological Inflammation

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Abstract

Inflammation is a protective response of mammalian tissue to infective agents such as bacteria, viruses, and fungi (fungal arthritis is caused by a fungus invading the body and causing inflammation), chemical toxins such as reactive oxygen species (which affect cytochrome P4502E1 by converting chemicals to neoantigens and causing immunological reactions), and physical age. Our immunity responds to etiologic agents (physical and chemical poisons) by inducing inflammation, which is different from infection. Infection is the invasion of poisons and their consequences, whereas inflammation is the combination of the inflammatory response and healing. Despite the fact that this is a defensive system, it can cause injury to the body, such as pyrexia and arthritis.

Virchow listed the renowned four cardinal indications of inflammation: rubor (redness), tumour (swelling), calor (heat), dolor (pain), and eventually "functio laesa" (loss of function). Apoptosis is a type of cell death that is triggered by physiologic or pathologic factors. Kerr Wyllie coined the term "apoptosis" in 1972, a century after Carl Vogt first coined the phrase in 1842. Apoptosis can be mediated by physiologic or pathologic processes. Physiologic processes include changes in the body, such as the involution of the thymus in childhood, which leads to cell death, whereas pathologic processes include diseased states, such as Alzheimer's disease, which is accompanied by various biochemical changes and morphological changes, such as proteolysis of cytoskeletal proteins or fragmentation of chromatin.

Keywords: Inflammation • Inflammatory response • Apoptosis • Apoptosis mechanism • Programmed cell death • Pathological inflammation • Biology of apoptosis • Aetiology of apoptosis

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Introduction

The phrase inflammation is used in connection with two of the five cardinal signs: rubor (redness) and calor (heat). Activation of inflammatory signalling pathways and recruitment of inflammatory mediators (such as cytokinins by leukocyte chemotaxis) in tissue by blood in the case of inflammation. Depending on the severity of the ailment and the source of inflammation, inflammation can be acute or chronic. When mice were exposed to HDM (House Dust Mite), which are natural allergens that cause bronchial inflammation and other symptoms depending on the time of exposure, recent research on assessing time course for chronic inflammation showed the anti-inflammatory efficacy of prednisolone and roflumilast when performed on mice [1] Apoptosis, on the other hand, is a programmed cell death mediated by physiologic and pathologic conditions; however, apoptosis is not linked to the inflammatory response, whereas necrosis (localised cell death or tissue degradation with hydrolytic enzymes liberated from dead cells) is linked to the inflammatory response and can be caused by a variety of agents including hypoxia, physical, chemical, and microbial agents. In histologic inspection, morphological traits can be seen using a light microscope. Many diseases are caused by abnormal control of apoptotic programmes, according to recent study [2].

Recent Research on Pathologic Inflammation

Inflammation is the body's defence mechanism, since it causes the immune system to activate, initiating motion repair systems and eventually accumulation macrophages such as Polymorphonuclear Neutrophils (PMNs) to develop early in the acute inflammatory response. Inflammation is classed as acute or chronic depending on the duration of

the response, the host's immunity, and the severity of the illness. Acute inflammation lasts for a brief period of time, can be healed quickly, and is followed by healing [3].

Acute inflammation is defined by the buildup of fluid and plasma on the activated site, as well as the activation of platelets and Polymorphoneutrophils (PMNs) in the vascular area of the affected tissue. The acute inflammatory mechanism can be divided into two parts: vascular events and cellular events. The presence of chronic inflammatory cells such as macrophages, plasma cells, and lymphocytes characterises chronic inflammation. Vasoactive amines, arachidonic acid, lysosomal components, platelet activating factors, cytokinins, and free radicals are examples of chemical mediators. Despite the fact that their methods are different, they have a similar mechanism. When damaging stimuli are detected by the cell's surface receptors, inflammatory pathways are activated, and inflammatory cells are produced and presented at the location [4]. Most chronic disorders, such as arthritis, are caused by inflammation. Inflammation is defined by the coordinated activation of inflammatory mediators and pathways in the affected area, as well as the build-ups of inflammatory cells from the circulation.

Pathogen Recognition Receptors (PRRs), which are germline encoded proteins and expressed in both immune and non-immune cells, are involved in pattern recognition receptor activation pathways. When PRRs are activated, an inflammatory response is triggered. Danger Associated Molecular Patterns (DAMPs) are endogenous biomolecules that have the ability to activate PRRs. DAMPs have the ability to trigger the anti-inflammatory response. In the absence of pathogens, the release of DAMPs can result in the recruitment of inflammatory mediators from the circulation. Toll-like Receptors (TLRs), such as Retinoic Acid Inducible Gene (RIG), and C-type lectin receptors, are members of the PRR class. TLRs are the PRRs that have been studied the most and are the most well-known. Myeloid differentiation factor 88 (MyD88) interacts with TLRs to activate PAMPs and DAMPs, which in turn initiates a cascade of signals that translocate nuclear transcription factors like (AP-1) and (NF-kB) (IF3) [5]. Intracellular stimuli trigger inflammatory pathways, which in turn trigger mediator synthesis. Interleukin-1b (IL-1b), Interleukin-6 (IL-6) and tumour necrosis factor are examples of stimuli that activate toll-like receptors to mediate inflammation (TLRs).

Prednisolone and roflumilast were found to be effective in treating BALB/c mice in a recent study to determine the time course of chronic inflammation in the HDM (House Dust Mite) model. HDM, an allergen known to elicit an inflammatory response in the lungs, was administered intranasal to BALB/c mice in this study. Bronchoalveolar Lavage Fluid (BALF) was tested for inflammatory cells [6]. After week 3, roflumilast (10 mg/kg) and prednisolone (10 mg/kg) were given orally twice. Extending HDM exposure resulted in peak lymphocyte, macrophage, and eosinophil counts after week 1. Mice experienced prevascular, peribronchiolar, and prealveolar inflammation, as well as epithelial hyperplasia/hypertrophy in the bronchi and bronchioles, which worsened after five weeks of HDM exposure. Though prednisolone and roflumilast therapy reduced the severity, this shows that they are effective in treating inflammation.

Mechanisms of Apoptosis

Apoptosis is a type of cell death that is planned and orchestrated. Apoptosis differs from necrosis in that necrosis is accompanied by inflammation and possibly some collateral tissue damage. Because the cell is no longer needed, the "cell suicide" or "cell death" pathway is activated in apoptosis. Apoptosis is mediated by both normal and pathologic mechanisms [7]. Pathologic processes include cell death by cytotoxic T cells as in graft *vs* host disease and autoimmune reactions, as well as degenerative diseases like Alzheimer's disease and Parkinson's disease, whereas physiologic processes involve organised tissue sculpting as an embryo develops.

Morphological characteristics

The histologic characters as viewed under a microscope revealed that there is involvement of clusters of cells that can be seen distinctly over the background of normal cells, apoptotic cells are round or oval in shape with eosinophilia cytoplasm and shrunken organelles, pyknosis or karyorrhexis is seen, cell surface can have some invaginations or projections, and spheri are present [8].

Pathways/Mechanisms

The extrinsic and intrinsic pathways for apoptosis are activated by their ligands in extrinsic apoptosis, whereas the intrinsic pathway is activated by intracellular stress and plays a significant role in mitochondria in intrinsic apoptosis.

Some apoptosis-related receptors are expressed on cell surfaces. The binding of Tumour Necrosis Factor (TNF) to TNF-R family receptors or the detection of Fas ligand by Fas receptor are two important examples [9].

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

There have been many advances in the theories of apoptosis since its rediscovery in 1972 by Kerr, one of which was a breakthrough in apoptosis research 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 that their worm counterparts regulate mammalian counterparts. Three genes, ced-3, ced-4, and ced-9, are revealed to be directly involved in the regulation of apoptosis in nematodes.

Conclusion

PRR pathways are well-studied inflammation pathways in which PRRs, a type of receptor, are responsible for inflammation. PRRs can be activated by endogenous biomolecules such as DAMPs, and the most well studied PRRs are TLRs, which are activated by inflammatory mediators, whereas apoptosis is the programmed death of cells that are no longer needed. Both processes have distinct meanings and mechanics. Both of these subjects are important in human pathology research. The genetic analysis found that mutations in the CED genes or activation by their RNA causes cell death in C. elegans, but there's still a long way to go because we know the CED genes are involved in cell death, but we don't know what expresses them.

References

1. Parke DV, Parke AL. Chemical-induced inflammation and inflammatory diseases. *Int J Occup Med Environ Health* 9: 211-217 (1996).
2. Valko M, Leibfritz D, Moncol J, et al. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 39: 44-84 (2007).
3. Valko M, Rhodes CJ, Moncol J, et al. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact* 160: 1-40 (2006).
4. Bennett JM, Reeves G, Billman GE, et al. Inflammation-nature's way to efficiently respond to all types of challenges: implications for understanding and managing "the epidemic" of chronic diseases. *Front Med (Lausanne)* 5: 316 (2018).
5. Deng Z, Liu S. Inflammation-responsive delivery systems for the treatment of chronic inflammatory diseases. Drug Deliv Transl Res. 23: 1-23 (2021).
6. Symons AM, King LJ. Inflammation, reactive oxygen species and cytochrome P450. *Inflammopharmacology* 11: 75-86 (2003).
7. Pospíšil P, Prasad A, Rác M. Role of reactive oxygen species in ultra-weak photon emission in biological systems. *J Photochem Photobiol* B 39: 11-23 (2014).
8. Van der Zee J, Krootjes BB, Chignell CF, et al. Hydroxyl radical generation by a light-dependent Fenton reaction. *Free Radic Biol Med* 14: 105-113 (1993).
9. Diociaiuti M, Gaudiano MC, Malchiodi Albedi F. The slowly aggregating salmon Calcitonin: a useful tool for the study of the amyloid oligomers structure and activity. *Int J Mol Sci* 12: 9277-9295 (2011).