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Inflammation – A Mini-Review

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ABSTRACT

Inflammation is a vital aspect of the innate immune system and subsequently the overall immune response to foreign entities. Research has also shown that inflammation is involved in the disease pathogenesis of many chronic diseases that affect the mortality of persons in our modern life. This mini review encompasses the medical history of inflammation, how it is manifested in two main types and how it underlies chronic diseases with a few examples.

Keywords: Inflammation, innate immunity, chronic diseases.

INTRODUCTION

Inflammation has become a catchphrase in everyday conversations, with it being seen in a negative context with regards to the health of the human body. This can be linked to inflammation being the unifying pathophysiological mechanism that is involved in various chronic diseases e.g. diabetes and cardiovascular disease(1). It is of note that inflammation will constantly be a frequent occurrence as humans are partly microbial and live in a microbial world (2). As such, the inflammatory response plays a major role in combatting infection and tissue injury(3). This review aims to look at the good and bad of Inflammation. Inflammation It is important to note that, like other biological processes, it is all dependent on context.

Discovery & History

Inflammation has been mentioned in historical texts from varying regions of the world including Mesopotamia, Egypt and Greece(4) and it is from historical medical texts that the

signs of inflammation originated. Roman medical encyclopaedist Aulus Cornelius Celsus (25 BC – 50 AD) described the Celsus tetrad of inflammation: calor, dolor, tumor and rubor (5). Hundreds of years later, Rudolf Virchow, in his book Cellular Pathology (1858), suggested the need for a fifth cardinal sign, "functio laesa" thus leading to the modern five cardinal signs of inflammation (4). It was in the 19th century that the discovery of phagocytes by Ilya I. Mechnikov that aided in the understanding of inflammation as phagocytosis is the first step in triggering inflammation (6)(7). Inflammation can be classified due to its duration: acute and chronic. It can also be classified by the initiating cause : microbial, autoimmune, allergic, metabolic, physical and constitutive (6). While the cause for the first five can be deduced by their names (microbes, autoimmune attack, allergens, metabolites and trauma), the sixth cause is due to the inborn(constitutive) errors of the innate immunity (6). Irrespective of the cause, inflammation can be seen as an immunological response to restore homeostasis (8). It is, of course, important to know the cause of inflammation and equally important is how the process of inflammation is modulated.

Process

A simple explanation of the process would be non-immune cells e.g. keratinocytes, mucosal epithelial and vascular endothelial cells along with polymorphonuclear leucocytes (PMNs), macrophages, dendritic cells (DCs) and natural killer cells (NK) both alert and manage the immune system with additional mediation afforded by cytokines (6). Of course, as with any other immunological process, it is not that simple. Following will be an explanation of the processes in the acute inflammatory response and the chronic inflammatory response.

Acute

Utilising a microbial infection as the initiating event, the inflammatory response can be characterised by increased blood flow and vascular permeability with the accumulation of fluid, leucocytes and cytokines at the initiating site (9). This entire process can only occur if there are sentinel leucocytes in the tissues i.e. mast cells and macrophages (10).The microbe can be recognised via Pattern Recognition Receptors (PRRs), found on the surfaces of various leucocytes including mast cells and macrophages. PRRs recognise Pathogen Associated Molecular Patterns (PAMPs) that are usually associated with various microbes. Engagement of the PRRs leads to phagocytosis of the invading pathogen and activation of transcription factors e.g., nuclear factor-kappa B (NF-kB) and signalling pathways. Ultimately there is the production of various inflammatory mediators and cytokines, progressing the inflammatory response. Cytokines involved in acute inflammation include Interlukin-1 (IL-1), IL-6, IL-8, IL-11, IL-16, IL-17, Colony stimulating factors (CSFs), Eotaxin and Tumour Necrosis Factor (TNF) (9,10). Cytokines can have "pro-"and "anti-" inflammatory effects. For this review, the emphasis will be on the "pro" functions. IL-1 triggers pyrexia and the release of histamine from mast cells which causes early vasodilation and increased vascular permeability (9,10). IL-1 also enhances the production of IL-2 and expression IL-2 receptors, thereby influencing the activation of T lymphocytes(11). It also augments B cell proliferation and antibody synthesis (11).IL-6 induces pyrexia and production of C-reactive protein and other acute phase proteins, mediates T cell activation and the differentiation of B and T lymphocytes (9,11). IL-8

has a chemotactic effect on neutrophil and can enhance neutrophil adherence to endothelial cells, thus enabling their diapedesis through vessel walls (9). As a functional homologue of IL-6, IL-11 also induces acute phase protein production and secretion; additional roles include increased platelet production and stimulation of T cell dependent antibody production (9). IL-16 is another chemokine with influence on $CD4^+$ T lymphocytes, monocytes, and eosinophils. The eotaxin family of chemokines attract eosinophils and TNF induces pyrexia and acute phase proteins production along with activation of neutrophils(10). IL-17 stimulates production of IL-6 and IL-8 and synergistically amplifies the pro-inflammatory cytokines (9,12).

The presence of the inflammatory mediators and cytokines facilitates a proximate inflammatory exudate to form. This exudate will contain plasma proteins and leucocytes, mostly neutrophils, that have now been granted permission to leave their restricted locations in the blood vessels and enter the extravascular tissue at the site of infection (8). Upon arrival the neutrophils are activated (via pathogen-contact or cytokines) and release granular effectors including leukotrienes to attract antigen presenting dendritic cells, defensins to recruit lymphocytes and reactive oxygen species (ROS) to eliminate the offending pathogen (10). Since these compounds cannot differentiate between pathogen and self, the host tissues are also affected. Elimination and neutralisation of the initiating pathogen is the critical requirement for the cessation of the inflammatory response (13). This is usually followed by the resolution and repair phase manifested mainly by tissue-resident and recruited macrophages (8). Apoptosis of inflammatory cells is the physiological method for the non-phlogistic removal of cells, preventing the release of their potentially histotoxic agents (13). Macrophages recognise these apoptotic cells and releases anti-inflammatory cytokines e.g. IL-10 which influence resolution of inflammation via increased phagocytosis of the apoptotic cells (13). The acute inflammatory response can occur very often to overcome the various initiating causes of inflammation. Issues arise, however, when this response is ongoing and there is no resolution. Failure to eliminate or neutralise the inflammatory stimuli or even the non-clearance of apoptotic inflammatory cells can cause the inflammatory process to persist and the possibility of chronic inflammation (14).

Chronic

Changes in the inflammatory response from acute to chronic may cause a breakdown in immune tolerance and major alterations in normal cellular physiology, tissues and organs which may be irreversible (15,16). Chronic inflammation may impair immune function, increase susceptibility to infections and tumours and elevate the risk of non-communicable diseases (16). Causation can include persistent pathogens, autoimmune responses and undegradable foreign entities (8). Monocytes/macrophages and lymphocytes are the prominent leucocytes involved in the chronic inflammatory response along with cytokines. Cytokines known to mediate chronic inflammation are numerous and can include IL-2, IL-6 and TGF-B (9,11). It should be noted that while acute inflammation can be distinguished by specific cytokines, e.g. IL-1, IL-6, there are no canonical standard cytokine biomarkers for chronic inflammation(16). In the transition from acute to chronic, the neutrophil infiltrate is replaced with macrophages and lymphocytes (8). When these cells are still unable to resolve the initiating issue, chronic inflammation is established and it may be characterised by granulomas and tertiary lymphoid tissues (8). In its role of protection of the host, macrophages, having been unsuccessful in

destruction of pathogen, will enclose the pathogen in layers: formation of granulomas (8). While the information imparted describes the chronic inflammatory process for infection-induced inflammation, it cannot be assumed that this is the same mechanism for other forms of systemic chronic inflammation(2,8,16).

Chronic Inflammation & Disease

Diseases such as diabetes mellitus, obesity, cancer, or rheumatoid arthritis all have different primary causative agents. Chronic inflammation, however, contributes significantly to the pathogenesis of these diseases, along with many others, and can be considered to be a risk factor (2,3,17). The clinical consequences can be detrimental to the health of individuals and may lead to increased morbidity and mortality worldwide.

Allergic Disorders

The constant/repetitive exposure to allergens by persons with allergies results in chronic allergic inflammation and lasting changes in the structure of affected organs along with functional abnormalities(18). Examples of these disorders include allergic rhinitis, atopic dermatitis, and asthma. Patients with chronic asthma present with inflammation in all layers of the airway wall and associated with structural changes including : increased numbers of goblet cells, areas of epithelial injury and repair and increased thickness of muscular layer of the airways (18). Chronic allergic inflammation is also associated with tissue remodelling in allergic disorders altering the barrier function of the of the affected epithelia (18). Impaired function of the skin barrier is seen in atopic dermatitis, and it is associated with increased risk of cutaneous infections and colonisation with *Staphylococcus aureus* (19). Increased susceptibility to chronic sinus infection by allergic rhinitis patients may be linked to impaired barrier function of the upper airway (20,21).

Cancer

Generally, the longer inflammation persists, the greater the risk of cancer (22). So it is unsurprising that chronic inflammation can influence the pathogenesis of cancer as many cancers have been found to arise from sites of chronic irritation and inflammation (22,23). The scenario is one of proliferating cells that sustain DNA damage and/or mutagenic assault in microenvironments filled with inflammatory cells and growth/survival factors i.e. tumours perform as wounds that fail to heal (23). While acute inflammation is resolving via mechanisms including anti-inflammatory cytokines that assist in arresting pro-inflammatory cytokines, chronic inflammation is non-resolving as there is a failure in the processes that arrests the inflammatory response. Tumourgenesis begins with the Initiation phase, which involves DNA alterations and is irreversible. The following phase is the Promotion phase, where the initiated cells are exposed to factors that induce cell proliferation, recruit inflammatory cells, increase production of ROS leading to DNA damage and reduce DNA repair (23). These conditions can be found in chronically inflamed tissues as cell death and repair programmes can be subverted by the ongoing inflammatory processes (23). There is a

hypothesis that many cancers even arise from areas of infection and inflammation due to the presence of ROS and reactive nitrogen species (RNS) that are produced in an inflammatory response and can react to form peroxynitrite, a mutagenic agent (22,24). So the chronic inflammatory environment, with the repeated destruction and regeneration of tissue in the presence of peroxynitrite interacts with DNA in proliferating cells leading to permanent genomic alterations i.e. tumourgenesis (23). There have been associations between chronic inflammation and cancers e.g. chronic ulcerative colitis and Crohn's disease and chronic *Helicobacter pylori* infection being identified as the world's leading cause of stomach cancer (23,25). Further evidence supporting the significance of inflammation in neoplastic progression is the decreased risk for cancer seen in long-time users of nonsteroidal anti-inflammatory drugs (NSAIDs) (23). Use of NSAIDs reduced colon cancer risk by 40-50% and may be preventative for lung, oesophagus and stomach cancer (23,26,27).

Diabetes

A worldwide chronic disease, diabetes has directly caused 1.5 million deaths in 2019 (28). Chronic inflammation may be an important pathogenic factor in the development of insulin resistance and Type 2 diabetes as insulin resistance can be found in ~ 90% of all patients with Type 2 diabetes (29). Activation of inflammatory signalling pathways can lead to inhibition of downstream signalling of the insulin receptor and contributing to insulin resistance (30). In non-diabetic patients, inflammatory markers CRP, IL-6 and TNF-a were elevated in association with quantitative measures of insulin resistance (31). Insulin resistance promotes inflammation as insulin exerts anti-inflammatory effects at the cellular and molecular level (32). In clinical trials involving pharmacological interventions for coronary heart disease prevention, there were statistically significant reductions in Type 2 diabetes incidence, due to reduction of inflammatory biomarkers e.g. CRP (31). The presence of inflammation has even been found to be predictive for the development of Type 2 diabetes utilising increased levels of inflammatory biomarkers e.g. IL-6 (32).

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Infection with SARS-CoV-2 leads to clinical expression of the coronavirus disease (COVID-19) (12). Patients with COVID-19 usually exhibit various symptoms including fever, dry cough, muscle pains, headaches, and respiratory distress. The pathophysiology of SARS-CoV-2 infection includes an aggressive inflammatory response leading to damage in the airways and progression to acute respiratory distress syndrome (ARDS) (33). There is also a vast release of cytokines i.e. the cytokine storm resulting in uncontrolled inflammation inflicting multi-organ damage and organ failure (33). Thus, while the inflammation seen in COVID-19 may not be considered "chronic" as it did not progress from the acute inflammatory phase, it is a non-resolving inflammation i.e., it is uncontrolled and subsequently damaging to the host's own systems. SARS-CoV-2 is a cytopathic virus (34) thus it can induce death of virally infected cells. Pryoptosis is a highly inflammatory form of apoptosis that is seen with cytopathic viruses (35) and can be a likely trigger for subsequent inflammatory responses (36). A retrospective, multicentre cohort study indicated that patients with severe COVID-19 had increasing levels of IL-6 over time along with increased levels of CRP (37). Non-survivors

of the disease also had elevated inflammatory markers throughout and increasing levels of inflammation tracked with clinical deterioration which preceded death (33,38). Thus the cytokine storm can contribute to an unrestrained inflammatory cell infiltration which may mediate damage in the lungs from excessive secretion of proteases and ROS (33).

Conclusion

Inflammation, like other immunological processes, is advantageous once it is efficiently regulated with the assistance from endogenous checkpoints to moderate its duration and magnitude. If anti-inflammatory cytokines and mechanisms fail, there is the possibility of progression to chronic inflammation. As previously noted, chronic inflammation can also be involved in chronic disease states such that controlling the underlying chronic inflammation can be as important as attacking the cause of the disease. Understanding the commonality of chronic inflammation in these diseases can aid in protection against them and the hopeful eventuality of overcoming them. Current therapeutics have involved treating chronic inflammation along with the cause of the disease e.g., cancers. Ultimately, the complex process that is inflammation must be understood so the beneficial aspects can be promoted while the pathological effects are controlled.

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