Inflammation and Metabolic Syndrome: An Overview

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ABSTRACT

Inflammation is a reaction to a disrupted tissue homeostasis. Basically it is a tissue-destroying process that involves the recruitment of blood-derived products. Rapidly destroy or isolate the underlying source of the disturbance, removes damaged tissue and restore tissue homeostasis is the primary function of inflammation. Inflammatory and chronic metabolic alterations that together are termed metabolic syndrome. The risk of developing serious pathological conditions such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) is significantly associated with inflammation and its concurrent multi-organ abnormalities which represent a great burden upon societies, as they require significant resources from health care systems. Thus, understanding the tissue-specific pathogenic processes that lead to disease progression is required for the development of more effective therapeutic approaches.

Key words: Inflammation, cytokines, chemokines and metabolic syndrome.

INTRODUCTION

Inflammation

Infection by microbial invaders is often implicated as the major convict that promotes inflammatory responses (Figure 1a). However, exposures to foreign particles, injury or trauma are also potent activators of inflammation¹. Infection often follows wounding, which implies that it would be advantageous to respond to trauma as if infection occurred. Both pathogens and wounding cause damage to cells and tissue which evoke similar inflammatory responses².

Isolation or rapidly destroy the underlying source of the disturbance, remove damaged tissue and then restore tissue homeostasis is the primary functions of inflammation¹. There are several genes whose disruption leads to inflammation, suggesting that when inflammatory stimuli are not present the inflammatory response is actively suppressed by regulatory gene products to maintain health³. If this response is not regulated properly excessive inflammation can have adverse effects, resulting in excessive collateral damage and pathology. Chemotaxis and phagocytosis like compounds are associated with inflammatory cascade which are employed by unicellular as well as multicellular organisms⁴.

Mechanisms of inflammation

Inflammation consists of a tightly regulated cascade that orchestrated by immune signalling molecules called cytokines. The first step of the inflammatory cascade involves identification of infection or damage (Figure 1b) which achieved by the detection of pathogen-associated molecular patterns (PAMPs) that is directed toward general
motifs of molecules expressed by pathogens that are essential for pathogen survival. Damage-associated molecular patterns (DAMPs) are recognized by the innate immune system, are endogenous molecules.

Trans membrane Toll-like receptors (TLRs), intracellular nucleotide binding domain and leucine-rich-repeat-containing receptors (NOD-like receptors or NLRs) are germ-line encoded receptors which recognized the damage signals. After recognition of ligands occurs, TLRs activate signalling pathways that culminate in the activation of NF-κB (nuclear factor kappa- B; Figure 1c) and activation of NF-κB does not require any new protein synthesis.

The third stage of cascade is transcription and translation of genes that induce the expression of pro-inflammatory cytokines such as interleukin-1-beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α) (Figure 1d). At the site of disturbance, in conjunction with chemokines and various co-stimulatory molecules monocytes and neutrophils are recruited by these soluble proteins (Figure 1e). Noxious chemicals (including reactive oxygen and nitrogen species) from cytoplasmic granules create a cytotoxic environment and to release these chemical glucose and oxygen is require which is known as the respiratory burst. These effector mechanisms are thus major contributors to host collateral damage.

These interactions leads to cardinal signs of heat, swelling, redness, pain and loss of function which are further regulated by the adaptive immune system (Figure 1f). The fourth and last critical phase is its resolution (Figure 1g). pro-inflammatory

Fig. 1: Primers of inflammatory cascade

\[ \text{IL}-1\beta, \text{IL}-6, \text{IL}-10, \text{IL}-12, \text{IL}-15, \text{IFN}-\gamma, \text{TNF}-\alpha \]
prostaglandins and leukotrienes recruit macrophage during acute inflammation. Further neutrophil recruitment is blocked by lipoxins and instead favor enhanced infiltration of monocytes which is important for wound healing.\(^\text{10}\)

**Pro-inflammatory cytokines and chemokines**

**TNF-α**

TNF-α is one of the cytokines produced chiefly by activated macrophages. Natural killer cells, neutrophils, mast cells, eosinophils, neurons and CD4+ lymphocytes also produced TNF-α. Regulation of immune cells is the primary role of this cytokine but studies showed that in obese subjects its level increases in adipose tissue (visceral than subcutaneous) and reduces as weight decreases.\(^\text{11}\)

**IL-6**

IL-6 is acts both as a pro-inflammatory cytokine and an anti-inflammatory myokine. To stimulate the immune response, it is secreted by T cells and macrophages. In human 15-35% of the systemic IL-6 is release by adipose tissue which increased in obesity.\(^\text{12}\)

**C-reactive protein (CRP)**

It is an acute-phase protein which increases by macrophages and T cells in response to inflammation following IL-6 secretion. Studies showed that the risk of hypertension, diabetes and CVD increased as its level increasing in human. Recent research suggests that patients with elevated basal levels of CRP are at an increased risk of diabetes, hypertension and cardiovascular disease.

**Monocyte chemoattractant protein-1 (MCP-1)**

MCP-1 is a cytokine that belongs to the CC chemokine family which recruits monocytes, T cells and dendritic cells to the sites of inflammation.\(^\text{13}\)

**Plasminogen activator inhibitor-1 (PAI-1)**

PAI-1 is produced by several tissues, including liver, endothelial cells and adipose tissue, is the most important physiological inhibitor of plasminogen activation. Elevated PAI-1 may be central to both the development of obesity and its metabolic consequences.\(^\text{14}\)

**Anti-inflammatory cytokines and chemokines**

**Adiponectin (ApN)**

ApN is produced by adipose tissue. Studies showed that circulating ApN is negatively correlated with the BMI and decreased in obesity, in patients with T2DM or CVD.\(^\text{15}\) Abnormal hormonal milieu together with the enhanced oxidative stress and pro-inflammatory state may be the mechanisms involve in the down regulation of ApN during obesity and the metabolic syndrome.\(^\text{16}\)

**IL-1ra**

IL-1ra is a functional members of the IL-1 family, IL-1a and IL-1b which produced by monocytes and macrophages and is released into the circulation after lipopolysaccharide (LPS) stimulation in human. Excess IL-1ra synthesis has been shown to increase susceptibility to arthritis, tuberculosis, and a variety of other infectious diseases.

**IL-4**

IL-4 is a highly pleiotropic cytokine, with marked inhibitory effects on pro-inflammatory cytokines. IL-1, TNF-a, IL-6 and IL-8 can be suppress by IL-4 macrophage cytotoxic activity, parasite killing and macrophage-derived nitric oxide production.

**IL-10**

IL-10 is the most important anti-inflammatory cytokine with potent inhibitor including Th1 cytokines, neutrophils cytokine production and inhibition of monocyte, neutrophil cytokine production.

**IL-11**

It is found mainly in stromal cells and fibroblasts which inhibits pro-inflammatory cytokine response. This marker can be used to see inflammatory bowel disease, thrombocytopenia, chemotherapy-induced mucositis and psoriasis.\(^\text{17}\)

**Inflammation and its outcomes**

Although a pivotal response to infection and tissue injury, inflammation has also been associated with many pathological processes. Overt acute inflammation leads to tissue damage and non resolving inflammation causes chronic tissue malfunction, suggesting an evolutionary trade-off between the rapid and effective response
to perturbations in tissue homeostasis and the collateral damage on tissue function. Obesity, raised fasting plasma glucose, high cholesterol and hypertension a cluster, is considered as a most dangerous risk factors are so-called metabolic syndrome. Due to the relatively recent appearance of these disorders in mere decades rather than the millennia over which humans have evolved, as well as the generally late onset of the disease in the life of an affected individual, it is conceivable that inflammation-induced metabolic disease has escaped the selection process of evolution and is becoming more apparent with increased life expectancy and the Western lifestyle.

Obesity

Obesity is characterized by a low grade chronic state of inflammation in which the level of pro-inflammatory cytokines such as TNF-α, IL-6 and CRP are increased. Hypoxia may be the etiology behind inflammation in obesity where, necrosis and macrophage infiltration in to adipose tissue leads to overproduction of pro-inflammatory chemokines which result in a localized inflammation in adipose tissue that disseminate an overall systemic inflammation associated with the development of obesity-related comorbidities.

Type 2 Diabetes Mellitus

T2DM is characterized by raised levels of glucose as a consequence of peripheral insulin resistance accompanied by decreased pancreatic insulin secretion. More than 62 million diabetic individuals currently diagnosed with the disease. Moreover, it is estimated that T2DM is the underlying cause or a contributing factor of 2,31,000 deaths per year. Thus, understanding the role of inflammation in the pathogenesis of T2DM is essential for curtailing its devastating effects in societies.

The first link between inflammation and insulin sensitivity came from early studies that demonstrated that the levels of pro-inflammatory cytokines were increased in the circulation and adipose tissue of obese and diabetic subjects. Studies using mouse models demonstrated that pro-inflammatory cytokines inhibit insulin signalling by direct serine phosphorylation of insulin receptor substrate-1 (IRS-1). In multiple mouse models studies showed that adipose tissue macrophages (ATMs) are directly correlated with insulin sensitivity and lipid ectopic accumulation.

Chronic levels of free fatty acids and glucose induces inflammation, results in increased apoptosis and impaired insulin secretion of á cells, which prompts the progression from obesity and insulin resistance to overt T2DM. Importantly, IL-1α plays a critical role in the atrophy of pancreatic islet function. IL-1α is preferentially expressed in á cells and infiltrating macrophages. Human clinical trials using IL-1RA significantly improved á-cell function and glycemic control in T2DM patients.

Atherosclerosis

CVD is the leading cause of mortality worldwide. Proximately 16.7 million deaths occur each year, and it is expected that the incidence of this deadly disease will continue to rise steadily in the following decades, reaching 25 million deaths per year in the third decade of this century. Atherosclerosis is a condition of the wall of mid-size and large-size blood vessels that is caused by lipid-induced inflammation which is underlying cause of CVD. As such, atherosclerosis is significantly associated with hyperlipidemia induced by obesity.

The pathogenesis of atherosclerosis is a process that requires a complex and orchestrated interaction between endothelial cells, smooth muscle cells and macrophages. Although, the biological agents that spark artery wall inflammation and the innate immune receptors that sense perturbations in blood vessel homeostasis have just begun to be elucidated. The initial stages of atherosclerosis are characterized by sub-endothelial retention of circulating LDL particles, which leads to their oxidative modification by ROS and enzymatic attacks. Subsequently mmLDLs can activate TLRs, resulting in the rapid transcription of inflammasome processed cytokines (e.g., IL-1α) as well as that of multiple other pro-inflammatory soluble factors such as chemokines and cytokines. The recruitment of myeloid cells and T cells into the intima is generated by the pro-inflammatory milieu where monocytes differentiate into macrophages and then into foam cells as a consequence of cholesterol accumulation. Foam cells are a pathognomonic feature of atherosclerotic plaques which play a critical role in progression of disease. Severity of atherosclerosis...
is elevated as plasma concentrations of IL-1α and IL-18 are elevated.

Non-alcoholic Fatty Liver Disease
The main cause of liver pathology in societies is NAFLD. Its prevalence reaches 30% in the population and up to 75–100% in obesity. Different degrees of severity characterize this disease; although the great majority of patients with steatosis are asymptomatic, nearly 20% eventually progress to develop chronic hepatic inflammation which can lead to portal hypertension, cirrhosis, hepatocarcinoma, and increased mortality. NASH is classified into primary NASH (associated with obesity and hyperlipidemia) and secondary NASH (related to pharmacological interventions, Wilson's disease, or jejunoileal bypass surgery). Surprisingly, although NAFLD/NASH is one of the most prevalent metabolic aberrations in humans, the insults that trigger inflammation have remained elusive.

Gout
Gout is a disease associated high concentrations of uric acid. The prevalence of gout increases in the population. Moreover, the prevalence has also increased affecting 21% of the adult population. The pathogenesis of gout is piloted by the accumulation and deposition of crystals of uric acid in the joints and as such these crystals are activating inflammasome. Clinical studies on gout shows that blockade of IL-1α significantly reduce severity of disease.

CONCLUSION
Inflammation is a critical component of metabolic syndrome. Great progress has been made in the understanding of how pro-inflammatory cytokines and specific immune cell populations promote metabolic disease progression. This review gives a framework for inflammation, its mechanisms, pro and pro-inflammatory markers such as acute phase proteins, cytokine and how it leads to chronic diseases like type 2 diabetes, atherosclerosis, non-alcoholic liver diseases and gout.

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