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Introductory Chapter: The Journey of Inflammation and Inflammatory Disease Research - Past, Present, and Future

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1. Introduction

Inflammation is known to ancient Indian Ayurvedic physicians dating back to 1500 BC that is well described in ancient Ayurvedic medicine textbooks (*Charaka Samhita*, *Susruta Samhita*, and *Astanga Samgraha*) [1]. Inflammation and the associated edema have gotten attention in Ayurveda as a pathological manifestation of the disease [2, 3]. Ayurvedic medicine mentioned inflammation in different ways, which include *Shotha and Shopha*, and many other terms (*Svayathu*, *Utsedha*, and *Samhata*) [2]. Ancient Ayurvedic medicine practitioners characterized inflammation in different ways, including elevation, edema, heaviness, and pain. The Greek physician, Hippocrates in the 5th century BC coined the term edema. Furthermore, Later on, Aulus Celsus (30 BC-38 AD) described the four major signs of inflammation, which include *Rubor*, *Calor*, *Tumor*, and *Dolor* [4]. Galen, the Roman physician introduced the fifth sign of inflammation as *loss of function*. However, *Virchow* in 1871 more precisely described the *function laesa* (loss of function) sign of inflammation [5, 6].

The modern terminology of inflammation has been derived from the Latin word *inflammare* (to set on fire) [6]. Now inflammation is considered as a host-generated protective host immune response in response to acute trauma or pathogens or their PAMPs (pathogen-derived molecular patterns) to contain the damage or to remove/kill the pathogen [7]. The inflammation pathogenesis is a complex process involving the network of cellular and molecular signaling to restore homeostasis and induce tissue/organ repair and regeneration. However, any dysregulation of the inflammatory process may lead to the development of severe inflammatory conditions, including systemic inflammation and sepsis (during infection). Furthermore, any persistent inflammation (staying for months and years) may cause chronic inflammatory disorders (cancer and autoimmune diseases) [8–10]. The cellular components of the immune system (macrophages, neutrophils, mast cells, dendritic cells (DCs), T cells, and B cells etc.) play a central role in the process of both acute and chronic inflammation involve (**Figure 1**) [11–14].

Figure 1. Schematic representation of immune cell activation in response to different pathogens, PAMPs, MAMPs through interacting with different PRRs (mentioned in the text) to generate inflammatory immune response. This immune response is governed by immunometabolic reprogramming, epigenetics, miRNAs, and the release of extracellular vesicles or exosomes, which directly or indirectly interact and affect each other.

2. Pattern recognition receptors (PRRs) in inflammation and inflammatory diseases

The receptors expressed by these immune cells called **pattern recognition receptors** (PRRs) (**Figure 1**) are present on the outer surface of the cell membrane as well as in the cytosol, including different toll-like receptors (TLR1-TLR13 in mammals, including humans), intracellular PRRs (NOD [Nucleotide-binding and oligomerization domain]-like receptors (NLRs; NOD1 and NOD2), absent in melanoma-like receptors (ALRs, AIM2), and many more mentioned somewhere else recognize the potential pathogen and/or inflammogen to mount a protective inflammatory immune response [1, 15–17]. The intracellular proteins (NLRC1 or NLPR1, NLRP3, NLRC4, pyrin, and AIM2 or absent in melanoma 2 that recognizes cytosolic DNA) form an inflammatory complex called inflammasome upon recognition of intracellular threat (damage-associated molecular patterns or DAMPs). The inflammasome also becomes activated upon the recognition of external danger called pathogen or microbe-associated molecular patterns (PAMPs or MAMPs) and DAMPs by cell surface PRRs, which signal these inflammasome proteins to activate and stimulate another cascade of inflammation resulting in the release of pro-inflammatory cytokines (IL-1 β , IL-18, and IL-33) and the cell death called pyroptosis that further aggravates the inflammatory process [18]. The details of inflammasomes in inflammation and inflammatory disease are

mentioned somewhere else [18, 19]. The activation of cell surface PRRs, including TLRs (TLR2 and TLR4), may activate the inflammasome or TLRs and inflammasomes work in cooperation to control the inflammatory process [20, 21]. Another, cytosolic PRR system called cGAS (cyclic GMP-AMP synthase, recognizes cytosolic dsDNA)-stimulator of interferon genes (STING) pathway recognizes cytosolic dsDNA and induces the synthesis of type 1 interferons (IFNs) [22, 23]. The over-activation of this pathway is involved in different autoimmune and auto-inflammatory diseases, along with other inflammatory conditions discussed in detail somewhere else [22–24]. The details of inflammatory pathways mediated by TLRs, inflammasomes, cGAS, and other PRRs have been discussed by the author somewhere else in detail [1, 18, 21, 22, 24–27].

3. Immunometabolism in inflammation and inflammatory diseases

Like, other non-immune cells, immune cells also have their energy demand that plays a crucial role in the maintenance of immune homeostasis and the mounting of the immune response to protect against invading foreign agents, including the pathogen and allergen. The metabolic changes occurring in immune cells from their normal/control stage (absence of inflammogen, pathogen, PAMPs, MAMPs, or DAMPs) to their activation or activated stage is called immunometabolic reprogramming [28]. Hence, the metabolic pathways governing or regulating the energy demand of immune cells to maintain immune homeostasis is called **immunometabolism** [28]. The metabolic demand of immune cells increases during the inflammatory process and reprogramming of different metabolic pathways governing the immune function takes place that depends on the immune cell type and the inflammatory conditions (**Figure 1**) [29]. The author has described immunometabolism of different immune cells and their immunometabolic reprogramming and its therapeutic targeting during inflammation and inflammatory diseases elsewhere [1, 30–35].

4. Epigenetics in inflammation and inflammatory diseases

Epigenetics (deals with the reversible impact of behavior and environmental factors on our genetic machinery without changing the DNA sequence. However, it may change the way of reading the genetic information coded by the DNA) also plays a crucial role in the inflammatory process and inflammatory diseases. The most frequent epigenetic changes involve aberrant DNA methylation and histone acetylation and deacetylation. The enzymes (arginine and lysine methyltransferases, DNA methyltransferase, histone acetyltransferases (HAT), and histone deacetylases or HDAC) involved in the process of epigenetics also control the inflammatory process, including airway inflammation, atopic dermatitis, and autoimmune diseases [36–41]. The histone modifications, DNA methylation, and noncoding RNAs (ncRNAs) have emerged as master regulators of gene expression, including the inflammatory genes [42]. The targeting of these enzymes, including HAT and HDAC, has shown great anti-inflammatory potential in diverse inflammatory diseases. However, advances in the biological sciences have shown the interaction between epigenetics and immunometabolism converges at inflammation and regulates different inflammatory diseases, including cancer (**Figure 1**) [42–45]. Hence, epigenetics-based immunotherapies are emerging for targeting chronic inflammatory diseases, including cancer and autoimmunity [46].

5. Extracellular vesicles in inflammation and inflammatory diseases

Extracellular vesicles (EVs) are generated by different cell types, including the immune cells to remove cellular waste and communicate with adjacent as well as distant cells [47]. These EVs may contain protein, DNA, RNA, micro RNA (miRNA or miRs), and cytokines depending on the cell type and cell/tissue microenvironment. The microvesicles (MVs), a kind of EVs released from apoptotic cells are less-inflammatory than those released from viable cells [48]. These MVs have different miRs (miR-155, miR-34b, and miR-34a), which get dysregulated in autoimmune diseases, including systemic lupus erythematosus (SLE) in comparison to normal individuals. EVs play a crucial role in cell–cell communication in pulmonary inflammation upon exposure to toxicants [49]. EVs also affect immunometabolism during diverse inflammatory conditions, including autoimmunity (**Figure 1**) [50, 51]. The different types of EVs, their contents (miRs), and their role in inflammation and therapeutic potential, including in sepsis and coronavirus disease-2019 (COVID-19) have been discussed somewhere else [47, 52–56].

6. MicroRNAs (miRNA) in inflammation and inflammatory diseases

MicroRNAs (miRNAs) are small non-coding RNAs (typical length, 18–24 nucleotide long), which are crucial in regulating protein-coding genes via post-transcriptional repression [57]. They play an important role in regulating innate and adaptive immunity from their developmental stages to function during diverse inflammation conditions, including cancer and autoimmunity as fine-tuners of the system [57–60]. For example, miR-181a and miR-223 are crucial in the establishment and maintenance of immune cell fate [58]. The miR-146 also regulates innate immunity through controlling TLR signaling and ensuing cytokine response. They (miR-155 and miR-181a) regulate central elements of the adaptive immune response such as antigen presentation and T cell receptor (TCR) signaling [58]. Chronic inflammatory diseases exhibit altered miR (miR-203 and miR-146) levels, indicating their crucial role in immunological pathologies/diseases. The details of miRs in immunity and inflammation are discussed somewhere else [59, 61]. The emerging evidences have shown the regulation of immune cell metabolism or immunometabolism by miRs [62, 63]. The non-coding RNAs (ncRNAs) also regulate inflammasome activity controlling the inflammatory immune response [64]. More recently an atlas of miR expression in 63 different mouse immune cell populations has been generated and connected with an assay for transposase-accessible chromatin using sequencing (ATAC-seq), chromatin immunoprecipitation followed by sequencing (ChIP-seq), and nascent RNA profiles to establish a map of miRNA promoter and enhancer usage in immune cells [65]. This will help to delineate the *cis*-regulatory elements controlling miRNA signatures of the immune system.

7. Conclusion

The story of inflammation had started from the Ancient Indian peninsula through the Ayurvedic medicine that further developed into its four peculiar signs (*rubor, tumor, calor, and dolor*) and fifth end-stage sign indicating the loss of function. The development in biomedical sciences, including immunology, cell signaling, pharmacology, epigenetics, and molecular biology or medicine has helped to understand the pathogenesis of inflammation (both, acute, and chronic) and

associated inflammatory disease, varying from autoimmunity to cancer to severe infectious diseases, including the current COVID-19 pandemic. Thus, the long journey of inflammation that started dating back to 1500 BC and 600 AD has seen significant development in understanding its pathogenesis under diverse conditions and therapeutic advancement. Further studies in the 21st century will open new avenues to control and prevent inflammatory diseases responsible for human morbidity and mortality.

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