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REVIEW

An overview of inflammation: mechanism and consequences

Afsar U. AHMED (✉)

Monash University Department of Medicine, Centre for Inflammatory Diseases, Monash Medical Centre, 246, Clayton Road, Clayton, VIC 3168 Australia

Abstract **Inflammation is an essential response provided by the immune systems that ensures the survival during infection and tissue injury. Inflammatory responses are essential for the maintenance of normal tissue homeostasis. The molecular mechanism of inflammation is quite a complicated process which is initiated by the recognition of specific molecular patterns associated with either infection or tissue injury. The entire process of the inflammatory response is mediated by several key regulators involved in the selective expression of proinflammatory molecules. Prolonged inflammations are often associated with severe detrimental side effects on health. Alterations in inflammatory responses due to persistent inducers or genetic variations are on the rise over the last couple of decades, causing a variety of inflammatory diseases and pathophysiological conditions.**

Keywords Inflammation, inflammatory diseases, proinflammatory cytokines, pattern-recognition receptors, transcription factors and chromatin structure

Inflammation

Inflammation is a protective strategy evolved in higher organisms in response to detrimental insults such as microbial infection, tissue injury and other noxious conditions. It is an essential immune response by the host that enables the removal of harmful stimuli as well as the healing of damaged tissue. Acute inflammation has therefore been considered as a part of innate immunity, the first line of host defense against foreign invaders and danger molecules. Mankind has known the classical symptoms of inflammation for hundreds of years, which include redness, pain, swelling and heat (Medzhitov, 2008). However, emerging literature suggests that inflammation operates as a much-sophisticated system than ever thought at the molecular level. The entire course of inflammation comes with many different processes involved in its initiation, regulation and resolution. Nowadays a diverse range of inflammations have been identified, with many different forms initiated by numerous stimuli and governed by various regulatory mechanisms. Due to its extensive and widespread nature, inflammation is believed to have an impact on every aspect of normal human physiology and pathology. The current concept on inflammation has grown significantly over the years because of the vast expansion of the field in more divergent directions. As a result, we are currently far from being able to fully comprehend the consequence of inflammation in human health and diseases.

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Correspondence: Afsar U. AHMED
E-mail: Afsar.Ahmed@monash.edu, afsaruahmed@gmail.com

Cellular homeostasis and inflammatory responses

As a protective strategy for the host, one of the main aims of inflammation is to reinstate cellular homeostasis in response to any damaging condition. The mechanism underlying the initiation of inflammation is therefore tightly connected to the physiological state of homeostasis. And so, inflammation is considered as an ‘adaptive response’ to any harmful effect threatening the integrity of the cellular homeostasis. It is quite plausible to understand that such an adaptive response operates at the expense of normal cellular functions (Medzhitov, 2010). As a result, the longer this response persists in, the host will encounter the more damaging consequences. In contrary to its beneficial role as a safeguard for cellular physiology, the inflammatory response is required to be least enduring in order to avoid any escalation of its unfavorable circumstances.

In response to a proper stimulant such as microbial infection, foreign invaders or any irritant (external or internal), inflammation is usually initiated within minutes in any host with a functional innate immune system. As innate immune system is the major contributor to inflammation, immune cells such as macrophages, dendritic cells, mast cells, neutrophils and lymphocytes play important roles in inflammatory responses (Akira et al., 2006). Apart from immune cells, non-immune cells such as epithelial cells, endothelial cells and fibroblasts also contribute to inflammatory processes. Based on the nature of stimulants, inflammatory pathways vary significantly and so are their target tissues. In the case of bacterial infection, the immune cells through specific receptors immediately sense pathogens. Activation of pathogen-specific receptors induces the production of inflammatory mediators such as inflammatory cytokines [e.g. tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6)] and chemokines. These mediators rapidly accelerate the progression of inflammation through the modification of vascular endothelial permeability as well as the recruitment of neutrophils and excess plasma (containing antibodies and complement factors) into the site of infection. At the same time, the invading pathogens are targeted and destroyed by the immune cells. The duration of inflammatory responses vary depending on the level of damage caused by the infection. In most cases, these responses extend toward systemic effects through the excessive production of inflammatory cytokines, which mediate the secretion of acute phase proteins (i.e. C-reactive protein and coagulation factors) by the liver cells. These proteins, in turn, induce brain endothelium and facilitate the production of prostaglandins, which are primarily responsible for the onset of symptoms (e.g. pain, and fever) through their effects on the central nervous system. With similar outcomes, the viral infection, on the other hand, leads to a distinct signaling pathway through the production of another class of cytokines such as type-1 interferons (IFNs) and also involves cytotoxic lymphocytes. Type-1 IFNs play central roles in antiviral responses. Then again, parasitic infections as well as allergens induce the production of IL-4, IL-5, IL-13 and histamine (Medzhitov, 2010).

Molecular mechanism underlying inflammation

Inflammatory stimuli are first recognized by the host cells through specific transmembrane receptors, called pattern-recognition receptors (PRRs), which are expressed by cells of both innate and adaptive immune systems. PRRs are germline-encoded receptors, which are responsible for sensing the presence of infecting microorganisms as well as the incidence of any cellular damage (Akira et al., 2006). They do so by recognizing structures conserved in microbes, called pathogen-associated molecular patterns (PAMPs), as well as endogenous molecules derived from internal injuries, called danger-associated molecular patterns (DAMPs). To date, a number of PRRs have been identified with the selective ability to detect PAMPs, DAMPs or both and these include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-1-like receptors (RLRs) and NOD-like receptors (NLRs).

The interactions of these receptors with the appropriate stimuli result in transmitting signals to nucleus where the activation of a selective set of genes takes place via both transcriptional and posttranscriptional mechanisms (Akira et al., 2006; Medzhitov, 2007). Inflammatory responses are coordinated by the products of such genes, precisely proinflammatory cytokines such as TNF, IL-1β and IL-6 are expressed in response to bacterial infection. Unlike TNF and IL-6, IL-1β is synthesized by a two-step mechanism. In the first step, IL-1β is expressed as IL-1β zymogen, pro-IL-1β, which is initiated by the synthesis of its mRNA in a TLR-dependent manner. The second step involves the maturation of IL-1β by the caspase-1 mediated cleavage of pro-IL-1β, a process requires a 'caspase-1-activating' high molecular weight complex called inflammasome. Inflammasomes are assembled by the oligomerisation of scaffold proteins including NLRs. In the case of viral infection, type-1 IFNs induce the phosphorylation and nuclear translocation of a complex, called IFN-stimulated gene factor 3 (ISGF3), which is composed of signal transducers and activators of transcription 1 (STAT1), STAT2 and IFN-regulatory factor (IRF) 3 (Honda et al., 2006). ISGF3, in turn, activates the expression of antiviral genes such as protein kinase R (PKR) and 2′,5′-oligoadenylate synthase (OAS). The proliferation of virus-infected cells is inhibited by PKR whereas OAS suppresses viral replication by cleaving viral nucleotides.

Signal transductions from PRRs often converge to the activation of a common set of transcription factors that drives the production of proinflammatory cytokines and chemokines. A substantial amount of earlier studies were devoted to the identification of transcription factors as well as DNA motifs on their target genes. NK-κB is the first transcription factor identified with a sequence-specific DNA binding activity induced only by an appropriate stimulus (Sen and Baltimore, 1986). NK-κB is also one of the most studied transcription factors, which has provided a great insight into the sophisticated regulatory mechanism for the selective activation of a distinct set of gene expressions. There are five proteins in the mammalian NK-κB family: p50, p52, c-Rel, RelA and RelB (Ghosh et al., 1998). The NK-κB family members share structural homology in their N terminus with the retroviral oncoprotein v-Rel, called Rel homology region (RHR), a region which supports the formation of stable homodimers and heterodimers. Most NK-κB proteins are retained in the cytoplasm of unstimulated cells by ankyrin repeat-containing IκB proteins. p50 and p52 are initially synthesized as precursor proteins p105 and p100, respectively, with IκB-like ankyrin repeat domain at their C

terminus. Upon stimulation, NK-κB dimers in the cytoplasm are released from IκB and translocated to the nucleus in order to induce selective gene expressions. The detachment of NK-κB dimers from IκB can be achieved either by the phosphorylation of IκB, leading to its ubiquitylation and proteosome-mediated degradation, or by the inducible proteolytic cleavage of the ankyrin-repeat domain of the p100:RelB heterodimer (Vallabhapurapu and Karin, 2009). Apart from NK-κB, several other transcription factors also play crucial roles in the selective induction of inflammatory genes. To mention a few, these include activator protein-1 (AP-1), a heterodimer of basic leucine zipper proteins c-Jun and c-Fos (Greenberg and Ziff, 1984; Bohmann et al., 1987); cyclic-AMP (cAMP) response element binding protein (CREB), a cAMP-induced factor (Montminy and Bilezikjian, 1987); E2F, a transcription factor activated by the adenovirus E1A protein in adenovirus-infected cells (Kovesdi et al., 1986); serum responses factor (SRF) and the associated ternary complex factors (TCFs), responsible for the serum induction of *Fos* transcription (Treisman, 1986; Prywes and Roeder, 1986; Dalton and Treisman, 1992). Activation of these transcription factors in response to inflammatory stimuli depends on a number of posttranslational mechanisms which include phosphorylation or dephosphorylation of these factors or of their inhibitors.

Even though the identification of transcription factors induced by inflammatory stimuli suggests a simple model in which the expression of a distinct set of genes depends exclusively on a single or a defined set of transcription factors, understanding the phenomenon of selective activation under physiological conditions cannot be confined to the mechanism of interaction between factors and DNA motifs. A growing number of evidence suggests that selective activation of most, if not all, genes are governed by the synergic effects of multiple transcription factors. A number of proinflammatory genes contain multiple DNA motifs recognized by transcriptions factors (Carey et al., 2009). For example, virus induction of human IFN-β requires the assembly of a multi-protein complex, called an enhanceosome, formed by the cooperative binding of inducible transcription factors including key factors such as NF-κB and IRF3/IRF7 (Thanos and Maniatis, 1995). Interestingly, transcription factors neither bind simultaneously to the selective DNA motifs nor hold direct protein–protein interactions between them in cooperative binding. In fact, the association of the transcription factors with a specific DNA motif is rather sequential and dynamic (Munshi et al., 2001; Bosisio et al., 2006; Hager et al., 2009). The sequential binding of transcription factors is largely governed by the conformational changes in the DNA structure (Panne et al., 2004; Panne et al., 2007). Upon factor binding, a conformational change in DNA structure makes a way for another transcription factor to the overlapping or adjacent site on the same DNA motif.

The mechanisms for selective transcription of inflammatory genes extend well beyond the differential binding of transcription factors to specific DNA sequences. Emerging evidence suggests that the transcriptional activation of eukaryotic genes is largely influenced by chromatin structure that makes up chromosomes. Chromatin is composed of nucleosomes (repeating units made of histones H2A, H2B, H3 and H4), linker histones as well as many nonhistone proteins (Luger et al., 1997). The differential effect of chromatin in selective transcription was observed decades earlier that the accessibility of transcription factor to active genes, but not to the inactive genes, is facilitated by chromatin (Weintraub and Groudine, 1976; Wu et al., 1979; Carey et al., 2009). The first conclusive evidence for a role of chromatin in transcriptional regulation came from the observation that Gcn5, a transcriptional coactivator in Saccharomyces *cerevisiae*, is in fact involved in the acetylation of histone H3 (Brownell et al., 1996). In addition, SWI/SNF, another important regulator of a subset of yeast genes, catalyzes the changes in nucleosome conformation, known as nuclear remodeling, by utilizing ATP hydrolysis (Cote et al., 1994; Imbalzano et al., 1994; Kwon et al., 1994). It was also demonstrated that mammalian SWI/SNF are immediately transported to chromatin upon T cell activation (Zhao et al., 1998), showing a link between nuclear remodeling and inducible transcription in immune cells. An analysis of TLR 4 ligand [lipopolysaccharide (LPS)]-induced gene expressions in mouse macrophages revealed that SWI/SNF is only indispensable for secondary response genes (which are induced slowly and require new protein synthesis) but not for most primary response genes (induced rapidly without the requirement for any new protein synthesis) (Ramirez-Carrozzi et al., 2006). Interestingly, SWI/SNF-independent genes exist as constitutively assembled into pre-active forms with high levels of histone acetylation and histone H3K4 trimethylation, which are quite reminiscent of those found in active genes and, therefore, the induction of these genes proceeds without any requirement for SWI/SNF (Ramirez-Carrozzi et al., 2009). Even though the primary response genes stay as constitutively assembled forms producing small quantities of precursor transcripts, the efficient transcription of these genes is essentially dependent on inducible transcription factors (Amir-Zilberstein et al., 2007; Hargreaves et al., 2009).

A growing number of evidence suggests that the regulation of inflammation is tightly controlled by an array of epigenetic mechanisms. Acetylation of histones is associated with relaxed structures of chromatin that facilitates transcription and therefore it seems to be critical for the induction of many inflammatory genes. For example, it was demonstrated that during inflammation acetylation of histone H3 at the promoter region of several inflammatory genes initiates an increased recruitment of NF-κB to these promoters (Barnes, 2009). It has been well-accepted that histone acetylation induces the activation of many inflammatory genes whereas the repression of these genes is mediated by the histone

deacetylase (HDAC) activity (Bayarsaihan, 2011). In contrast, histone methylation can either activate or repress gene transcription by keeping chromatin in a relaxed or condensed state, respectively, depending on the type of methylation (Bayarsaihan, 2011). For example, H3K9 methylation, which correlates with transcriptional repression, was detected at the promoters of some LPS-inducible genes in unstimulated cells but not under LPS stimulation (Saccani and Natoli, 2002). The removal of histone methylations from the inducible genes at the onset of stimulation suggests the recruitment of specific histone demethylases. Interestingly, a histone demethylase, Jmjd3, was found to be associated with a subset of inducible genes in macrophages exposed to bacterial products (De Santa et al., 2007). Apart from histone modifications, DNA methylation is also essential for the regulation of many inflammatory genes. The inflammatory response to bacterial peptidoglycan in cystic fibrosis epithelial cells is associated with DNA hypomethylation at the promoter of TLR2 gene (Shuto et al., 2006). Inflammatory processes within gastric mucosa caused by *Helicobacter pyroli* also induce aberrant DNA methylation in gastric epithelial cells (Niwa et al., 2010). Last but not the least, microRNAs (miRNAs), small non-coding RNAs that negatively regulate the expression of target genes through interaction with their mRNAs based on sequence complementarity at the 3′ UTR, have recently been reported as important regulators of inflammatory response. The LPS-induced stimulation of macrophages results in upregulation of miR-155 targeting mRNA of CCAAT/enhancer binding protein Beta, which promotes the expression of certain genes through interaction with their promoters (Worm et al., 2009). A miRNA, miR-132, facilitates acetylcholine-mediated suppression of inflammation in both the peripheral and the central nervous system by targeting acetylcholinesterase, an enzyme which hydrolyzes acetylcholine (Shaked et al., 2009). Furthermore, miR-147 acts as a critical negative regulator of excessive inflammatory response in macrophages and its expression is also induced by TLRs through the activation of both NF-κB and IRF3 (Liu et al., 2009).

Further studies suggest that nuclear remodeling for the selective induction of proinflammatory genes may be subject to multiple regulatory layers. This concept was first envisaged by the observation that the recruitment of NF-κB to its targets proceeds with variable kinetics depending on the gene (Saccani et al., 2001). This study suggests a potential existence of a 'nucleosome barrier' for transcription factors in order to activate some, but not all, genes. The recruitment of SWI/SNF complexes to selective genes was also shown to be dependent on new protein synthesis (Weinmann et al., 1999; Ramirez-Carrozzi et al., 2006), suggesting that the activation of many secondary genes through the recruitment of SWI/SNF complexes may precisely rely on the products of primary genes. In consistent with this view, a significant proportion of SWI/SNF-dependent genes, which are induced by LPS, are reliant on IRF3 for their activation, containing IRF3 binding sites on their promoters (Ramirez-Carrozzi et al., 2009). LPS induced nuclear remodeling of their promoters was also completely abolished in *IRF3*$^{-/-}$ mice, showing a role of IRF3 in nuclear remodeling. The requirement for IRF3 by the SWI/SNF-dependent genes represents a nucleosome barrier that restricts the expression of these genes, but not of the primary genes, in response to stimuli. Another recent report revealed the involvement of a calcium signaling pathway in the nuclear remodeling at the promoters of LPS-induced gene (Lai et al., 2009), implying that the magnitude of the regulatory layers involved in the selective activation of proinflammatory genes can be far more diverse than we could have ever imagined.

Chronic inflammations

As inflammation is evolved as a beneficial strategy for the host in response to any potential danger, the inflammatory response is normally terminated once the potential danger is eradicated. Usually the reversion of the inflammatory response to the homeostatic state proceeds quite rapidly, a highly regulated process known as the resolution of inflammation. The resolution of inflammation is dominated by many anti-inflammatory mediators such as IL-10, TGF-β and glucocorticoids, and it also involves the recruitment of monocytes for the clearance of cell debris (Serhan and Savill, 2005). If the resolution of inflammation fails for any reason, the acute inflammation turns into a chronic stage. Chronic inflammations have been a subject to extensive studies over the decades not only for the growing burdens of the associated pathological conditions in the modern societies but also for the underlying mechanisms which remain largely unresolved. A chronic inflammation is generally believed to develop if the elimination of the triggering stimulus fails to happen, such as any persistent infection or chronic cellular injury (Kumar et al., 2003; Majno and Joris, 2004). However, the initial trigger for a vast majority of the chronic inflammatory conditions has not been well defined yet, making the understanding of their pathological processes much more complicated due to the lack of any microbial infection or tissue damages. Chronic inflammation is not just a primary cause of these conditions, but it is the major driver of the pathogenesis. In chronic inflammatory conditions, the major damages done to the host are mediated by the host inflammatory response itself, not by the foreign invaders such as pathogens. The importance of chronic inflammatory conditions in this modern era of medical science cannot be overestimated because of their involvement in many diseases such as atherosclerosis, obesity, type 2 diabetes, asthma, inflammatory bowel diseases, neurodegenerative diseases, rheumatoid arthritis and cancer.

Inflammatory diseases

Inflammatory diseases are a group of clinical disorders which are characterized by abnormal inflammatory responses (i.e. chronic inflammation) as a major hallmark. Chronic inflammation is so tightly linked to the pathogenesis of inflammatory diseases that it becomes difficult to pinpoint both cause and effect of these disorders. For example, inflammation is caused by obesity, whereas chronic inflammation can lead to obesity-associated diabetes partly because of insulin resistance (Hotamisligil, 2006). Similar feedback mechanisms are also evident for other inflammatory disorders. Thus, the chronic nature of the inflammation associated with these diseases is controlled, at least in part, by the pathological outcome of these diseases, making them quite different from those induced by persistent infection. Rheumatoid arthritis is another perfect example of a chronic inflammation-associated disorder. In rheumatoid arthritis, the synovium, the lining of the joint, undergoes chronic inflammation by the infiltration of macrophages and lymphocytes, and the activation of synoviocytes, synovial cells, which produce synovial fluids. The synovial fluid during rheumatoid arthritis is invaded by billions of neutrophils everyday (Hollingsworth et al., 1967). It has been suggested that neutrophils, which have a half-life of about 4 h, make a significant contribution to the chronic nature of the inflammation in synovial tissue. It is hypothesized that one of the enzymes of neutrophils, cytosolic peptidyl arginine deaminase whose activity depends on the levels of extracellular Ca^{2+}, is released from the dead neutrophils and activated. This enzyme creates citrulline in some proteins by converting the guanidine side chains of L-arginine residues to ureido residues. Interestingly, autoantibodies associated with rheumatoid arthritis are found to react with citrullinated proteins (Uysal et al., 2009). The mechanism of inflammatory response in some inflammatory diseases can be more complex compared to others. For example, asthma and allergic inflammations are caused by dysregulated interactions between mucosal epithelia and innate immune cells. Further studies demonstrated a much wider involvement of the immune systems in asthma pathogenesis than ever thought. Apart from the innate immunity, cells of adaptive immunity such as CD4 T helper 2 (Th2) cells as well as Th2-associated cytokines are found to be strongly linked to asthma (Robinson et al., 1992). The initial cause of asthma seems much more complicated than ever imagined. Even though genetic predisposition to asthma has been reported for years, recent genome-wide studies suggest relatively small hereditary contributions to asthma (Rogers et al., 2009). Alternatively, environmental factors have been considered as major determinants of asthma risk. For example, numerous reports suggest several viral upper respiratory infections early in life along with genetic predisposition within families influence a significant risk for asthma (Locksley, 2010). The impact of inflammatory disorders on human health is very diverse, creating diseases, which affect almost every single function of our body. To mention a few, inflammation is associated with many neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and multiple sclerosis (Glass et al., 2010). Inflammatory bowel disease affects our intestine (Garrett et al., 2010) whereas glomerulonephritis is caused by the inflammation of the glomeruli, small blood vessels, in the kidneys (Fakhouri et al., 2010).

Inflammation and cancer

Over the last decade it has become evident that inflammation plays a critical role in promoting cancer, in particular the tumorigenesis, a process of tumor formation. In addition to cancer cells, various types of immune cells are commonly found within tumors. Interestingly, an inflammatory microenvironment is also more frequently found as an essential part of all tumors (Mantovani et al., 2008; de Visser et al., 2006). It has been demonstrated that the inflammatory response triggered by infection is also associated with increased cancer risk (de Martel and Franceschi, 2009). A recent study has revealed that lung tumorigenesis caused by tobacco smoke is in fact initiated by IKKbeta and JNK1-mediated chronic inflammation, suggesting that the pathways of both tumorigenesis and inflammation are closely linked (Takahashi et al., 2010). It is believed that apart from the tumor-promoting inflammatory response, an active anti-tumor immunity is also present in most tumor microenvironments. It is thus suggested that the progression of tumorigenesis is dictated by the battle between tumor-promoting inflammation and anti-tumor immunity. Obviously, in established tumors, anti-tumor immunity is profoundly dominated by tumor-promoting inflammation (Smyth et al., 2006; Lin and Karin, 2007). Studies show that inflammatory microenvironments not only promote cancer cell growth but also increase mutation rates, possibly by producing reactive oxygen species and nitrogen intermediates which can cause DNA damage and genomic instability (Grivennikov et al., 2010). The role of inflammation in genomic instability is supported by the observation that activation-induced cytidine deaminase (AID), an enzyme which triggers genomic instability and is usually overexpressed in many cancers, is induced by inflammatory cytokines (Okazaki et al., 2007). Apart from genomic instability, environmental factors such as carcinogens, infectious microbes, tobacco smoke and inhaled pollutants have been considered to play critical roles in inflammation-induced cancers (Aggarwal et al., 2009). Therefore, not all chronic inflammatory diseases are connected to cancer risk. For example, rheumatoid arthritis does not promote cancer whereas inflammatory bowel disease and chronic hepatitis do due to the exposure to dietary and environmental carcinogens. The connection between inflammation and cancer does not operate in one direction only as numerous studies showed that DNA damage can also lead to inflammation. Using the model of hepatocellular carcinoma induced by the carcinogen

diethylnitrosamine (DEN), several reports demonstrated that the DNA damage-induced necrotic cell death lead to inflammation (Maeda et al., 2005; Sakurai et al., 2008). Cancer-associated oncoproteins such as Ras, Myc and RET can also lead to inflammation by activating signaling pathways involved in the production of proinflammatory cytokines and chemokines (Mantovani et al., 2008). Last of all, tumor-associated inflammation can also be instigated by the modern cancer therapy itself such as radiotherapy and chemotherapy. These therapies are usually associated with a substantial amount of necrotic death of not only cancer cells but also surrounding normal cells, which in turn activates the inflammatory response (Zong and Thompson, 2006). Therefore, based on the literature, it can be concluded that inflammatory response is an integrated part of cancer biology, right from the beginning of tumorigenesis toward the application of therapeutic interventions.

Concluding remarks

It has been well established that the inflammatory response is usually initiated in response to two types of signals such as injury and infection. In contrast, inflammatory stimuli for many chronic inflammatory diseases are not clearly identified. Surprisingly, most chronic inflammatory conditions lack a defined and continuing inducer, making the therapeutic intervention for these diseases quite unfeasible. Recent advances indicated that certain stress responses are linked to chronic inflammatory conditions (Hotamisligil, 2006; Imai et al., 2008). It would be quite essential to understand whether stress responses have any widespread implications in most inflammatory diseases. Clearly further investigations will be required to unlock the mysterious mechanisms that induce and sustain chronic inflammation. Even though a close connection between innate immunity and inflammation has been well documented, the role of adaptive immunity in inflammatory response still needs further clarification. The involvement of adaptive immunity in inflammation has been documented by recent observations (Rubtsov et al., 2008; Ouyang et al., 2008; Koch et al., 2009). However, delineating the role of adaptive immunity as a critical parameter in the inflammatory response in general warrants further studies. Due to our limited understanding on the biological complexity of chronic inflammatory diseases, the development of anti-inflammatory therapy remains a critical challenge. It has become a difficult task to envisage a therapy without any potential risk of increased infection or other potential serious toxic side effects for the host. Inflammation research has come a long way in the last two decades and our concept on inflammation has been developed to a significant extend. We are now aware of its complexity and the challenges lying ahead. Only our continued efforts and future discoveries will enlighten the way to the successful cure for inflammatory diseases.

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