Journal of Immune Research

Open Access

Austin Publishing Group

Review Article

Inflammation and its Disease Consequences

Saqib U[1], Sarkar S[2] and Baig MS[3]*

[1]Divsion of Chemistry, School of Basic Sciences, Indore, MP, India

[2]Department of Biochemistry, BRS College, Kolkata, West Bengal, India

[3]Centre for Biosciences and Biomedical Engineering (BSBE), Indian Institute of Technology (IIT), Indore, MP, India

***Corresponding authors:** Mirza S. Baig, Centre for Biosciences and Biomedical Engineering (BSBE), Indian Institute of Technology (IIT), Indore, MP, India

Received: March 02, 2017; **Accepted:** March 28, 2017; **Published:** April 03, 2017

Abstract

Inflammation is a self-defense event which is a result of any perturbation or interruption of body's homeostasis caused by biological, chemical, or physical agents as in infection and injury. This event leads to the initiation of inflammatory cascade which involves the production of pro-inflammatory mediators. In most cases this is an extremely important step in combating the pathogen, however when this inadvertently leads to a non-stop cascade not ready to slow down, the actual complications arise. The most dangerous aspect of this uncontrolled signaling is the birth of many diseases including cancer, atherosclerosis, arthritis, type 2 diabetes, sepsis etc. Although the basic players of all these diseases resulting from uncontrolled or chronic inflammation remain same, they differ in the propagation of the signal which in turn is dictated by the location and internal milieu of the organ it buds from. The review details the inflammatory pathway as well as the clinical implications diverging from it.

Introduction

Inflammation is the body's immediate response to damage to its tissues and cells by biological pathogens such as bacteria, fungi, viruses and chemical agents or physical injury (toxic pollutants, shock, burns, allergens etc) [1]. The primary function of inflammation is to rapidly destroy or combat this external stimuli or the underlying source. However, things go wrong when either the primary effect is sustained for a longer period of time or when it produces too many pro-inflammatory cytokines to be handled by the system.

Inflammation is generally of two types; acute or chronic, which depends on the type of stimulus as well as the defense machinery which deals with it.

Acute inflammation as the name suggests is quick to happen and relatively quicker to last, generally ranging from minutes to few days [2]. Neutrophil trafficking is the major signal of acute inflammation, which itself results after anaphylatoxins are released at the site of inflammation. This, in turn stimulates mast cells to release histamine, serotonin and prostaglandins causing blood vessels to expand (vasodilation) and become highly permeable. This attracts neutrophils to migrate to the affected tissue through the capillary wall (diapedesis) and respond to the stimuli. The visible effect of acute inflammation is seen by pus formation, swelling, redness and pain at the site of the external stimuli. Acute inflammation successfully eliminates damaging agents via the procedure described above; however, when it is unable to do so, it will bypass to the chronic inflammation process. Hence chronic inflammation occurs when the cause of inflammation is persistent, as seen in certain viral infections and hypersensitivity reactions. The defense army of chronic inflammation is different than that of acute inflammation, with more on-site lymphocytes and macrophages [3]. Also, the chronic inflammation leads to many severe implications like vascular proliferation, fibrosis, and tissue destruction [4].

Mechanisms of Inflammation

Inflammation is a tightly regulated signaling event with well-defined phases [5]. The first phase involves the recognition of external stimuli through specific transmembrane receptors, called pattern recognition receptors (PRRs) [5]. PRR's detect pathogen-associated molecular patterns (PAMPs), which are directed toward general motifs of molecules expressed by pathogens and danger-associated molecular patterns (DAMPs) which are endogenous molecules produced from internal injuries. PRRs have been distinguished based on their selective ability to detect PAMPs, DAMPs or both and are classified as transmembrane Toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-1-like receptors (RLRs) and intracellular nucleotide binding domain and leucine-rich-repeat containing NOD-like receptors (NLRs) [6,7]. These receptor-stimuli interactions initiate the signaling pathways which eventually lead to the translocation of signals to nucleus where the activation of selective set of genes takes place via both transcriptional and posttranscriptional mechanisms [8]. This includes the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); which is a key transcription factor found in almost all cell types and exists in an inactivated state upon binding to an inhibitor protein, IκB [9]. NF-κB is released from IκB after signal transduction and subsequently translocates to the nucleus, where transcription is upregulated through binding to target genes. Further, the inflammatory responses are coordinated by the products of these target genes, which mostly comprise proinflammatory cytokines such as TNF, IL-1β and IL-6. Hence, the transcription and translation of genes by NF-κB leads to the expression of proinflammatory cytokines, such as interleukin-1-beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), and others [10-13]. Besides, NF-κB, many other transcription factors also play important roles in the induction of pro-inflammatory cytokines. Among these, activator protein-1 (AP-1), is highly important due to its binding to the DNA responsive elements leading to the initiation of expression of pro-inflammatory genes in macrophages [14,15]. Signal transducer and activators of transcription (STAT) are a family of transcription factors that mediate antiviral functions of immune system through interferon signaling [16]. STAT1 homodimer translocates to nucleus and prompt to reprogram the target gene expression after activation of STAT1 signaling in response to IFN Type II (IFNy) [17]. Interferon regulatory factors (IRFs) are a family

Citation: Saqib U, Sarkar S and Baig MS. Inflammation and its Disease Consequences. J Immun Res. 2017; 4(1): 1027.

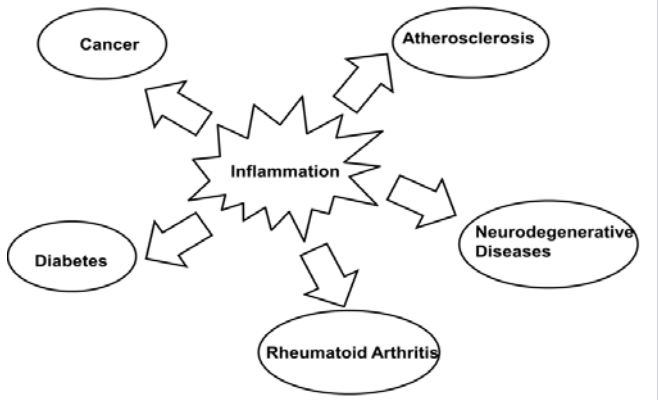

Figure 1: Disease Conditions resulting from Inflammation.

of transcription factors which are activated by Antiviral pattern recognition receptor TLR4, after LPS insult [18].

The net effect of the expression of pro-inflammatory mediators culminates in the local signs of inflammation including swelling, redness, pain, and loss of function. In most cases, this is followed by the resolution of inflammatory response, where the cells hosting the inflammatory event revert back to a non-inflammatory phenotype. This phase starts soon after the granulocytes signal a termination sequence and promote the switch of arachidonic acid–derived prostaglandins and leukotrienes to lipoxins and the recruitment of neutrophil followed by their apoptosis by resolvins and protectins [19]. Consequently, macrophages phagocytose these apoptotic neutrophils leading to neutrophil clearance and cellular debris. Further the release of anti-inflammatory and reparative cytokines such as transforming growth factor- β1 mark the end along with the clearance of macrophages through the lymphatics [20]. However, when this acute phase of inflammation does not meet it usual end, then the actual complications arise leading to the development of chronic inflammation. It is this chronic inflammation which triggers the development of many diseases discussed in the review, Figure 1. The current review highlights the mechanism of inflammation in general as discussed above and further diverges into its various disease implications.

Inflammation in cancer

The discussion of the link between inflammation and cancer could not start without mentioning the pioneer hypothesis given by German pathologist Rudolf Virchow in 1863 [21]. He detected inflammatory infiltrates in solid malignancies and concluded that cancers are more prone to occur at sites of chronic inflammation. After this pioneering observation and much research, it is now a well-established fact that inflammation plays a critical role in promoting cancer. An inflammatory microenvironment forms the niche for all tumors [22,23]. Improper resolution of inflammation and an unchecked inflammatory reaction can induce chronic inflammation, predisposing the host to cancerous consequences [24]. This all happens with a random growth of a tiny tumour which starts growing from a few cells and scavenges enough oxygen and nutrients from its surroundings. As it grows further, macrophages and granulocytes infiltrate the tumour, where they release cytokines which further initiate the growth of blood vessels or angiogenesis.

Studies show that the inflammatory microenvironments not only triggers cancer cell growth but also causes mutations in the cells by producing reactive oxygen species (ROS) and Nitric oxide Synthase (NOS)-derived nitrogen intermediates causing much DNA damage and genomic instability [25]. For instance, there is an evidence which proves that pro-inflammatory cytokines, namely TNF-α and IL-6, induce breast cancer cell growth and tumor formation, and induce adhesive recruitment of metastatic breast cancer cells [26,27]. The association between inflammation and cancer could further be observed in the case of colorectal cancer whose risk was 10-fold greater if linked with inflammatory bowel disease, such as ulcerative colitis and Crohn's disease [28,29]. Similarly, in the gastrointestinal tract, gastric *Helicobacter pylori* infection is the leading cause of adenocarcinoma and mucosa-associated lymphoid tissue lymphoma [30,31]. This is the reason why the risk of esophageal cancer, pancreatic cancer, and gallbladder cancer may be increased by inflammatory diseases, such as esophagitis, Barrett's metaplasia, and chronic pancreatitis [31,32].

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. Cancer-associated onco-proteins such as Ras, Myc and RET can also lead to inflammation by activating signaling pathways involved in the production of pro-inflammatory cytokines and chemokines [22]. Therefore, based on the literature, it can be concluded that inflammatory response is an integral part of cancer biology, either resulting in or beginning from tumorigenesis. In both ways; either tumor resulting from inflammation or inflammation resulting from tumor, the key players constituting the pro-inflammatory cytokine remain the same.

Inflammation in atherosclerotis

Inflammation plays a key role in the formation and progression of atherosclerotic plaques. Hence, nowadays, anti-inflammatory treatments are evaluated as novel treatments for atherosclerosis [33]. Much experimental work has elucidated the molecular and cellular pathways of inflammation that promote atherosclerosis by an inflammatory subset of monocytes/macrophages which accumulate in atherosclerotic plaque and produce pro-inflammatory cytokines.

Normally, endothelial cells (ECs), which form the innermost surface of the artery wall, resist adhesion and aggregation of leukocytes and promote fibrinolysis. However, external stimuli like hypertension, smoking, hyperglycemia, obesity or insulin resistance can initiate the expression of adhesion molecules by ECs that selectively recruit various classes of leukocytes to the arterial wall [34]. Hence, the normal homeostatic functions of these adhesion molecules are disturbed which then make their way into the intima. Although, it is the property of the endothelial monolayer to resist this leucocyte adhesion coming from the flowing blood, however there are helpers which aid this process. The first of these include the vascular cell adhesion molecule-1 (VCAM-1) which helps in the attachment of leucocytes to the arterial wall or intima [35]. Further, after a high atherogenic diet the modified lipoprotein particles including the oxidized phospholipids and fatty acids induce the pro-inflammatory cytokines such as interleukin (IL)-1b or tumour-necrosis factor-α (TNF-α) which eventually activate nuclear factor-kB (NF-kB) for the transcriptional activation of the VCAM-1 gene, thus further aiding

the leucocyte adhesion [36]. It could also be noted that the oxidized LDL which assist in this process arose from the modulation by nitric oxide (NO) and other products resulting from the neuronal nitric oxide synthase (nNOS) [37,38]. Once recruited, the leukocytes make their way to the intima by diapedesis between endothelial cells at their junctions. Factors like monocyte chemoattractant protein-1 (MCP-1) and IL-8 play important roles as a leukocyte chemoattractant during atherogenesis [39]. The resulting Atheroma further overexpresses the chemokines that may contribute to more lymphocyte recruitment. These leucocytes further undergo maturation to become macrophages after going through a series of morphological changes. This marks the appearance of what we call the "foam cell formation", a hallmark of atherosclerosis [40]. These macrophages which constitute the foam cells continue to release various growth factors and cytokines (eg, platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-), macrophage-colony stimulating factor (M-CSF), involved in lesion progression and complication. All these events further accelerate the replication of macrophages within the intima. It has been identified that most of the macrophage related activities including its maturation from monocyte to the lipid-laden macrophage, migration and proliferation could be attributed to M-CSF [41]. This could be directly reflected in animal experiments where mice lacking M-CSF show retarded lesion development with markedly reduced macrophage accumulation [42,43]. Further, the lipid-enriched fatty streak developed from the macrophages along the vessel wall evolve into complicated atheroma through multiplication of smooth muscle cells which accumulate in the plaque and lay down an abundant extracellular matrix. This eventually narrows down the arterial lumen and further hampers the coronary circulation leading to clinical complications like angina pectoris, acute myocardial infarction etc [44].

The pivotal role played by inflammation is crucial to the pathogenesis of atherosclerosis. The multiple oxidation events in chronic inflammation form the basis of the complications associated with inflammation driven atheroschelorsis.

Inflammation in diabetes

The close link between metabolism and immunity is unquestionable. It has been evident from many studies that chronic inflammation is associated with obesity linked diabetes [45]. The molecular and cellular signaling pathways leading to obesity-induced inflammation enormously contribute to diabetes. The interesting observation by the scientists on the connection of metabolic syndrome and activation of the immune response provided direct clues of a link between diabetes and inflammation. Many clinical events take place leading to the onset of Diabetes. Mechanisms including glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum (ER) stress, alterations of the gut microbiota, endocannabinoids and the formation of amyloid deposits in the islets etc are all associated with inflammatory responses [46-48]. The association between Diabetes and inflammation though straightforward, has still many missing links. However, with data published so far, many theories linking inflammation-driven mechanisms to diabetes could be understood in detail. One among those is the obesity linked factor where there is a subsequent polarization of Macrophages to the "classically activated macrophages" phenotype, M1 which secrete pro-inflammatory cytokines such as IL-1b, IL-6, TNF-a, from the "alternatively activated macrophages" phenotype, M2 which produce anti-inflammatory cytokines such as IL-10 [49]. Obesity not only leads to adipose tissue macrophages infiltration, but also causes a phenotypic switch from the anti-inflammatory M2 to pro-inflammatory M1 phenotype. The downstream signaling from these M1 macrophages impairs insulin signaling [50]. Another widely accepted theory emphasizing the idea that it could be other way round, with the increase in the level of glucose triggers inflammation which subsequently prompts for diabetes [51]. This happens in pancreatic islets where elevated glucose concentrations increase the metabolic activity of islet cells, leading to elevated formation of reactive oxygen species (ROS). ROS promotes activation of the NLRP3 inflammasome and release of IL-1β [52]. Other factors leading to increased production of IL-1β, include ER stress due to increased insulin demand and production, lipopolysaccharides from bacterial cell walls (endotoxins) or free fatty acids bound to Fetuin A and thus activating NF-κB via TLR2 or TLR-4 [53,54]. IL-1β further induces IL-6, IL-8, tumour necrosis factor (TNF) and monocyte chemoattractant protein 1 (MCP1) which consequently attract macrophages and other immune cells. In macrophages, the high accumulation of glucose and lipids promote the formation of inflammasomes that lead to the splicing of pro-IL-1β to active IL-1β [55,56], which further carry forward the signaling by attracting multiple immune cells thereby promoting insulin resistance.

Inflammation in neurodegenerative diseases

The adult human central nervous system (CNS) consists of billions of neurons and glia cells, namely microglia [57]. Microglia is basically macrophages present in the brain and spinal cord and form the frontline defense mechanism of its innate immune system. Under physiological conditions the resting microglia displays a deactivated phenotype and surveys the microenvironment and produce factors that influence surrounding astrocytes and neurons. However, any disturbance in the CNS environment caused by alterations formed by pathogen invasion or tissue damage, results in microglia and astrocyte activation. This activated phenotype of microglia promotes an inflammatory response that serves to initiate the tissue repair by producing and releasing neurotrophic factors or cytokines. However, in case of prolonged neuronal damage, they release pro-inflammatory cytokines by astrocytes and microglia which further leads to an enhanced local inflammatory reaction. The activated microglia and astrocytes can produce ROS along with the pro-inflammatory cytokines which further contribute to neurodegeneration process due to its high reactive ability [58-60]. This forms the basis of several neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Infact the presence of pro-inflammatory cytokines and activated immune cells, is an important feature of all neurodegenerative diseases [61,62,63]. Since, there is clear indication of the presence of a common link between various neurodegenerative diseases and activation of innate immune responses, the role of inflammation could be easily understandable. This could be understood in more detail by individually looking into few of the important neurodenerative diseases.

Alzheimer disease: AD is one of the most common causes of dementia in the elderly people. Clinically, it is characterized by loss of memory, cognitive impairment and various neuropsychiatric disorders including behavioral and neuropsychiatric disturbances

[64]. The typical neuropathological feature in AD is the accumulation of extracellular β-amyloid plaques (Aβ) composed of aggregated, cleaved products of the amyloid precursor protein (APP) and intracellular neurofibrillary tangles (NFTs). This is also formulated mainly by comprising the hyper phosphorylated forms of microtubule-binding protein tau. These aggregates of Aβ have been shown to activate microglia which successively induce the production of inflammatory factors like nitric oxide (NO), ROS as well as pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), and chemokines (e.g., IL-18) [65]. Other studies also suggest that Aβ fibrils trigger inflammatory responses through TLR4/TLR6 in the presence of CD36 [66].

Parkinson disease: PD is a chronic progressive neurodegenerative disease, which is clinically characterized by motor symptoms (bradykinesia, tremor, rigidity, and postural instability) and non-motor-related symptoms (olfactory deficits, autonomic dysfunction, depression, cognitive deficits, and sleep disorders) [67,68]. PD is also due to abnormal accumulation and aggregation of misfolded α-synuclein. There are reports clearly indicating the direct role of α-synuclein in increased ROS production which results in oxidative damage, mitochondrial dysfunction, and ultimately cell death, thus creating a vicious cycle promoting neurodegeneration [69-72]. Microglia activation is the key to neurodegeneration of neurons in the substantia nigra (SN). Various *in vivo* studies have demonstrated that the serum and cerebrospinal fluid of PD patients have higher levels of IL-1β, TNF-α, and IL-2 and also $CD4^+$ and $CD8^+$ T lymphocytes.

Studies have also revealed that PD patients show elevated serum levels of TNF-α and TNF-α receptor 1 as compared to control subjects. This could contribute to PD pathogenesis [73-75]. Many proinflammatory cytokines including IL-1β, TNF-α, and IL-6, have also been described in SN of postmortem tissue of patients [68].

Multiple sclerosis: Multiple sclerosis (MS) is a heterogeneous and complex autoimmune disease of the central nervous system (CNS) due to autoimmune aggression against myelin and neuronal antigens [76]. It was noticed in the earliest studies on multiple sclerosis pathology [77] that axonal injury and loss occur in the disease lesions and their extent correlates with the degree of inflammation. The major characteristic of MS lesions is infiltration of lymphocytes and antibody-producing plasma cells into the perivascular region of the brain and spinal cord white matter. This is aggravated by an increase in activated microglia and demyelination [78].

Inflammation in rheumatoid arthritis (RA)

RA is a progressive, inflammatory autoimmune disease characterized by chronic, symmetric and erosive synovitis occurred mainly in peripheral joints [79]. Many inflammatory pathways including Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT), the stress-activated protein kinase/mitogen-activated protein kinase (SAPK/MAPK) and Phosphatidylinositide-3-Kinase/AKT/mammalian Target of Rapamycin (PI-3K/AKT/mTOR) pathways have been shown to be involved in RA [80-84]. As discussed previously, pro-inflammatory cytokines like TNF and IL-1 are a key component in the process of chronic joint inflammation and the concomitant erosive changes in cartilage and bone. As a matter of fact, TNF-α and several of the interleukins (IL) including, IL-1, -6, -7, -8, -12/23, -15, -17, -18, -32, -35 and proteins of the interferon (INF) family were found to be elevated in RA sera [85]. In fact excess levels of IL-6 are produced in people with RA, specifically in the tissue layer covering the joint. There are clear reports of the role of deregulated activation of JAK/STAT pathway along with its cross-talk with SAPK/MAPK, PI-3K/AKT/mTOR pathways [80-84] in rheumatoid arthritis. Also, spleen tyrosine kinase (Syk) [86], the sphingosine kinases, SphK1 and SphK2, transforming growth factor β-activated kinase-1 (TAK1) [87], bone marrow kinase (BMX) [88] and nuclear factor-κB-inducing kinase (NIK) [89] are involved in the onset and progression of RA. Also, direct evidence shows the role of BMX in p38 kinase and JNK phosphorylation as well in the activation of NF-κB [89]. Hence, BMX may be responsible for regulating the activation of p38, JNK and NF-κB, all of which are critical to the inflammatory response cell survival and apoptosis. The proinflammatory cytokines and growth factors activate the STAT proteins in the JAK/ STAT pathway, while the increase in neutrophil, macrophage and eosinophil chemotaxis and activation of T- and B-cells resulted in Tumor Necrosis-Related Apoptosis-Inducing Ligand (TRAIL) and IL-15 induced activation of PI-3K/AKT/mTOR pathway. All these factors clearly indicate the important role played by inflammatory signaling in the onset and progression of Rheumatoid Arthritis.

Conclusion

This review provides key links between the inflammatory signaling pathways and various diseases. Inflammation appears to play a critical role in many chronic diseases. Inflammation as a first defense mechanism of the body is helpful in combating incoming pathogens inside the body. It is this primary acute inflammation which protects and heals the body after an injury or infection which is essential and normal. However, when the acute phase is prolonged by excess or consistent stimuli, it results in becoming chronic which deteriorates the situation in many diseases.

Many diseases discussed above have either been a result of the inflammatory pathway already going on at the site of action or the disease itself triggers an inflammatory response which further aggravates the situation. However, in almost all cases inflammatory cells and cytokines take the lead in further progression of the disease. From past many years, investigators have understood the signaling mechanisms linking inflammation to diseases. Hence, reaching the root cause of the disease has become much easier, considering that most of these have an inflammatory angle to it. Through this review, we tried to focus on various diseases derived directly or indirectly by inflammatory pathways and how a careful observation in each of these would bring in important targets for therapeutic intervention.

Acknowledgments

This work was supported by the Science & Engineering Research Board (SERB) Young Scientists Start-Up Research Grant under grant number YSS/2015/001279 to U.S, Department of Biotechnology sponsored DBT-Ramalingaswami fellowship and CSIR-EMR-II funding to MSB. The authors also gratefully acknowledge the facilities provided by the Indian Institute of Technology Indore, for providing facilities and other support.

References

1. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;

454: 428-435.

2. Kadl A, Leitinger N. The role of endothelial cells in the resolution of acute inflammation. Antioxid Redox Signal. 2005; 7: 1744-1754.

3. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol. 2005; 6: 1191-1197.

4. González-Chávez A, Elizondo-Argueta S, Gutiérrez-Reyes G, León-Pedroza JI. Pathophysiological implications between chronic inflammation and the development of diabetes and obesity. Cirugía y Cir. 2011; 79: 209-216.

5. Medzhitov R. Inflammation 2010: New Adventures of an Old Flame. Cell. 2010; 140: 771-776.

6. Kawai T, Akira S. Pathogen recognition with Toll-like receptors. Curr Opin Immunol. 2005; 17: 338-344.

7. Kawai T, Akira S. The roles of TLRs, RLRs and NLRs in pathogen recognition. Int Immunol. 2009; 21: 317-337.

8. Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature. 2007; 449: 819-826.

9. Sankar Ghosh, Michael J. May and, Kopp EB. NF-κB AND REL PROTEINS: Evolutionarily Conserved Mediators of Immune Responses. 2003.

10. Pahl HL. Activators and target genes of Rel/NF-κB transcription factors. Oncogene. 1999; 18: 6853-6866.

11. Gilmore TD. Introduction to NF-κB: players, pathways, perspectives. Oncogene. 2006; 25: 6680-6684.

12. Hayden MS, West AP, Ghosh S. NF-κB and the immune response. Oncogene. 2006; 25: 6758-6780.

13. Perkins ND. Post-translational modifications regulating the activity and function of the nuclear factor kappa B pathway. Oncogene. 2006; 25: 6717-6730.

14. Eferl R, Wagner EF. AP-1: a double-edged sword in tumorigenesis. Nat Rev Cancer. 2003; 3: 859-868.

15. Jeong D, Lee J, Yi Y-S, Yang Y, Kim KW, Cho JY. p38/AP-1 Pathway in Lipopolysaccharide-Induced Inflammatory Responses Is Negatively Modulated by Electrical Stimulation. Mediators Inflamm. 2013; 2013: 1-11.

16. Pfitzner E, Kliem S, Baus D, Litterst CM. The role of STATs in inflammation and inflammatory diseases. Curr Pharm Des. 2004; 10: 2839-2850.

17. Ramana C V, Gil MP, Schreiber RD, Stark GR. Stat1-dependent and -independent pathways in IFN-γ-dependent signaling. Trends Immunol. 2002; 23: 96-101.

18. Honda K, Yanai H, Negishi H, et al. IRF-7 is the master regulator of type-I interferon-dependent immune responses. Nature. 2005; 434: 772-777.

19. Serhan CN. Resolution phase of inflammation: novel endogenous anti-inflammatory and pro resolving lipid mediators and pathways. Annu Rev Immunol. 2007; 25: 101-137.

20. Gautier EL, Ivanov S, Lesnik P, Randolph GJ. Local apoptosis mediates clearance of macrophages from resolving inflammation in mice. Blood. 2013; 122: 2714-2722.

21. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001; 357: 539-545.

22. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008; 454: 436-444.

23. de Visser KE, Korets LV, Coussens LM. De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell. 2005; 7: 411-423.

24. Wu Y, Antony S, Meitzler JL, Doroshow JH. Molecular mechanisms underlying chronic inflammation-associated cancers. Cancer Lett. 2014; 345: 164-173.

25. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010; 140: 883-899.

26. Bhatelia K, Singh A, Tomar D, et al. Antiviral signaling protein MITA acts as a tumor suppressor in breast cancer by regulating NF-κB induced cell death. Biochim Biophys Acta - Mol Basis Dis. 2014; 1842: 144-153.

27. Geng Y, Chandrasekaran S, Hsu J-W, Gidwani M, Hughes AD, King MR. Phenotypic switch in blood: effects of pro-inflammatory cytokines on breast cancer cell aggregation and adhesion. PLoS One. 2013; 8: e54959.

28. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol. 2004; 287: G7-G17.

29. Seril DN, Liao J, Yang G-Y, Yang CS. Oxidative stress and ulcerative colitis-associated carcinogenesis: studies in humans and animal models. Carcinogenesis. 2003; 24: 353-362.

30. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420: 860-867.

31. Macarthur M, Hold GL, El-Omar EM. Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy. Am J Physiol Gastrointest Liver Physiol. 2004; 286: G515-G520.

32. Whitcomb DC. Inflammation and Cancer V. Chronic pancreatitis and pancreatic cancer. Am J Physiol Gastrointest Liver Physiol. 2004; 287: G315-G319.

33. Frostegård J, Gimbrone M, Topper J, et al. Immunity, atherosclerosis and cardiovascular disease. BMC Med. 2013; 11: 117.

34. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988; 37: 1595-1607.

35. Hwang SJ, Ballantyne CM, Sharrett AR, et al. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. Circulation. 1997; 96: 4219-4225.

36. Marui N, Offermann MK, Swerlick R, et al. Vascular cell adhesion molecule-1 (VCAM-1) gene transcription and expression are regulated through an antioxidant-sensitive mechanism in human vascular endothelial cells. J Clin Invest. 1993; 92: 1866-1874.

37. Carr AC, McCall MR, Frei B. Oxidation of LDL by Myeloperoxidase and Reactive Nitrogen Species : Reaction Pathways and Antioxidant Protection. Arterioscler Thromb Vasc Biol. 2000; 20: 1716-1723.

38. Bloodsworth A, O'Donnell VB, Freeman BA. Nitric oxide regulation of free radical- and enzyme-mediated lipid and lipoprotein oxidation. Arterioscler Thromb Vasc Biol. 2000; 20: 1707-1715.

39. Papadopoulou C, Corrigall V, Taylor PR, Poston RN. The role of the chemokines MCP-1, GRO-alpha, IL-8 and their receptors in the adhesion of monocytic cells to human atherosclerotic plaques. Cytokine. 2008; 43: 181-186.

40. Aviram M. Macrophage foam cell formation during early atherogenesis is determined by the balance between pro-oxidants and anti-oxidants in arterial cells and blood lipoproteins. Antioxid Redox Signal. 1999; 1: 585-594.

41. Devaraj S, Yun J-M, Duncan-Staley C, Jialal I. C-reactive protein induces M-CSF release and macrophage proliferation. J Leukoc Biol. 2009; 85: 262-267.

42. Smith JD, Trogan E, Ginsberg M, Grigaux C, Tian J, Miyata M. Decreased atherosclerosis in mice deficient in both macrophage colony-stimulating factor (op) and apolipoprotein E. Proc Natl Acad Sci U S A. 1995; 92: 8264-8268.

43. Rajavashisth T, Qiao JH, Tripathi S, et al. Heterozygous osteopetrotic (op) mutation reduces atherosclerosis in LDL receptor- deficient mice. J Clin Invest. 1998; 101: 2702-2710.

44. Saitoh T, Kishida H, Tsukada Y, et al. Clinical significance of increased plasma concentration of macrophage colony–stimulating factor in patients with angina pectoris. J Am Coll Cardiol. 2000; 35: 655-665.

45. Ehses JA, Ellingsgaard H, Böni-Schnetzler M, Donath MY. Pancreatic islet inflammation in type 2 diabetes: From α and β cell compensation to dysfunction. 2009.

46. Westwell-Roper CY, Ehses JA, Verchere CB. Resident macrophages mediate islet amyloid polypeptide-induced islet IL-1β production and β-cell dysfunction. Diabetes. 2014; 63: 1698-1711.

47. Westwell-Roper C, Dai DL, Soukhatcheva G, et al. IL-1 blockade attenuates islet amyloid polypeptide-induced proinflammatory cytokine release and pancreatic islet graft dysfunction. J Immunol. 2011; 187: 2755-2765.

48. Jourdan T, Godlewski G, Cinar R, et al. Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes. Nat Med. 2013; 19: 1132-1140.

49. Fujisaka S, Usui I, Bukhari A, et al. Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. Diabetes. 2009; 58: 2574-2582.

50. Jung UJ, Choi M-S. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014; 15: 6184-6223.

51. Deopurkar R, Ghanim H, Friedman J, et al. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. Diabetes Care. 2010; 33: 991-997.

52. Feng H, Gu J, Gou F, et al. High Glucose and Lipopolysaccharide Prime NLRP3 Inflammasome via ROS/TXNIP Pathway in Mesangial Cells. J Diabetes Res. 2016; 2016: 6973175.

53. Böni-Schnetzler M, Boller S, Debray S, et al. Free fatty acids induce a proinflammatory response in islets via the abundantly expressed interleukin-1 receptor I. Endocrinology. 2009; 150: 5218-5229.

54. Pal D, Dasgupta S, Kundu R, et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. Nat Med. 2012; 18: 1279-1285.

55. Koenen TB, Stienstra R, van Tits LJ, et al. Hyperglycemia activates caspase-1 and TXNIP-mediated IL-1beta transcription in human adipose tissue. Diabetes. 2011; 60: 517-524.

56. Vandanmagsar B, Youm Y-H, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med. 2011; 17: 179-188.

57. Azevedo FAC, Carvalho LRB, Grinberg LT, et al. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J Comp Neurol. 2009; 513: 532-541.

58. Emerit J, Edeas M, Bricaire F. Neurodegenerative diseases and oxidative stress. Biomed Pharmacother. 2004; 58: 39-46.

59. Hsieh H-L, Yang C-M, Hsieh H-L, Yang C-M. Role of redox signaling in neuroinflammation and neurodegenerative diseases. Biomed Res Int. 2013; 2013: 484613.

60. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol. 2014; 24: R453-R462.

61. Amor S, Puentes F, Baker D, van der Valk P. Inflammation in neurodegenerative diseases. Immunology. 2010; 129: 154-169.

62. Wee Yong V. Inflammation in neurological disorders: a help or a hindrance? Neuroscientist. 2010; 16: 408-420.

63. Zipp F, Aktas O. The brain as a target of inflammation: common pathways link inflammatory and neurodegenerative diseases. Trends Neurosci. 2006; 29: 518-527.

64. Selkoe DJ, Citron M, Scheuner D, et al. Alzheimer's disease: genotypes, phenotypes, and treatments. Science. 1997; 275: 630-631.

65. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell. 2012; 148: 1204-1222.

66. Stewart CR, Stuart LM, Wilkinson K, et al. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. Nat Immunol. 2010; 11: 155-161.

67. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol. 2006; 5: 355-363.

68. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 2009; 8: 382-397.

69. Orth M, Tabrizi S., Tomlinson C, et al. G209A mutant alpha synuclein expression specifically enhances dopamine induced oxidative damage. Neurochem Int. 2004; 45: 669-676.

70. Junn E, Mouradian MM. Human α-Synuclein over-Expression Increases Intracellular Reactive Oxygen Species Levels and Susceptibility to Dopamine. 2002; 320: 146-150.

71. Paxinou E, Chen Q, Weisse M, et al. Induction of alpha-synuclein aggregation by intracellular nitrative insult. J Neurosci. 2001; 21: 8053-8061.

72. Ahn T-B, Kim SY, Kim JY, et al. alpha-Synuclein gene duplication is present in sporadic Parkinson disease. Neurology. 2008; 70: 43-49.

73. Reale M, Iarlori C, Thomas A, et al. Peripheral cytokines profile in Parkinson's disease. Brain Behav Immun. 2009; 23: 55-63.

74. Scalzo P, Kümmer A, Cardoso F, Teixeira AL. Increased Serum Levels of Soluble Tumor Necrosis Factor-α Receptor-1 in Patients with Parkinson's Disease. 2009; 216: 122-125.

75. Dufek M, Hamanová M, Lokaj J, et al. Serum Inflammatory Biomarkers in Parkinson's Disease. 2009; 15: 318-320.

76. Stüve O, Patejdl R. Immune-mediated CNS diseases: A review on nosological classification and clinical features. Autoimmun Rev. 2012; 11: 167-173.

77. Kornek B, Lassmann H. Axonal Pathology in Multiple Sclerosis. A Historical Note. Brain Pathol. 1999; 9: 651-656.

78. Lassmann H, Brück W, Lucchinetti C. Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. Trends Mol Med. 2001; 7: 115-121.

79. Turesson C, Jacobsson LTH. Epidemiology of extra-articular manifestations in rheumatoid arthritis. Scand J Rheumatol. 2004; 33: 65-72.

80. Malemud CJ, Pearlman E. Targeting JAK/STAT Signaling Pathway in Inflammatory Diseases.

81. Malemud C. Differential activation of JAK enzymes in rheumatoid arthritis and autoimmune disorders by pro-inflammatory cytokines: potential drug targets. Int J Interf Cytokine Mediat Res. 2010; 2: 97.

82. Burmester GR, Feist E, Dörner T. Emerging cell and cytokine targets in rheumatoid arthritis. Nat Rev Rheumatol. 2013; 10: 77-88.

83. Malemud CJ, Reddy SK. Targeting Cytokines, Chemokines and Adhesion Molecules in Rheumatoid Arthritis.

84. Wu T, Mohan C. The AKT Axis as a Therapeutic Target in Autoimmune Diseases. Endocrine, Metab Immune Disord - Drug Targets. 2009; 9: 145-150.

85. Szekanecz Z, Koch AE. Macrophages and their products in rheumatoid arthritis. Curr Opin Rheumatol. 2007; 19: 289-295.

86. Ghosh D, Tsokos GC. Spleen tyrosine kinase: an Src family of non-receptor kinase has multiple functions and represents a valuable therapeutic target in the treatment of autoimmune and inflammatory diseases. Autoimmunity. 2010; 43: 48-55.

87. Dai L, Aye Thu C, Liu X-Y, Xi J, Cheung PCF. TAK1, more than just innate immunity. IUBMB Life. 2012; 64: 825-834.

88. Gottar-Guillier M, Dodeller F, Huesken D, et al. The tyrosine kinase BMX is an essential mediator of inflammatory arthritis in a kinase-independent manner. J Immunol. 2011; 186: 6014-6023.

89. Razani B, Reichardt AD, Cheng G. Non-canonical NF-κB signaling activation and regulation: principles and perspectives. Immunol Rev. 2011; 244: 44-54.