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Abstract

Both stress and inflammatory responses play a key role in maintaining homeostasis in the body. Stress responds to threats while inflammation responds to injury and infection by some physiological mechanisms in our life. In physiological status, our body is in dynamic equilibrium. Once the homeostasis is disrupted by acute or chronic stressor, a stress response will be triggered to restore normalcy, indicating that stress can be thought of as a protective function in maintaining physiological condition. Of interest, inflammatory response will be triggered to eliminate or promote adaptations to the stressor if the stress response is insufficient to recover homeostasis state. Growing evidences indicate that stress hormones and many types of stress such as endoplasmic reticulum stress and oxidative stress may induce inflammatory responses in multiple tissues and organs if the homeostasis cannot be recovered. On the other hand, long-term stress-induced inflammation will cause a majority of diseases including cardiovascular disease, metabolic diseases, neurodegenerative disease, cancer, and arthritis, indicating that the relationship between stress and inflammatory is ambiguous and it's well worth illuminating. Since stress-induced inflammation gains more foci in research and clinical practice, clarifying the relationship between the stress and inflammation and exploring correlated signaling pathways may provide new strategies for the treatment of inflammatory diseases. Therefore,

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in this chapter, we systemically summarized and discussed the correlation between the stress and inflammation and associated diseases.

Keywords

Stress · Inflammation · Homeostasis · Inflammatory diseases

12.1 Stress and Diseases

Stress is not only a feeling but also a physiological mechanism which responds to threats in our life. The stress response system is made up of psychological, affective, and neuroendocrine components that can be activated by a range of physical and psychosocial stressors. When we're stressed, our blood pressure increases and pulse rises, and we breathe faster. Stress is generally consist of two types, acute stress and chronic stress. Acute stress (also known as the fight-or-flight response) is an immediate and short-term body response to the presence of something that is terrifying, either mentally or physically.

Chronic stress is the activation of a stress mechanism that is exposed to different stressors for a long time. Exposure to chronic stress can cause long-term or permanent changes in emotional, physiological, and behavioral responses, thereby affecting the susceptibility and duration of the disease [1]. Chronic stress could destroy tissue structure and raise blood pressure and damage the heart by inducing cortisol and adrenaline [2]. Therefore, prolonged or repeated activation of the stressor-elicited endocrine response systems may interfere with their control of other physiological systems, leading to an increased risk of physical and mental illness, such as cardiovascular dysfunction, diabetes, cancer, autoimmune syndrome, and mental illnesses [3].

As mentioned, chronic stress may be related to changes in parts of the brain, which may extend to other functionally related areas and cause cognitive, emotional, and behavioral dysfunctions. The effects of stress on the regulation of immune and inflammatory processes may affect the occurrence of depression; cause infections and autoimmune disease; and arise specific viruses-induced cancers and coronary artery disease [3]. And stress-induced depression can further affect susceptibility to disease and subsequent recovery [4].

Glucocorticoids (GCs) released under stress cause the aging process and neuron loss [5]. A recent study has shown that exposure to stress can accelerate the erosion of DNA fragments which are called telomeres [6]. Shorter telomere length is related to age, as well as to the disease morbidity and mortality. It is well known that the stress of early years can have an influential direct negative impact on future health. Hence, telomere erosion is a potential mechanism linking childhood stress to health problems later in life [7]. In addition, psychological stress induces acute phase reactions related to infection and tissue damage and increases the levels of circulating cytokines and various biomarkers of inflammation [8]. Therefore, stress plays an important role in multiple diseases.

12.2 Inflammation and Diseases

Inflammation is part of the body's immune response to injury and infection. It sends a signal to the body to defend against foreign invaders such as viruses and bacteria, as well as repair the damaged tissues. The symptoms of inflammation depend on whether the response is acute or chronic.

Acute inflammation is a short-term response that starts rapidly with local effects and may become severe in a short space of time. Generally, stress is correlated with chronic inflammation. Chronic inflammation is a long-term and whole-body effect. Under certain circumstances, acute inflammation can turn into chronic inflammation. An overreactive immune response will happen when it's unable to eliminate some factors remaining in the system that cause acute inflammation. For example, pathogens produce stable and low levels of inflammation throughout the body. This low level of inflammation can trigger an immune response. However, due to mistaking targets, the white blood cells start attacking internal organs or other healthy tissues and cells that eventually leads to a variety of chronic inflammatory or autoimmune diseases and conditions, including certain cancers, rheumatoid arthritis, and atherosclerosis [9, 10].

Chronic inflammation has been linked to heart disease and stroke because plaques can form when inflammatory cells stay in the blood vessels for a long time. The human body considers plaque as a foreign substance so that it tries to clear the plaque with flowing blood. If the plaque becomes unstable and ruptures, it can form a clot that blocks blood flow to the heart or brain, causing a heart attack or stroke [11, 12].

During inflammation, a large number of macrophages are accumulated, inflammasomes are formed, and a large amount of tumor necrosis factor- α (TNF- α) and IL-6 are produced, which lead to atherosclerosis [13]. In addition, inflammation is a crucial factor in the development of metabolic diseases. Recent work has shown that inflammasomes and caspase-1 play key roles in the regulation of obesity, insulin resistance, and cardiovascular disease (CVD) [14].

Chronic inflammation can also be caused by chronic infections. Hepatitis B and C virus infections are related to liver cancer; HIV increases the risk of other viruses and very rare cancers such as aggressive B-cell non-Hodgkin lymphoma and invasive cervical cancer [15]. In addition to being associated with many infectious diseases, inflammation is closely related to non-communicable diseases [16]. Cancer is one of the diseases associated with chronic inflammation. The tumor microenvironment composed of inflammatory cells is an essential participant in tumorigenesis by promoting tumor cell proliferation, survival, and migration [17]. Cytokines produced during the inflammatory process may stimulate the growth of blood vessels that bring oxygen and nutrients to the tumor. The process may also generate molecules called free radicals that further damage the DNA as well and implicate at every stage of tumorigenesis [18, 19]. Other evidence demonstrates that the Ras cancer gene plays a role in inflammation, which illustrates the role of chronic inflammation in many cancers at various stages of their progression [20].

Another major category of diseases related to chronic inflammation are those involving progressive and irreversible damage to the central nervous system. The

brain is considered to be an “immune-privileged” organ. It is not susceptible to inflammation or immune activation and is considered largely immune to systemic inflammation and immune responses. However, recent results suggest that inflammation in the central nervous system can cause many acute and chronic degenerative diseases and may even lead to certain mental illnesses. Inflammation of the central nervous system has a potential role in diseases such as acute brain injury, stroke, epilepsy, multiple sclerosis, motor neuron disease, dyskinesia, and Alzheimer’s disease. And some mental illnesses have also recently appeared, such as depression, anxiety, and schizophrenia [5].

12.3 Stress and Inflammation

Although it is uncontroversial that both stress and inflammatory responses belong to protective responses that maintain homeostasis, the relationship between them is ambiguous and the connection is needed to illuminate. Under physiological status, the system (cells, tissues, and organs) is in a homeostatic condition when the values of regulated variables are within an acceptable dynamic range. Then, a stress response will be triggered while the homeostatic capacity is insufficient to maintain these values (e.g., due to external interventions). If the stress response is insufficient to recover homeostasis, an inflammatory response will be engaged. Both stress response and inflammation are induced to eliminate the stressor, to promote adaptations to the stressor, and ultimately to return the system to the homeostatic state [21].

Accumulating evidence indicates that many types of stress can affect the inflammatory response in multiple tissues or organs. For example, GCs are one of the major stress hormones released during stress responses that are well known for their immunosuppressive and anti-inflammatory properties. GCs could decrease the expression of pro-inflammatory cytokines including TNF- α and IL-6 and increase the expression of anti-inflammatory cytokines including IL-10 and TNF- β [22]. However, the opposite role of GCs has been revealed by other studies. The studies found that GCs could promote the expression and function of inflammasome NLRP3 and in turn upregulate the secretion of IL-1 β and IL-18 upon ATP [23]. Above all, the innate immune system has been activated through stimulated with GCs in response to danger signals.

The function of the endoplasmic reticulum (ER) tends to be particularly vital in immune cells because these cells produce a very large amount of proteins. ER stress usually causes inflammation, which in turn restrains impairment of tissue and promotes the repairment of tissue. In ER stress induced-inflammation, many signaling pathways are activated. Nucleotide-binding oligomerization domain 1 (NOD1), as an intracellular pattern recognition receptor (PRR), is associated with the innate immune response because its stimulation induces activation of NF- κ B and promotes induction of cytokines upon ER stress-induced unfolded protein response (UPR). Likewise, the closely related PRR NOD2 has also been linked to inflammation by responding to the ER stress [24].

It has been found that ER stress could drive neuroinflammation involving in astrocytes and microglia [25]. ER stress-induced activation of the STAT3/JAK1 axis induces the expression of IL-6. Furthermore, the activation of the STAT3 signaling pathway is linked to PERK, a vital component of the ER stress response, which is phosphorylated by JAK1. Inhibition of PERK expression restrains ER stress-induced activation of STAT3 and subsequent gene expression. In addition, ER-stressed astrocytes trigger activation of microglia, leading to the production of IL-6 and oncostatin M (OSM) via paracrine signaling. Then, these cytokines can synergize with ER stress in astrocytes to drive inflammation [25, 26].

Oxidative stress is another typical stress response and is also linked to the inflammatory response. Reactive oxygen species (ROS) are generated during glucose or free fatty acid oxidation by mitochondria and from metabolic processes elsewhere in the cell. In physiological status, cells exhibit a self-protective activity against oxidative damage made up of enzymatic and non-enzymatic components [27]. However, the production of ROS is increased, and disruption of the balance between oxidant and antioxidant factors results in a pro-oxidative condition [28]. This oxidative stress can then damage cellular structures and trigger an inflammatory response [29].

Collectively, the stress response may induce an inflammatory response when the cell has no capacity to recover homeostasis. Long-term stress-induced inflammation would cause a majority of diseases, such as CVD, metabolic diseases, neurodegenerative disease, cancer, and arthritis diseases.

12.3.1 Stress, Inflammation, and Cardiovascular Disease

Cardiovascular disease (CVD) is a class of diseases that involve the heart and blood vessels. The disease has been classified to be the leading cause of death all over the world. Accumulating evidence has indicated that chronic stress, like early life stress or adult stress, has been linked to rising coronary heart disease (CHD) risk [30]. People who experienced more family conflict in childhood or high intensive stress usually led to higher blood pressure and cholesterol, leading to CVD [31, 32]. Besides, obesity and diabetes mellitus, which are associated with oxidative stress and metabolic stress, are linked to CVD [33].

More and more evidence reveals that chronic stress probably induced chronic low-grade inflammation and further contributed to the early process, progression, and thrombotic complications of atherosclerosis. Exposure to PM_{2.5} could trigger oxidative stress and simultaneously increase the expression of the anti-oxidative gene, nuclear factor (erythroid-derived 2)-like 2-related factor (Nrf2), to activate the downstream anti-oxidative pathway [34]. Furthermore, long-term exposure to PM_{2.5} induces cardiac dysfunction, which even could enhance the cardiovascular events and atherosclerosis [34]. In the PM_{2.5} exposure animal model, Nrf2^{-/-} mice display more severe inflammation and activate IκBα/NF-κB signaling pathway [35].

Atherosclerosis, a kind of CVD, mainly results from endothelial injury that causes cholesterol-containing LDL particles depositing in the arterial wall, and

then the inflammatory response could be triggered [36]. Both adaptive and innate immunity are activated to contribute to the initiation and progression of atherosclerosis. For example, monocytes could differentiate into macrophages in the intima of the arterial wall and then transform into foam cells in the lipid necrotic core of the atheroma [37, 38]. Inflammation could be activated by crystals of cholesterol and other DAMPs located in the atherosclerotic lesion. The activation of inflammasomes promotes the release of IL-1 β , IL-18, and other pro-inflammatory cytokines that are chemotactic for other immune cells for driving atherosclerosis [39, 40]. Late stage of atherosclerosis is featured by enormous number of cells undergoing senescence and apoptosis. In line with the results, necrotic core could be formed, finally causing plaque fragility and rupture, thrombus formation, and acute vascular occlusion [41].

It has been reported that IL-6 and C-reactive protein (CRP), rather than other inflammatory cytokines, are considered as the biomarkers of systematic inflammation and atherosclerosis [42]. High-sensitivity CRP (hs-CRP) levels could be decreased by statins, indicating that inhibition of inflammation could be applied as a therapeutic strategy to treat CVD [42, 43]. Collectively, these studies illuminate the correlation among stress, inflammation, and CVD, and anti-inflammatory drugs may have a synergistic effect with conventional antihypertensive drugs on the prevention and treatment of stress-related CVD.

12.3.2 Stress, Inflammation, and Metabolic Diseases

Stress is thought to be involved in the pathogenesis of several metabolic diseases, such as obesity, insulin resistance, and type 2 diabetes [44–46]. Metabolic ER stress disorders can disrupt the balance of glucose and energy metabolism. During overnutrition, obesity factors (such as fatty acids and LPS) activate macrophages, thereby enhancing M1 polarization in the intracellular environment that inhibits M2 polarization. Such M1-M2 imbalances in turn severely limit the energy utilization capabilities of brown and beige fats and enhance insulin resistance, which ultimately promote the progression of metabolic diseases [45].

It is thought that metabolic diseases are mainly driven by inflammation [47]. The emergence of chronic inflammation in obese individuals can lead to impaired insulin action, which in turn leads to the development of metabolic abnormalities [48, 49]. During obesity, the total number of macrophages dramatically increases. This is largely due to the recruitment of M1 polarized macrophages, which exhibit a more inflammatory phenotype and secrete TNF- α cytokines. In addition, the anti-inflammatory cytokines IL-4 and IL-13 produced by eosinophils can promote the differentiation of macrophages into alternately activated M2 polarized cells. Congenital type 2 lymphoid cells (ILC2s) play a key role in maintaining metabolic homeostasis by producing IL-5 and IL-13 in eosinophils and adipose tissue. An increase in the number of macrophages and an increase in the ratio of M1 to M2

macrophages are signs of adipose tissue inflammation caused by obesity and are related to the development of insulin resistance and metabolic diseases [50].

12.3.3 Stress, Inflammation, and Neurodegenerative Diseases

Neurological diseases include Alzheimer's disease (AD), vascular dementia (VAD), Parkinson's disease (PD), and multiple sclerosis (MS). Increasing evidence indicates that the pathogenesis of these diseases is not only limited to the neuronal compartment but also included the interactions with immune mechanisms in the brain, which is called neuroinflammation. Neuroinflammation is mainly driven by microglia, macrophages, and astrocytes in the brain. These cells play a central role in many aspects of brain metabolism and physiology under non-pathological conditions, maintaining the blood-brain barrier (BBB) integrity [51]. One of the common characteristics of these multiple diseases is that their neuropathological features differ from microglia and astrocytes and trigger an innate immune response characterized by the release of inflammatory mediators, leading to the progression and severity of neurodegenerative disease degree [52].

In the central nervous system, chronic neurodegenerative diseases are featured with neuroinflammation mitochondrial dysfunction. ROS and nitrogen species (RNS) are overexpressed and result in intensively oxidative stress under the two conditions and further result in neuronal damage and subsequently induce inflammation, causing to a feed-forward loop of neurodegeneration.

Repeated immune attacks result in plaque formation characterized by the formation of glial scars, leading to mitochondrial damage and dysfunction [53]. In mitochondrial injury and dysfunction, excessive production and release of ROS produced by oxidative stress have been proposed as a general pathological mechanism for all major chronic neurodegenerative diseases [54, 55]. NF- κ B activation can induce NOX2 and iNOS to effectively produce ROS/RNS under pro-inflammatory conditions [56]. In addition, the activation of NF- κ B promotes COX-2 and cPLA2 expression correlated to prostaglandin production, thereby further promoting oxidative stress. It has been proved that there is a intensive correlation between the production of ROS/RNS and the induction of pro-inflammatory cytokines, which exacerbates neurodegeneration [56, 57].

One of the important cytokines, TNF, can activate and recruit immune cells through TNF receptor 1 (TNFR1), indicating that it plays a key role in inflammation pathogenesis. Furthermore, TNFR1 could increase ROS production and RNS-producing enzymes via induction of oxidative stress. Hence then, TNF-induced inflammation and oxidative stress cooperatively facilitate neurodegeneration. Additionally, TNF also interacts with TNF receptor 2 (TNFR) 2 to generate a neuroprotective effect and promote tissue regeneration, suggesting that TNF plays a dual role in neurodegenerative diseases [58].

Once TLR-mediated signaling is activated, astrocytes and microglia release cytokines, chemokines, and ROS to promote inflammation and exacerbate neuron damage [59]. The continued existence of neuronal damage will lead to the sustained

activation of microglia and astrocytes, which in turn produces a neuroinflammatory environment to promote neurodegeneration [54, 60]. Collectively, there is a close correlation among stress, inflammation, and neurodegenerative diseases, and elucidation of the correlation is helpful for developing the intervention to treat neurodegenerative diseases.

12.3.4 Stress, Inflammation, and Cancer

Accumulating evidence suggests that psychological stress mediate influence on cancer by producing the key stress-related mediators and their corresponding receptors, which involve in multi-fold pathways [61]. These stress-related mediators act as immunosuppressors or mitogens in the micro-environment of tumor [62]. The psychological stress mediates the effects on cancer cells via the stress mediators, receptors and cytokines to activate the pro-migratory and pro-proliferative signaling pathway. Eventually, the molecular clock of cancer cells will be reset [61].

Classic stress signal, β -adrenergic signaling activation is considered as the main cause of progression and invasion in pancreatic cancer, acute lymphoblastic leukemia, and breast cancer [63]. Furthermore, selective α 2-adrenergic blockade mimics the accelerating effect of chronic stress on breast cancer progression [64].

More recently, stress-mediated immune modulation of cytokines including IL-6, TNF- α , and IL-1, has been suggested as indicators of cancer progression, metastasis, and recurrence. Epidemiological data indicate that over 25% of all cancers are related to chronic infections and other types of unresolved inflammation [65, 66]. Certain cancers develop in tissues that are severely damaged by chronic inflammation, such as lung cancer caused by asbestos or cigarette smoke, gastric (stomach) cancer caused by *H. pylori* infection, liver cancer caused by hepatitis B or hepatitis C infection, cervical cancer caused by human papillomavirus infection, and ovarian cancer caused by pelvic inflammatory disease [67]. Accumulating study has addressed the role of the cytokines, chemokines, transcription factors, and eicosanoid to explain the correlation between inflammation and carcinogenesis [68].

Additionally, these cytokines secreted by tumor cells help to drive and sustain pro-tumorigenic inflammatory loops in colon cancer and lung cancer [69]. IL-6 trans-signaling-dependent activation of STAT3 can drive cancer progression through the transcription of target genes, including JunB, cFos, C/EBP β , and C/EBP δ [70]. Although the connection among stress, inflammation, and cancer onset and progression has been investigated, the underlying mechanism needs to be intensively determined, which will be helpful to understanding every step of carcinogenesis and in turn propose effective therapy for cancer.

12.3.5 Stress, Inflammation, and Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that not only impairs psychological function but also mediates psychological stress on the patients. Stress is now

recognized as an important risk in the pathogenesis of RA by influencing hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system and the immune system [71]. It has been reported that the affected individuals are characterized by an increased level of anxiety and depression, and stress management interventions produce important clinical benefits for the persons with RA [72, 73].

As mentioned, the stress response results in the release of neurotransmitters (norepinephrine), hormones (cortisol), and immune cells which serve to send an efferent message from the brain to the periphery [74]. It has been reported that stress vulnerability, immune and HPA axis activity aggravate the symptoms of RA [75].

Signalings in cellular stress responses, including the heat shock response, ER stress response, NF- κ B, and Nrf2-ARE-HO-1 axis, involve the activation of adaptive and innate immune responses, leading to arthritis [76–78]. Accordingly, ER stress-induced inflammation, the correlated pathways and their constituent elements are attractive targets for RA drug development [79].

Oxidative stress is significantly involved in cartilage degradation in experimental arthritis. Activation of the Nrf2-ARE-HO-1 axis contributes to reducing the oxidative stress by decreasing ROS production. It has been reported that Nrf2 is activated in the joints of arthritic mice and of patients with RA. Nrf2-knockout mice had more oxidative damage and more severe cartilage injuries compared to their wild-type littermates. Remarkably, a number of spontaneously fractured bones have been found in Nrf2-knockout mice with antibody-induced arthritis (AIA) [80]. In coinciding with the study, compounds targeting Nrf2 signaling significantly ameliorated symptoms of collagen-induced arthritis (CIA) in mice [81, 82]. Wu et al. demonstrated for the first time that S-propargyl-cysteine (SPRC, also known as ZYZ-802), an endogenous H₂S modulator, exerted anti-inflammatory properties in RA by upregulating the Nrf2-antioxidant response element (ARE) signaling pathway (Fig. 12.1) [83]. Recently, another study from the same research group reported that suppressing JMJD3 expression by the transcription factor Sp-1 was likely responsible for the ability of Cystathionine- γ -lyase (CSE) to negatively modulate the inflammatory response (Fig. 12.2) and reduce the progression of RA [84].

These studies illuminate the importance of stress in arthritis and pave a new way to treat arthritis.

12.4 Conclusion

In conclusion, stress-induced inflammation has drawn much attention not only in research but also in clinical practice. New proteins and signaling pathways might be discovered, and the efficient blockage of the upregulation of these unwanted proteins could open a new avenue for the treatment of inflammatory diseases.

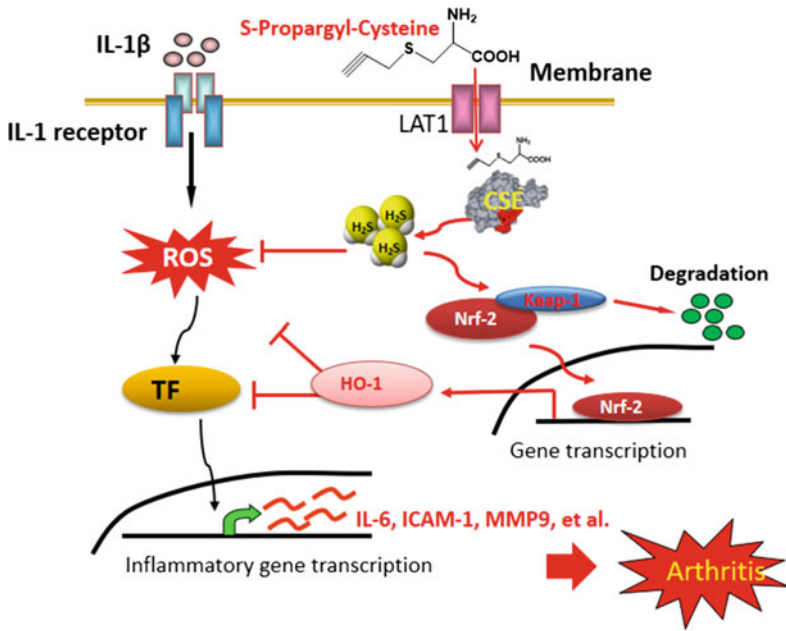


Fig. 12.1 S-propargyl-cysteine attenuates inflammatory response in rheumatoid arthritis by modulating the Nrf2-ARE signaling pathway

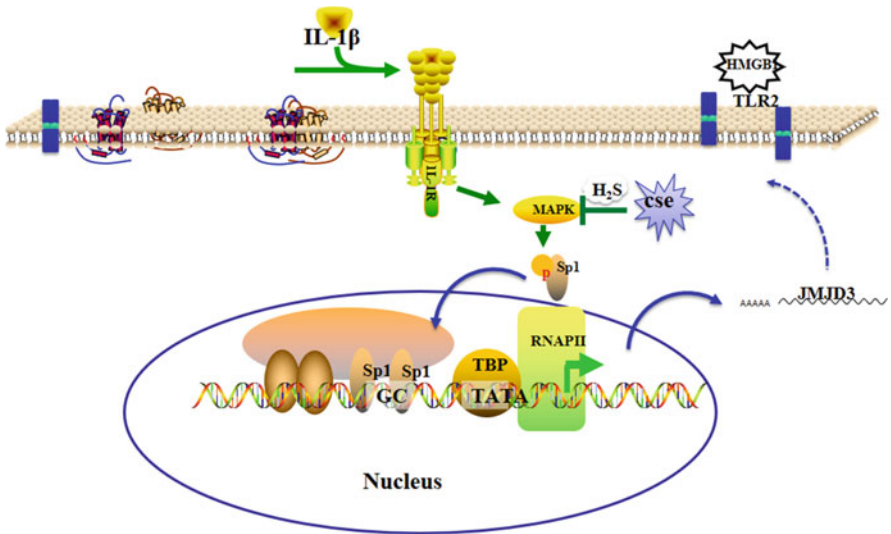


Fig. 12.2 Cystathionine- γ -lyase ameliorates the histone demethylase JMJD3-mediated autoimmune response in rheumatoid arthritis

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