Review Article

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Experimental Neurobiology

Control of Inflammatory Responses: a New Paradigm for the Treatment of Chronic Neuronal Diseases

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The term 'inflammation' was first introduced by Celsus almost 2000 years ago. Biological and medical researchers have shown increasing interest in inflammation over the past few decades, in part due to the emerging burden of chronic and degenerative diseases resulting from the increased longevity that has arisen thanks to modern medicine. Inflammation is believed to play critical roles in the pathogenesis of degenerative brain diseases, including Alzheimer's disease and Parkinson's disease. Accordingly, researchers have sought to combat such diseases by controlling inflammatory responses. In this review, we describe the endogenous inflammatory stimulators and signaling pathways in the brain. In particular, our group has focused on the JAK-STAT pathway, identifying anti-inflammatory targets and testing the effects of various anti-inflammatory drugs. This work has shown that the JAK-STAT pathway and its downstream are negatively regulated by phosphatases (SHP2 and MKP-1), inhibitory proteins (SOCS1 and SOCS3) and a nuclear receptor (LXR). These negative regulators are controlled at various levels (e.g. transcriptional, post-transcriptional and post-translational). Future study of these proteins could facilitate the manipulation of the inflammatory response, which plays ubiquitous, diverse and ambivalent roles under physiological and pathological conditions.

Key words: inflammation, JAK-STAT, nuclear receptor, liver X receptor, post-transcriptional regulation, MKP-1

INTRODUCTION

Inflammatory responses are defense mechanisms that protect the human body from microbial infection or external damage.

The Roman physician, Celsus, is credited with providing the first record of the fundamental symptoms of inflammation, which are still recognized in modern textbooks. With recent advances in immunology, inflammatory responses are receiving new attention because of their involvement in the link between innate immunity and disease. Stepping forward from classical concepts of the immune response (i.e. the concept of self or non-self), scientists have accepted that immune responses are induced by danger or damage. Although autoimmune diseases cannot be easily explained by the concept of self or non-self, they can be explained by the danger theory of inflammatory response. This theory could also be applied to understanding the inflammatory responses

in the brain, where external intrusions are rare but immune/inflammatory responses occur, sometimes to a pathogenic degree (i.e. in degenerative brain disease). Neuroglial cells, including astrocytes and microglia, are the primary tissue-resident cells responsible for immune/inflammatory responses in the brain. If such responses are improperly regulated or terminated, nerve cell dysfunction can occur as a pathophysiology of brain disease. In this review, we outline a possible approach for targeting inflammatory responses in an effort to treat chronic inflammatory brain diseases.

ENDOGENOUS INFLAMMATORY STIMULATORS IN THE BRAIN

Researchers studying inflammatory/immune processes in the brain must often refer to work done on peripheral inflammatory responses. Because the endogenous stimulators of inflammatory/immune responses in the brain have not yet been clarified, researchers working with glial cells have looked to studies done in peripheral macrophages. To activate neuroglial cells, these researchers have used lipopolysaccharide (LPS) and zymosan (components of the bacterial cell wall and fungal cell membrane, respectively) or inflammatory cytokines, including tumor necrosis factor (TNF)-α and interferon (IFN)-γ (well-known activators of peripheral macrophages) [1-3]. However, LPS and zymosan rarely occur in the brain, making this model unsuitable for the study of brain pathophysiology. Therefore, researchers have sought to identify endogenous substances that may be used as a model for brain disorders (Fig. 1). Two membrane components that are release from damaged nerve cells, gangliosides [4] and chromogranin [5], have been reported to cause inflammation and are currently being investigated as endogenous activating materials. Many reports have shown the presence of long-term blood-brain barrier leakage in degenerative brain disease [6,7]. Based on these reports, researchers have hypothesized that components in the blood could intrude into the brain parenchyma and cause inflammation in the brain. Efforts to identify inducers of neuroglial activation among blood components found that thrombin [8], prothrombin [9], plasminogen [10], and tissue plasminogen activator [11] can all activate neuroglial cells. Aggregations of proteins (e.g. prions, amyloid-β and α-synuclein), which are thought to be a common feature in Alzheimer's and Parkinson's diseases (two typical degenerative brain diseases), have been identified as the main neuroglial cell-activating substances [12,13]. In addition, intermittent hypoxia occurred in the brain is accompanied by oxidative stress and low-grade chronic inflammation, resulting in neurological deficits and disorders such as Alzheimer's and Parkinson's diseases [14,15]. These recent studies have shown that inducers trigger inflammatory responses that can act as a major progression factor for (if not a direct cause of) degenerative diseases. Thus, it seems reasonable to speculate
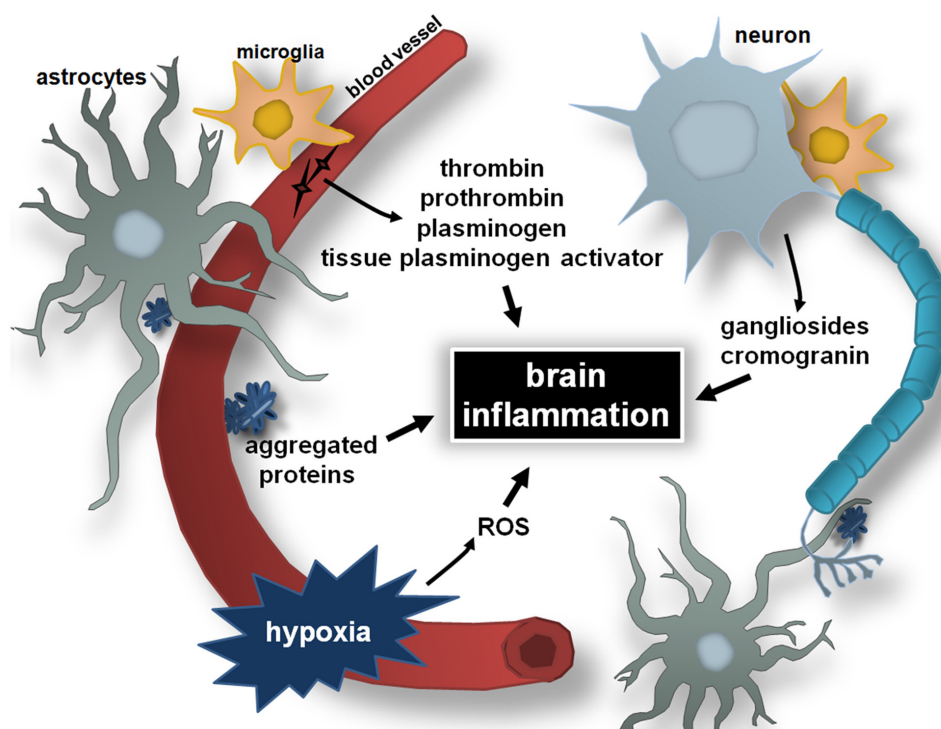

Fig. 1. Endogenous inflammatory mediators in the brain. Brain inflammation can be caused by: aggregated proteins, such as prions, amyloid-β and α-synuclein; cell membrane components, including gangliosides and chromogranin (which are released from damaged nerve cells); and blood components, such as thrombin, prothrombin, plasminogen and tissue plasminogen activator (which can leak through a rupture of the blood brain barrier). In addition, oxidative stress due to intermittent hypoxia is accompanied by chronic inflammation.

that the regulation of inflammatory responses could prevent or slow disease progression.

INFLAMMATORY SIGNALING IN THE BRAIN

Given that the endogenous stimulators of brain glial cells appear to trigger inflammation, we might next question which signaling pathways are activated by endogenous inflammatory stimulators in the brain. Studies on the inflammatory signals in the brain have also drawn from work done in peripheral inflammatory cells. For example, nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), two typical inflammatory signals, are reportedly activated in neuroglial cells by substances such as LPS [2,13]. Moreover, endogenous stimulators, such as gangliosides [4] and thrombin [8], appear to cause inflammatory responses via NF-κB and MAPKs. Researchers are currently seeking to identify new inflammatory signaling molecules and pathways in the brain, in efforts to construct an activator- and cell type-specific roadmap. Because the inflammatory signals are believed to have both shared and unique pathways according to the stimulus and/or tissue, researchers expect that a synergistic effect will be obtained by controlling the inflammatory signals or modulating their interactions.

JAK-STAT as an anti-inflammatory target

We identified Janus kinase-signal transducer and activators of transcription (JAK-STAT) as a new inflammatory signal in the brain and showed that its inflammatory signals can be activated by LPS, IFN-γ, gangliosides and thrombin [4,16]. The receptor activated by these ligands or cytokines phosphorylates JAKs, leading to the phosphorylation (i.e. activation) of STAT molecules. Activated STATs form dimers and translocate to the nucleus, where they act as transcription factors; they induce the expression of inflammatory genes that have STAT-binding sites in their promoter regions, thereby activating subsequent inflammatory responses (Fig. 2) [17]. Based on the role of JAK-STAT signaling in brain inflammation, we screened anti-inflammatory substances to see if they could inhibit the JAK-STAT pathways, and if so, whether we could determine the underlying mechanism and identify a novel anti-inflammatory target. We found that curcumin (which is a main ingredient of curries and has anti-inflammatory and anticancer effects), rosiglitazone (an agonist for peroxisome proliferator-activated receptor γ; PPARγ) and 15-deoxy-delta12,14-prostaglanding J_2 (15d-PGJ_2, an anti-inflammatory prostaglandin) limit inflammation by inhibiting STAT signaling [18-20]. Because the JAK-STAT pathways mediate the actions of numerous growth factors and cytokines *in vivo*, their negative feedback pathways are well developed and tightly regulated. The endogenous negative feedback molecules include phosphatases and inhibitory proteins, such as the suppressor of cytokine signaling (SOCS) proteins. Curcumin activates SH2-containing phosphatase 2 (SHP2) [18], while rosiglitazone and 15d-PGJ_2
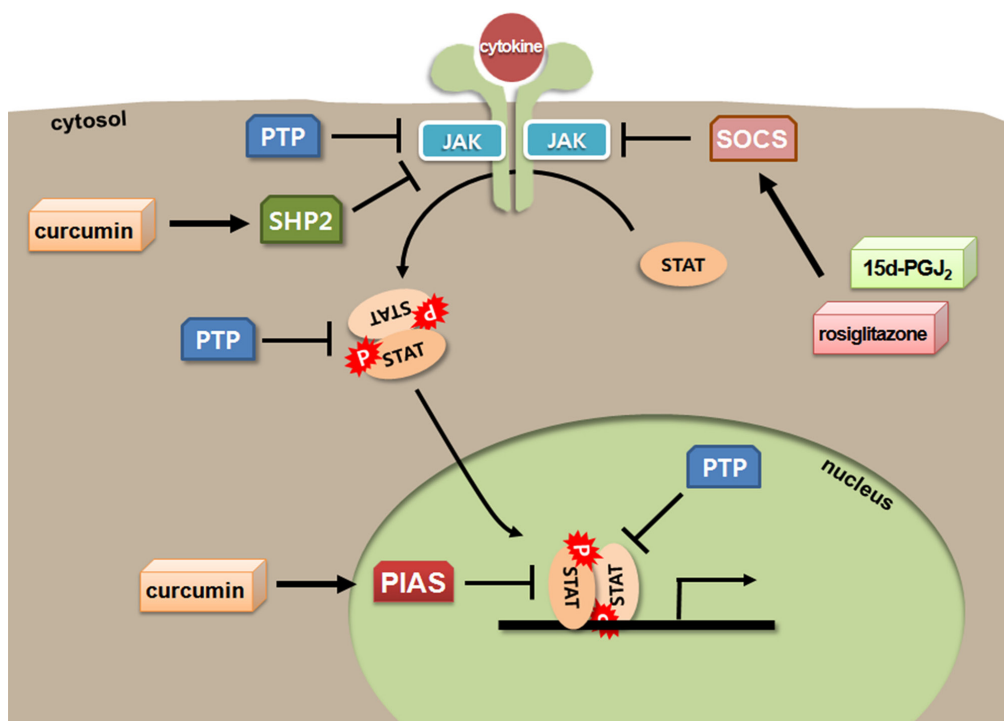

Fig. 2. JAK-STAT signaling as an anti-inflammatory target. JAK-STAT signaling mediates the brain inflammation induced by LPS, IFN-γ, ganglioside and thrombin. Curcumin activates SH2-containing phosphatase 2 (SHP2), while rosiglitazone and 15d-PGJ_2 increase the expressions of SOCS1 and SOCS3. SHP2 and the SOCS proteins are typical negative feedback molecules of the JAK-STAT pathway.

increase the expression levels of SOCS1 and SOCS3 [19]. SHP2 and SOCS proteins are typical negative feedback molecules of the JAK-STAT pathway. Because the individual SOCS family proteins regulate different molecules of the JAK-STAT signaling pathways, we could possibly use them to specifically or synergistically control different JAK-STAT pathways. Indeed, the anti-inflammatory properties of many clinically available drugs, including aspirin, are mediated via SOCS proteins [20]. Thus, it is particularly interesting to consider the development of additional SOCS-targeting drugs.

Nuclear receptors as anti-inflammatory targets

Steroids are representative anti-inflammatory drugs that act specifically through glucocorticoid receptors (GRs). Despite the development of many new drugs, steroids are still broadly used to treat intractable diseases and pathological states, including inflammation, autoimmune disorders, and cancers. Although steroids have demonstrated remarkable clinical efficacy, the exact mechanisms underlying such effects have only recently been unveiled. GR is a prototype ligand-activated transcription factor that belongs to the nuclear receptor (NR) family and regulates gene expression by either transcriptional activation [21] or transcriptional repression (transrepression) [22]. In polysaccharide and lipid metabolism, steroid-activated GR forms a dimer, migrates into the nucleus and binds glucocorticoid response elements (GREs) to induce target gene transcription [23]. However, GREs are absent from the promoter regions of most inflammatory genes [24], meaning that glucocorticoid-mediated anti-inflammation acts indirectly. Indeed, the anti-inflammatory mechanism of steroids was found to act via transrepression, with ligand-activated GR indirectly suppressing the activity of inflammation-related transcription factors by inhibiting the binding of co-activators that promote transcription or by recruiting co-repressors to inhibit transcription [25].

NRs other than GR also exert anti-inflammatory effects via transrepression. PPARα and PPARγ, which are two typical NRs involved in lipid metabolism and adipocyte differentiation, are known to have anti-inflammatory actions [26,27]. An anti-inflammatory effect has been reported for liver X receptor (LXR). Our group and other researchers showed that these NRs could exert anti-inflammatory effects in the central nervous system and peripheral inflammatory cells [1,28]. Moreover, post-translational modifications of NRs contribute to this process, leading to stimulus- and/or tissue-specific regulation of the inflammatory response. We reported that oxysterols suppress IFN-γ-induced inflammatory responses via LXR in astrocytes (Fig. 3) [1]. Because most of the inflammatory mediators and cytokines that are activated by IFN-γ do not have LXR binding

sites within their promoters, the inhibitory action of LXR results (as in the case of GR) from indirect action. Although we showed that SUMOylation of LXR plays a decisive role in tethering STAT1 to LXR [1], the details of the underlying mechanism are still unknown. One possibility is mediation by (i.e. interaction with) another NR. We are presently investigating whether the orphan nuclear receptor, short heterodimer partner (SHP), is involved in the LXR-dependent inhibition of STAT1 transcriptional activity. SHP lacks the conserved DNA binding domain common to other NRs [29], suggesting that it may function by binding to other NRs. Our preliminary results show that SHP appears to mediate LXR-dependent STAT1 inhibition (unpublished data).

Post-transcriptional regulation as an anti-inflammatory target

The anti-inflammatory chemicals and drugs described above inhibit inflammatory signaling pathways or suppress the expression of inflammation mediator-encoding genes via transrepression. When tissues are damaged or infected by microbes, however, inflammatory mediators and cytokines should be released quickly and at high levels, requiring more efficient regulatory routes, such as through post-transcriptional alterations in their RNA levels [30]. Many transcripts encoding pro-inflammatory cytokines and chemokines are present in an unstable state, undergoing rapid degradation due to the presence of AU-rich elements (AREs) in their 3'-untranslated regions (3'-UTRs). The typical inflammatory genes that undergo regulation at the post-transcriptional step include cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1) and IFN-γ. Various RNA-binding proteins and microRNAs play important roles in the post-transcriptional regulation of mRNA maturation, degradation, and translation. Thus, these regulatory elements to control RNA quality and quantity may also be viable targets for anti-inflammatory drugs. As researchers continue to study RNA metabolism and uncover the detailed mechanisms underlying the creation and destruction of RNA, other new potential anti-inflammatory drug targets may be identified. Indeed, our group has shown that 5,8,11,14-eicosatetraynoic acid (ETYA) [27], 15d-PGJ$_2$ [31,32] and 22(R)-hydroxycholesterol (22R-HC) (unpublished data) suppress inflammation by altering the expression of MAKP phosphatase-1 (MKP-1), which dephosphorylates and inactivates Jun N-terminal kinase (JNK) (Fig. 4). These drugs increase the stability of the MKP-1 transcript in an HuR-dependent manner, thereby increasing the protein expression of MKP-1. Interestingly, the mechanism through which MKP-1 expression is regulated differs by drug: in contrast to ETYA and 15d-PGJ$_2$, dexamethasone (a synthetic glucocorticoid) increases MKP-1 expression by blocking
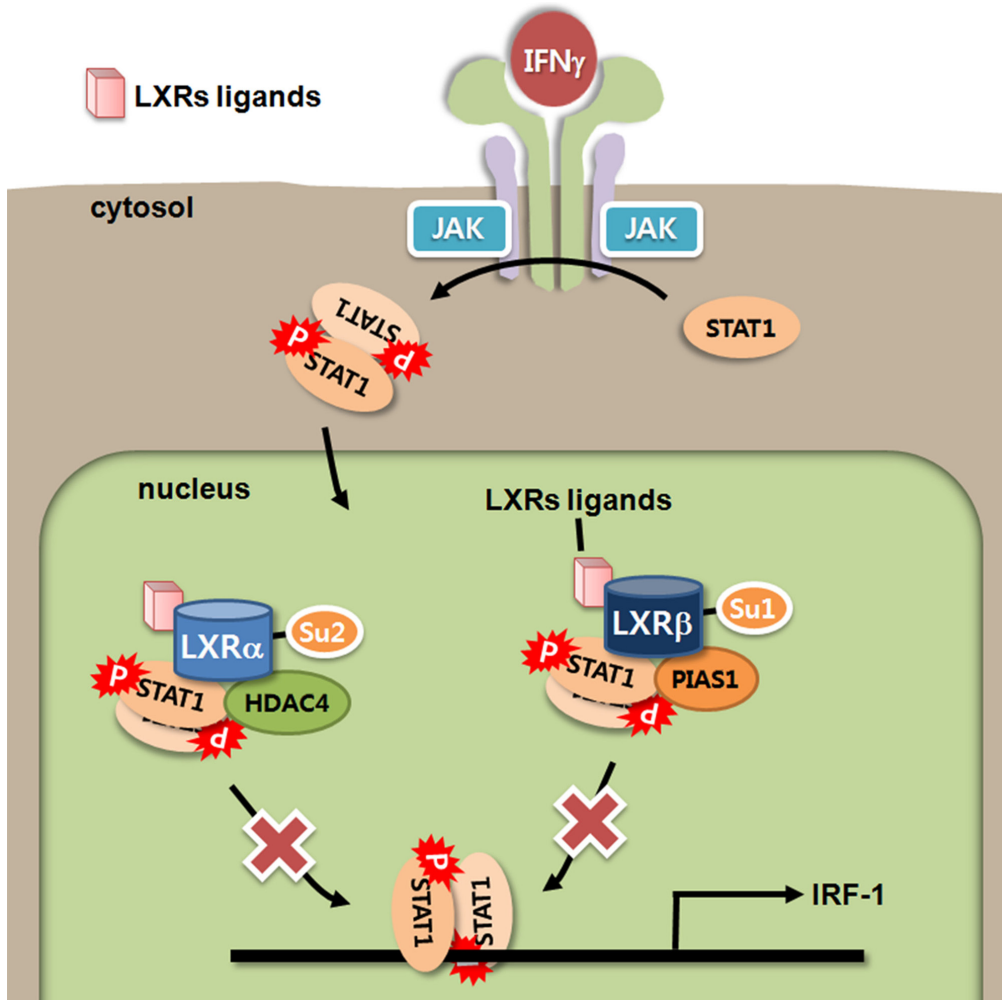
Fig. 3. Schematic of the anti-inflammatory mechanisms of LXR ligands in IFN-γ-stimulated astrocytes (18). IFN-γ triggers an early response in which STAT1 is phosphorylated and translocated to the nucleus, thereby inducing inflammatory gene expression. Synthetic and oxysterol derivatives of LXR ligands trigger the formation of PIAS1 (or HDAC4)-pSTAT1-LXR β (or LXR α) trimers, a process mediated by the differential conjugation of SUMO (Su) to individual LXRs. This blocks the binding of STAT1 to the promoters of its target genes.

its proteasomal protein degradation [33].

TISSUE- AND INDUCER-SPECIFIC CONTROL OF INFLAMMATION VIA NRS

Inflammation takes place in almost every tissue, and is designed to protect the body from microbial infection or external damage. To make use of it for therapeutic purposes while minimizing unwanted side effects, we need to uncover the exact control mechanisms. For example, clinically available COX-2 inhibitors utilize the difference between COX isotypes to reduce the side effects on the gastrointestinal system, selectively inhibiting COX-2 while having less effect on COX-1 [34]. Most NRs are important transcription factors involved in metabolism, so any strategy to target them with anti-inflammatory drugs must preserve their effects on metabolism. For example, estrogen receptor inhibitors, which are used to treat breast cancer, were developed based on tissue-specific differences in estrogen receptor complex

formation [35]. These inhibitors selectively block the estrogen receptor in the mammary gland while having no effect on bone metabolism and minimizing adverse effects in tissues other than the mammary gland. The development of anti-inflammatory drugs targeting other NRs should take advantage of similar selectivity when possible. For example, the distribution of LXR isotypes differs between tissues: LXRβ is ubiquitously expressed at low levels in almost all tissues, while LXRα is abundantly expressed in tissues involved in lipid metabolism and transport (e.g. liver, intestine, lungs and adrenal glands) [36,37]. Both LXR isoforms are expressed at significant levels in various regions of brain, with the level of LXRβ about 2- to 5-fold higher than that of LXRα [38]. Thus, differences in tissue distribution could be used for tissue-specific control in the therapeutic context. Similarly, tissue- and stimulus-specific differences in the compositions of NR complexes, which can determine the differential expression of target genes [39], could confer therapeutically relevant control. Finally, selective control could potentially be achieved through
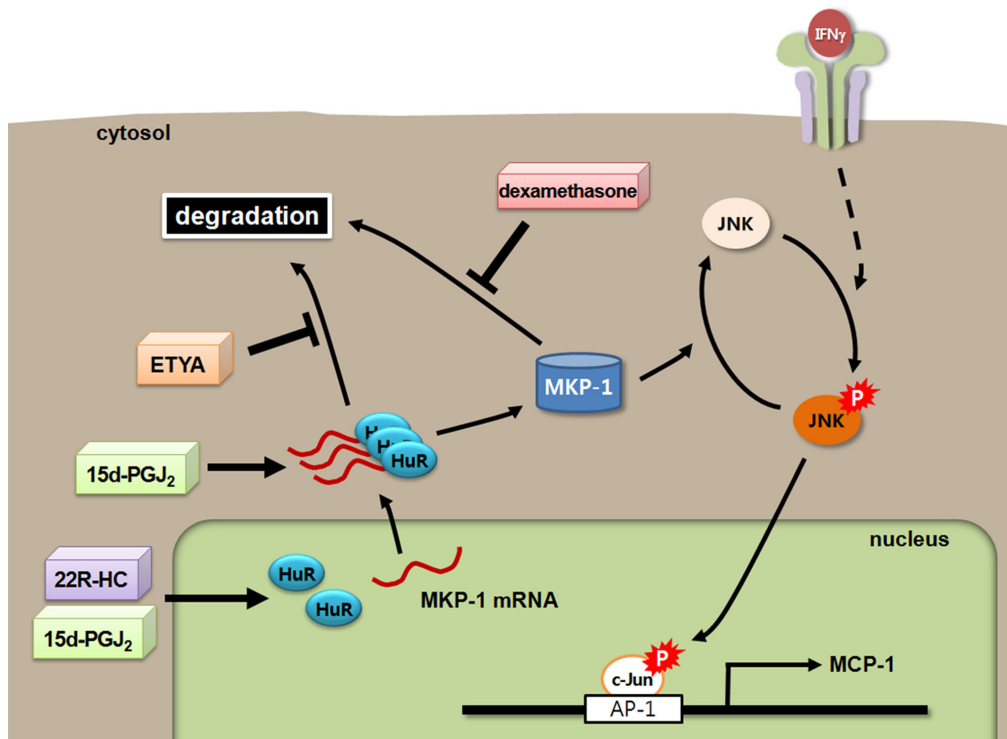
Fig. 4. MKP-1 as an anti-inflammatory target. The expression of MCP-1, a crucial molecule in initiating inflammatory responses, is regulated by JNK. MKP-1 dephosphorylates and inactivates JNK, suppressing MCP-1 expression. 15d-PGJ2, ETYA, and 22(R)-hydroxycholesterol (22R-HC) induce MKP-1 expression via HuR-dependent post-transcriptional regulation.

alterations in the tissue-, stimulus- and target-gene-specific post-translational regulation (e.g. SUMOylation and glycosylation [1,40]) of various signaling pathway components.

CONCLUSION

Despite years of research, inflammatory responses and the mechanisms underlying the actions of anti-inflammatory drugs remain to be clarified. Current studies in the field of immunology are expected to provide new insights into inflammation responses, inflammation-regulating drugs, and the relevant control mechanisms. Some antibodies and drugs used in clinical practice are capable of directly targeting specific signaling molecules/receptors. In the case of anti-inflammatory drugs, however, most such specific targeting therapeutics have been used only casually or experimentally. Detailed information is now being obtained regarding the pharmacological actions of typical non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and steroids. If we hope to effectively regulate inflammation for the treatment of diseases, the mechanism(s) responsible for controlling the inflammatory response need to be firmly established. We should also seek to better understand the cause-and-effect relationships between inflammatory responses and the pathogenesis/progression of related human diseases. Here, we reviewed the tissue- and stimulus-specific mechanisms believed to regulate

inflammation, and discussed the need for new insights into their cause-and-effect relationships in the context of disease. Given that inflammatory/immune responses are physiological phenomena that can provide protection or cause damage, their therapeutic modulation must be precisely controlled in quantitative, qualitative and temporal terms. Improper control could compound the disease processes or cause a new disease. Thus, additional research is warranted to improve our understanding of the inflammatory response.

ACKNOWLEDGEMENTS

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