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Targeting HMGB1 for Inflammatory Diseases: Therapeutic Strategies and Translational Challenges

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Abstract. Inflammation imbalance exists at the core pathological stage of many difficult-to-treat diseases such as sepsis and autoimmune disorders. Traditional anti-inflammatory treatments mainly target early pro-inflammatory factors, which have limitations such as a narrow therapeutic window and low disease specificity. High mobility group box protein B1 (HMGB1), as a late damage-related molecular pattern, is widely regarded as a promising therapeutic target in anti-inflammatory drug research. However, the characteristics and transformation bottlenecks of various targeting strategies for HMGB1 inhibitors have not been systematically reviewed. This article synthesizes important recent literature and clinical trial evidence to summarize the basic information of HMGB1 and review various HMGB1-targeting inhibitors, analyzing the challenges in their development. However, most current evidence comes from animal models, and the functional differences of HMGB1 in different diseases and the clinical administration norms have not been clarified. In the future, focused efforts can be made on the development of precise and selective formulations and the exploration of biomarkers and combination therapies. Targeting HMGB1 treatment strategies provide new treatment opportunities for many difficult-to-treat diseases, but their wide clinical application still requires more clinical trials for verification.

Keywords: HMGB1, Inhibitor, Targeted therapy, Inflammation

1. Introduction

High-mobility group box-B1 (HMGB1) is a non-histone chromosomal-binding protein that exists within eukaryotic cells. It participates in various biological processes such as gene transcription, DNA repair, recombination of germ cell fragments, differentiation, and development. It is also an important inflammatory cytokine. When cells are damaged, stressed, or stimulated by inflammation, HMGB1 can be passively released from necrotic cells or actively released by activated macrophages into the extracellular space. As a typical damage-associated molecular pattern (DAMP), it promotes inflammatory responses and plays a crucial role in the biological behaviors of tumors, sepsis, arthritis, burns and shock, atherosclerosis, diabetic vascular lesions, and multiple organ dysfunction syndrome. Currently, research on HMGB1 has extended to various diseases such as tumors, sepsis, arthritis, burns and shock, atherosclerosis, diabetic vascular lesions, and multiple organ dysfunction syndrome [1].

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The conventional treatment regimens for inflammatory and immune-related diseases in the early clinical stage mostly relied on broad-spectrum anti-inflammatory and immunosuppressive measures. However, they had limitations such as weak targeting, significant side effects during long-term use, easy triggering of systemic immunosuppression, difficulty in intervening in advanced inflammatory mediators, and poor efficacy in treating chronic inflammation. In recent years, with the improvement of the molecular targeted therapy system, precise intervention of key inflammatory regulatory factors has become a key research direction for drugs. A large number of basic and clinical studies have shown that HMGB1, as a key upstream regulatory factor in the inflammatory cascade and a late-stage inflammatory factor, is a potential therapeutic target with broad research prospects.

Among the drugs targeting the inhibition of HMGB1, small molecule inhibitors, nucleic acid aptamers, and monoclonal antibody drugs have entered the clinical trial stage, while other technologies such as microRNA targeted therapy and gene silencing technology are still at the basic research stage. Currently, the main focus is on the role of HMGB1 in specific diseases, but the precise molecular mechanism of this effect is still unclear [2]. In different disease contexts, the biological functions of HMGB1 vary significantly, and there is currently no systematic study on this phenomenon, which increases the complexity of targeted therapy. During the treatment process, targeted drugs generally have low selectivity, poor therapeutic effects, and limited short-term efficacy. Therefore, there are currently no mature HMGB1-targeted drugs widely used in clinical practice.

Based on this, this article systematically reviews various drugs and intervention methods targeting HMGB1 in recent years, summarizes the mechanism of action, application scenarios, advantages and disadvantages of different targeted drugs, and concludes the potential application of HMGB1-targeted therapy in various diseases. The aim is to provide theoretical references and research ideas for the development of new HMGB1-targeted drugs, clinical applications, and subsequent mechanism studies.

2. The structure and biological effects of HMGB1

2.1. The structural characteristics of HMGB1

The high-mobility group box 1 protein (HMG) was first isolated and identified by Goodwin et al. in 1973. It has a molecular weight of approximately 30KD and is named for its fast migration rate in polyacrylamide gel electrophoresis. The HMG protein can be classified into three types: HMGB1, HMGB2, and HMGB3. Among them, HMGB1 is widely present in eukaryotic cells and the amino acid sequences of HMGB1 in humans and various organisms have high homology. HMGB1 consists of three domains, including the A-box at the amino terminus, the C-tail at the carboxyl terminus, and the B-box between the two, where the A-box and B-box are each composed of three α helices and have strong positive charges as non-specific DNA-binding domains. Additionally, the C-tail at the carboxyl terminus can participate in regulating the affinity of HMGB1 for DNA through its own conformational changes. Each domain contains approximately 80 amino acid residues. The A-box has anti-inflammatory effects and is regarded as a therapeutic target, while the B-box domain contains the pro-inflammatory cytokine function of the molecule [3].

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2.2. HMGB1-related signaling pathway

2.2.1. Toll-like receptors (TLRs) pathway

It is the most classic inflammatory regulation pathway related to HMGB1, and it is involved in diseases such as sepsis, osteoarthritis, and atherosclerosis.

TLRs are proteins that play a crucial role in both innate immunity and adaptive immunity, typically serving as the body's first line of defense against pathogens. In this pathway, HMGB1 can exert its effects through TLR2 and TLR4, and each HMGB1 molecule and the HMGB1-DNA complex can activate the TLR pathway. After multiple Toll-like receptors interact with HMGB1, they activate myeloid differentiation protein 88 (MYD88), an adapter molecule involved in the signal transduction of most TLRs. After activating the MYD88-dependent pathway, NF-κB is activated, which then leads to the synthesis and release of pro-inflammatory factors, initiating the inflammatory response and cell apoptosis process [4].

2.2.2. CXCR4 pathway

The chemokine receptor 4 (CXCR4) is a specific receptor for the chemokine CXCL12, and their binding is highly specific. One HMGB1 can form a complex with two CXCL12 molecules, enhancing the activation ability of CXCL12 on CXCR4, thereby promoting the migration of white blood cells and inflammatory responses. At the same time, the CXCR4 signaling pathway has partial regulatory and synergistic effects with the TLRs signaling pathway. For example, in the choroidal endothelial cells, lipopolysaccharide (LPS, the ligand of TLR4) can significantly upregulate the expression of CXCR4 and CXCR7, and this process may be related to the activation of inflammatory signaling pathways such as NF-κB [5]. After TLR4 is activated, the inflammatory factors released (such as IL-1β, TNF-α) may upregulate CXCR4 through paracrine pathways, and this mechanism is also manifested in chronic inflammatory diseases such as osteoarthritis [6].

2.2.3. RAGE pathway

The receptor for advanced glycation end-products (RAGE) is a member of the immunoglobulin superfamily and is expressed on the surfaces of mononuclear phagocytes, vascular smooth muscle cells, and neuronal cells. The binding of HMGB1 to the RAGE receptor activates IκB kinase (IKK), leading to the phosphorylation and degradation of IκB, the release of NF-κB, and its nuclear translocation, resulting in the release of inflammatory factors, cell apoptosis, autophagy, and migration. Mitogen-activated protein kinase (MAPK) is a serine/threonine protein kinase. Currently, four types of MAPK proteins have been discovered in mammals. Among them, extracellular signal-regulated kinase (ERK) can be activated by various stimuli such as tyrosine kinases and G protein-coupled receptors, and participates in the proliferation, differentiation, and apoptosis of tumors. Studies have shown that HMGB1 can promote the expression of p-ERK in hepatocellular cholangiocarcinoma cells, and it can be significantly blocked by RAGE inhibitors. Therefore, the HMGB1/RAGE signaling pathway may promote the proliferation and invasion of hepatocellular cholangiocarcinoma cells through the MAPK/ERK signaling pathway [7].

2.2.4. TIM3 pathway

TIM3 is a surface marker molecule of helper T cell 1 (Th1). When it binds to its corresponding ligand galectin, it will negatively regulate the function of Th1 and induce its apoptosis. TIM3 is

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expressed on terminal Th1 cells and is also highly expressed in various innate immune cells such as NK cells, macrophages, and dendritic cells. HMGB1 binds to TIM3, which can inhibit macrophage activation, induce T cell apoptosis, and interact with the TLR2/4-induced NF-kB pathway to exert inhibitory effects. In the sepsis environment, it mainly participates in immunosuppression and promotes the apoptosis of immune cells [8].

2.2.5. Protein kinase C (PKC) pathway

PKC can directly phosphorylate HMGB1, and this process is a necessary condition for HMGB1 secretion. After stimulation by endotoxin, the activation of PKC leads to the phosphorylation of HMGB1, which subsequently promotes its translocation from the nucleus to the cytoplasm and secretion. After PKC is activated, it triggers the release of calcium from the calcium store through downstream calcium signaling pathways, such as the PLC-IP3 pathway, forming a positive feedback loop, resulting in the release of HMGB1 through non-classical secretion pathways [9]. Lee et al. discovered through kinase inhibitor screening that only the PKC-specific inhibitor can significantly inhibit the secretion of HMGB1, while inhibitors of other kinases (such as ERK or p38 MAPK) have no such effect [9].

2.2.6. CD24 pathway

CD24 is an anchored phosphatidylinositol glycoprotein expressed on the cell surfaces of various types of cells in humans and mice. It exerts protective effects by inhibiting DAMP-mediated inflammatory responses. CD24 is expressed on the cell surfaces of various types of cells, such as B cell precursors, epithelial cells, stem cells, renal tubules, and nerve cells. It can participate in the process of tumor occurrence and development by promoting the proliferation, invasion, and metastasis of tumor cells. HMGB1 binds to CD24, which can promote B cell proliferation and activation. The CD24 protein can be used as a marker to determine whether T cells, B cells, etc. are mature, and it participates in regulating the immune response of the body, thus being closely related to autoimmune diseases.

2.3. The biological effects of HMGB1

HMGB1 can be secreted by activated cells and macrophages, or passively released by necrotic or damaged cells. It plays a dual regulatory role in maintaining physiological homeostasis and in pathological inflammatory responses, and is a key damage-associated molecular pattern (DAMP) of the body [10]. Under physiological conditions, it is mainly located in the cell nucleus and acts as a DNA molecular chaperone, participating in the maintenance of nucleosome stability, and promoting the binding of transcription factors to DNA by bending the DNA. It plays a crucial role in DNA recombination, replication, repair and gene transcription, maintaining the normal physiological functions of the body.

When the body is infected, tissue is damaged or cells are stressed, innate immune cells such as macrophages and dendritic cells can actively release HMGB1 in response to pathogen stimulation and inflammatory activation. Necrotic and pyroptotic cells can release large amounts of intracellular HMGB1 passively. Free HMGB1 mainly activates downstream signaling pathways by binding to pattern recognition receptors such as TLR4 and RAGE on the cell membrane, initiating inflammatory cascades such as NF-κB, and inducing the synthesis and secretion of inflammatory mediators such as interleukins (IL)-1α, IL-1β, and macrophage inflammatory protein α/β by

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monocytes/macrophages, neutrophils, and dendritic cells. These mediators can further enhance the secretion effect of HMGB1, forming a positive feedback loop to continuously amplify local and systemic inflammatory responses.

In the heart toxicity induced by sonidegib, HMGB1 binds to autophagy genes (Beclin 1) to regulate autophagy-induced sonidegib heart toxicity, and HMGB1 activates the phosphorylation level of Bcl2, further promoting the binding of Bclin 1 to HMGB1, while glycyrrhizic acid can alleviate heart toxicity by inhibiting HMGB1 [11]. In glioma and gastric cancer, high expression of HMGB1 promotes cancer cell invasion and migration by regulating the cell cycle (such as G1/S phase transition) and matrix metalloproteinases (MMPs) [12].

3. The mechanism of action of drugs targeting HMGB1

3.1. Direct inhibitor of HMGB1

By directly combining and neutralizing extracellular HMGB1 and blocking its interaction with receptors. Examples include dociparstat sodium (DSTAT), N-(1-phenylethyl)-3-(2-furanyl)acrylamide, anti-HMGB1 monoclonal antibodies, SB-17170, salivary agglutinin receptor complex, thrombin-sensitive substances, etc.

DSTAT is a multi-targeted drug that can simultaneously inhibit various key proteins such as cell adhesion molecules CXCL12, P-selectin, and HMGB1. DSTAT can bind to HMGB1 with negatively charged sulfate groups and block the interaction between HMGB1 and receptors, thereby inhibiting downstream inflammatory signaling pathways. In acute lung injury models, DSTAT may reduce HMGB1 in bronchoalveolar lavage fluid by inhibiting its binding to RAGE, reducing immune cell infiltration in the lungs [13], but the specific molecular mechanism is still unclear. The inhibitory effect of DSTAT on CXCR4 and the neutralization effect of HMGB1 may synergistically block the amplification loop of the inflammatory pathway in acute myeloid leukemia (AML) [14]. SB-17170 is a prodrug of the active metabolite SB1703. It can regulate the immune response by specifically binding to HMGB1 and inhibiting the secretion of various cytokines by activated macrophages.

Direct neutralization of extracellular HMGB1 as the most direct inhibitory method is currently the main intervention approach for HMGB1, but it also has some limitations. Antibody drugs have problems such as short half-life and poor penetration through the blood-brain barrier, such as the need for intraventricular injection to ensure efficacy in epilepsy treatment. Small molecule inhibitors may require frequent administration due to rapid metabolism, and the drug dose safety threshold still needs to be verified through clinical trials.

3.2. Inhibitors that suppress the release of HMGB1

Glycyrrhizic acid (GLR) can reduce HMGB1 release by preventing HMGB1 from detaching from DNA. This inhibits the activation of immune receptors by HMGB-1 and subsequent inflammatory mechanisms, as well as the release of pro-inflammatory cytokines (such as TNFα), thereby reducing nitrosative stress and nitrotyrosine expression, and increasing the expression and activity of eNOS peptides to treat hyperhomocysteinemia (HHcy). In a mouse model of depression-like behavior, glycyrrhizic acid can significantly inhibit HMGB1 release, and its mechanism may be related to the inhibition of the HMGB1/NLRP3 inflammatory pathway [15]. Acetaldehyde dehydrogenase 2 (ALDH2) activators can inhibit HMGB1 release by reducing its acetylation, and have shown potential value in the treatment of sepsis. Inhibiting HMGB1 release is a promising therapeutic direction, but the biological function of HMGB1 has duality, such as pro-inflammatory and repair

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functions. Complete inhibition may interfere with the normal physiological functions of the body. Therefore, how to precisely inhibit HMGB1 in the affected area remains a problem that needs to be studied.

3.3. Epigenetic regulatory inhibitor

Some miRNAs can exert therapeutic effects by targeting HMGB1 or its signaling molecules. For instance, miR-34a can inhibit the malignant biological behavior of gastric cancer cells by targeting HMGB1, and sevoflurane can exert anti-tumor effects by upregulating miR-34a [16]. miR-19 can affect the atherosclerotic process by targeting PTEN and mediating the influence of HMGB1 [17]. siRNA-hmgb1 can target and interfere with the HMGB1 gene in laryngeal cancer cell lines, thereby inhibiting the proliferation, migration ability and invasion ability of laryngeal cancer cells, and also reducing the drug resistance of laryngeal cancer cells [18]. However, siRNA is easily degraded by serum nucleases and difficult to penetrate the cell membrane. Current studies mostly rely on liposomes or viral vectors, but there are problems such as low transfection efficiency (for example, only 50% silencing efficiency in hepatic stellate cells) and immunogenicity. The impact of these siRNAs on the functions of other high-mobility group proteins and the short half-life issue also need to be taken into consideration.

In addition, there are also HMGB1 A-box proteins, n-butyric acid sodium,cisplatin , quercetin, fetuin, antithrombin III, and Chinese herbal components such as daidzinone, Baicalin, berberine, Shikonin,Oridonin and Eupalimolide B that have the inhibitory or releasing effects on HMGB1.

4. The application potential of HMGB1-targeted drugs

4.1. The value of HMGB1-targeted therapy

In clinical practice, traditional anti-inflammatory and immunomodulatory interventions mainly focus on early pro-inflammatory factors such as TNF-α and IL-1β, or adopt broad-spectrum immunosuppressive strategies. These approaches have shortcomings such as a narrow therapeutic window, difficulty in effectively blocking the positive feedback loop of damage-mediated inflammation, limited response rates, and prominent adverse reactions during long-term use. There is still a significant unmet clinical need for a large number of acute and chronic sterile inflammatory diseases. For example, in sepsis, traditional anti-inflammatory drugs (such as glucocorticoids) may exacerbate immune paralysis and increase the risk of secondary infection, with an infection rate of up to 40%-50% in patients, related to improper immune regulation [19].

As a typical late alarm signal and damage-related molecular pattern, extracellular HMGB1 can connect tissue damage and excessive immune activation, and is a key driving molecule for the transition from acute to chronic inflammation. It makes it an intervention target with great translational potential.

HMGB1 is released significantly later than TNF-α and IL-1β, and is secreted in large quantities 8-24 hours after inflammatory stimulation. Even when the levels of early pro-inflammatory factors decline, HMGB1 can still continuously activate the TLR4 and RAGE signaling pathways, inducing the continuous release of downstream pro-inflammatory factors, and amplifying local and systemic inflammatory damage. Animal experiments have confirmed that intervention targeting HMGB1 can still exert protective effects when administered at a later stage of inflammation initiation, having a wider potential therapeutic window than early cytokine targets. HMGB1 can be passively released by necrotic cells without relying on immune cell activation, so traditional biologics have difficulty

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blocking the inflammatory pathways driven by this DAMP, and targeting HMGB1 can block the cascade amplification effect of inflammation from the source, compensating for the deficiency of existing drugs in interfering with this link.

A large number of studies have shown that neutralizing or inhibiting HMGB1 can alleviate multi-organ damage and reduce the degree of tissue remodeling in chronic inflammation. It has demonstrated good protective effects in various disease models such as sepsis, autoimmune diseases, some cancers, diabetes, and acute lung injury. Currently, most targeted HMGB1 drugs are still in the early translational stage, but their unique position in inflammation regulation provides new ideas for refractory and chronic inflammatory diseases, and have high potential clinical value and transformation prospects.

4.2. The challenges in the development of targeted drugs

Although a large number of preclinical studies have demonstrated that HMGB1, as a key mediator of inflammation amplification, has significant intervention value, the current transformation of drugs targeting HMGB1 still faces multiple bottlenecks, which restrict its progress from basic research to clinical application. HMGB1 itself has multiple biological functions, and it exists in various post-translational modification subtypes such as oxidation-reduction modification and acetylation. Different subtypes have different biological activities, so extensive inhibition of HMGB1 may interfere with normal physiological activities of the body. Most small molecule HMGB1 inhibitors are insufficiently specific and have extensive off-target effects; neutralizing antibodies have relatively strong specificity, but there is still a lack of targeted formulations for the pathogenic subtypes, making it difficult to precisely block the effects of the relevant HMGB1 subtypes of inflammation. Therefore, a precise targeted delivery system still needs to be studied.

Secondly, due to the overly extensive biological functions of HMGB1, its role varies in different diseases and different disease courses, and the molecular mechanism of HMGB1's action in most diseases is still unclear. This leads to the complexity of its precise targeted inhibition. Currently, there is still a lack of research on the biological effects of HMGB1 in different disease models. The optimal administration time point in different diseases and disease courses has not been determined, and there is a lack of a biomarker system that can guide clinical administration, making it difficult to screen patient populations that can benefit from HMGB1 blockade.

In addition, most of the current evidence comes from rodent models such as mice, and there are certain differences in the HMGB1 regulatory pathways between species. The existing clinical data is relatively scarce, and no drugs have completed large-scale Phase III clinical trials to verify efficacy and long-term safety. This is also an area that needs to be overcome in the subsequent development of drugs targeting HMGB1.

5. Conclusion

HMGB1, as an important late inflammatory mediator, has been extensively studied and its significant role in sepsis, pneumonia, autoimmune diseases, and cancer has been well-established. It is expected to become a new direction for future clinical targeted therapy. As a late warning signal bridging tissue damage and excessive immune activation, HMGB1 targeted therapy has overcome the limitations of traditional anti-inflammatory treatments, which only target early pro-inflammatory factors and have a narrow therapeutic window. It provides a new research perspective for many refractory diseases and builds a relatively complete theoretical framework for the subsequent screening of new drugs and exploration of mechanisms. However, the functional heterogeneity of

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HMGB1 post-translational modification subtypes, the complexity of its mechanism of action in different disease backgrounds, and the relative scarcity of high-quality clinical evidence are still key factors restricting the in-depth development of this field. There are still many areas that need to be overcome in future research, such as the development of precise targeted formulations for the pathogenic part of HMGB1, the establishment of a biomarker system that can guide clinical decisions, the exploration of multi-target combination therapy strategies, and the study of the specific molecular mechanism of HMGB1's action. This will help promote the transformation of HMGB1 targeted intervention from basic research to clinical application. It is believed that with the continuous deepening of clinical research, HMGB1 targeted therapy can bring new and more effective treatment methods for more diseases.

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