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Hyaluronic Acid and Its Function on Inflammatory Response

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ABSTRACT

Hyaluronic acid (HA) is a naturally found polysaccharide that is extensively prevalent in the human body, particularly in the skin, eyes, and synovial fluid, and it plays a crucial role in a range of physiological and pathological processes. This article examines the connection between hyaluronic acid and inflammatory responses, especially its anti-inflammatory properties.

KEYWORDS

Hyaluronic acid (HA); Natural polysaccharide; Anti-inflammatory properties

1. EFFECTS OF MOLECULAR WEIGHT

The anti-inflammatory properties of hyaluronic acid are influenced by its molecular weight, which is a key factor affecting its biological roles. Research has shown that low-molecular-weight hyaluronic acid (LMW-HA) may have pro-inflammatory effects, activating certain inflammatory pathways and increasing the production of inflammatory cytokines [1]. In contrast, high-molecular-weight hyaluronic acid (HMW-HA) is generally linked to anti-inflammatory effects. It can alleviate inflammatory responses by inhibiting the production of pro-inflammatory mediators. This form of hyaluronic acid is effective in modulating immune cell functionality and encouraging the generation of anti-inflammatory cytokines, thereby enhancing tissue repair and regeneration [2]. This variation can be explained by the different mechanisms through which hyaluronic acid interacts with cell surface receptors, which in turn affects cellular signaling pathways [2]. Moreover, hyaluronic acid's ability to attach to various receptors in different inflammatory contexts enables it to demonstrate a range of biological activities.

2. INTERACTION WITH RECEPTORS

The anti-inflammatory properties of hyaluronic acid mainly result from its interaction with receptors located on the surface of cell membranes, such as the CD44 receptor, Toll-like receptor, and ICAM-1 receptor, among others.

2.1. CD44 Receptor

CD44 serves as a primary receptor for hyaluronan and is widely found in various cell types, notably in immune cells. Upon attaching to CD44, hyaluronic acid can influence several cellular activities, such as migration, proliferation, and differentiation. This interaction has been shown to suppress inflammatory reactions and facilitate tissue healing [3, 4]. High molecular weight hyaluronic acid has been proven to reduce the levels of pro-inflammatory cytokines, including tumor necrosis factor-

alpha (TNF-alpha), by engaging the CD44 receptor and triggering the MAPK-ERK signaling pathway [5, 6].

2.2. Toll-like Receptor

Another crucial category of receptors includes Toll-like receptors, notably TLR2 and TLR4. These receptors play a vital role in detecting pathogens and regulating immune responses.

The diverse structural and compositional characteristics of hyaluronic acid influence its interaction with toll-like receptors (TLRs), which in turn modulate the intensity of the inflammatory response [7]. Low molecular weight hyaluronic acid has been demonstrated to induce the production of a range of pro-inflammatory cytokines through the activation of Toll-like receptors (TLRs), which may serve to exacerbate the inflammatory response [2, 8]. Conversely, high molecular weight hyaluronic acid exerts anti-inflammatory effects by inhibiting the TLR signalling pathway and reducing the production of inflammatory cytokines [2, 9]. For example, bioactive hyaluronic acid fragments have been demonstrated to inhibit lipopolysaccharide-induced inflammatory responses, thereby underscoring the importance of TLR4 in hyaluronic acid-mediated anti-inflammatory processes [10].

2.3. ICAM-1 Receptor

Additionally, hyaluronic acid has been demonstrated to influence leukocyte adhesion and migration by binding to intercellular adhesion molecule-1 (ICAM-1). This mechanism plays a pivotal role in regulating inflammatory cell infiltration and tissue damage [2].

3. ANTI-INFLAMMATORY MECHANISMS

The anti-inflammatory effects of hyaluronic acid may influence the course of the inflammatory response by interacting with a variety of immune cells or by modulating the expression and activity of inflammatory factors through multiple pathways.

3.1. Function Regulation of Immune Cell

The presence of hyaluronic acid has been demonstrated to influence the function of immune cells, including macrophages and lymphocytes. This has been shown to result in a shift towards an anti-inflammatory phenotype and a reduction in the intensity of the inflammatory response [11].

3.1.1. Interaction with macrophages

Hyaluronic acid has the capacity to modulate the activity of CD44 and Toll-like receptors (TLRs) on the surface of macrophages through binding to them. HMW-HA was observed to inhibit macrophage activation and reduce the release of pro-inflammatory cytokines, thereby attenuating the inflammatory response [1, 2]. Conversely, LMW-HA has been demonstrated to promote the inflammatory response in macrophages, indicating that the molecular weight of hyaluronic acid plays a pivotal role in regulating immune cell function.

Furthermore, hyaluronic acid has been demonstrated to exert anti-inflammatory effects by influencing the polarization state of macrophages. It has been demonstrated that the presence of hyaluronic acid facilitates the activation of M2-type macrophages (anti-inflammatory) but not M1-type macrophages (pro-inflammatory), consequently reducing the release of pro-inflammatory cytokines such as IL-6 and IL-8 [12, 13]. This alteration in cellular polarisation is fundamental to the alleviation of chronic inflammatory responses and the promotion of tissue repair.

3.1.2. Regulation of T-cell activity

Additionally, hyaluronic acid has been demonstrated to influence T-cell functionality. High-molecular-weight hyaluronic acid (HMW-HA) has been observed to impede the proliferation and activity of T-cells, consequently limiting their contribution to the inflammatory response, which has significant implications for the management of chronic inflammatory conditions [14, 15].

3.1.3. Impact on neutrophil migration

The presence of hyaluronic acid has been demonstrated to inhibit the migration of neutrophils, thereby reducing their accumulation at sites of inflammation. This effect may be related to the mechanism of action of hyaluronic acid in the extracellular matrix, which has the capacity to limit neutrophil activity by forming a sticky matrix.

3.2. Modulation of Inflammatory Factors

3.2.1. Release inhibition of pro-inflammatory cytokine

High molecular weight hyaluronic acid has been demonstrated to inhibit the synthesis of a range of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF-α), interleukins (IL-1, IL-6, etc.), thereby reducing inflammatory responses.

Hyaluronic acid is capable of interacting with specific cytokines (e.g. IL-8), thereby modulating the function of immune cells [16].

Hyaluronic acid has been demonstrated to inhibit the release of pro-inflammatory cytokines, including tumour necrosis factor α (TNF-α) and interleukin-1β (IL-1β), thereby attenuating the intensity of the inflammatory response [2]. This is primarily accomplished by modulating the NF-κB pathway, whereby hyaluronic acid is capable of downregulating NF-κB activity and reducing the expression of these factors.

3.2.2. Secretion promotion of anti-inflammatory factors

Hyaluronic acid has been demonstrated to inhibit the release of pro-inflammatory factors and to promote the production of anti-inflammatory factors, including transforming growth factor beta (TGF-β) [17], IL-10 [5, 18, 19].

Inhibition of cell adhesion molecule expression: hyaluronic acid was observed to reduce the expression of intercellular adhesion molecule 1 (ICAM-1), thereby demonstrating an anti-inflammatory effect in a model of severe non-bacterial inflammation. This indicates that hyaluronic acid may exert an anti-inflammatory effect by inhibiting cell adhesion and migration [2].

Modulation of nitrogen oxide (NO) and cytokine production: in in vitro experiments, hyaluronic acid was able to reduce the production of inflammatory mediators, such as NO and some pro-inflammatory cytokines (e.g., IL-6 and TNF-α), which are normally secreted in activated macrophages [5, 19].

This dual action enables hyaluronic acid to function as a moderating factor in the inflammatory response, both inhibiting excessive inflammation and facilitating tissue repair and regeneration.

4. APPLICATIONS

The anti-inflammatory effects of hyaluronic acid have been substantiated by a substantial body of evidence derived from rigorous scientific investigations, including numerous clinical trials. In these studies, the use of hyaluronic acid was observed to not only improve the quality of life of patients, but also to reduce the symptoms associated with inflammation. Hyaluronic acid's multifaceted biological functions have positioned it as a pivotal area of investigation in the study of inflammatory diseases, with a particular focus on its potential as an anti-inflammatory therapeutic agent[9, 19]

Excessive inflammation may result in the disruption of the skin barrier function, which can be effectively mitigated through the use of hyaluronic acid [20]. Hyaluronic acid has been demonstrated to modulate a range of inflammatory factors linked to dermal health, thereby assisting in the preservation of the skin's barrier function. Hyaluronic acid has been demonstrated to reduce the inflammatory response of the skin and to alleviate the symptoms of a number of dermatological conditions, including eczema and psoriasis. Additionally, hyaluronic acid plays a pivotal role in the wound healing process. It facilitates cell migration and proliferation, and enhances the formation of new tissue. Hyaluronic acid is therefore an excellent treatment for diabetic foot, trauma and surgical wounds.

The anti-inflammatory properties of hyaluronic acid make it an effective agent for the treatment of joint inflammation. A number of studies have demonstrated that hyaluronic acid injections can exert considerable anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and chemotactic factors, and by reducing the inflammatory response in the joints [19]. Hyaluronic acid is also a principal constituent of synovial fluid, which serves to lubricate joints and reduce friction, thereby alleviating pain and discomfort. This action renders it an efficacious option for the treatment of osteoarthritis [21].

In the field of ophthalmology, hyaluronic acid is employed primarily for the treatment of dry eye and the facilitation of recovery from eye surgery. Its lubricating properties facilitate the improvement of ocular surface hydration and the alleviation of discomfort [9, 21]. Furthermore, the utilisation of hyaluronic acid in ophthalmic surgical procedures, including cataract and retinal surgeries, has exhibited its efficacy in reducing inflammation and promoting healing. This has been shown to expedite patient recovery by attenuating the postoperative inflammatory response [17].

Additionally, hyaluronic acid is employed in the field of dentistry, predominantly for the purpose of facilitating gingival healing and attenuating postoperative inflammation [21, 22].

5. CONCLUSIONS

In conclusion, hyaluronic acid, being a crucial biomaterial, plays a rather complex role in modulating inflammatory factors, encompassing diverse mechanisms and pathways. Its anti-inflammatory efficacy, outstanding biocompatibility, safety, and multiple other biological attributes make it highly valuable in medical research and clinical applications. Not only does it alleviate the inflammatory response by regulating the release of cytokines and influencing cell migration, but it also promotes the healing process by facilitating tissue repair and regeneration.

While the current study establishes a scientific foundation for the anti-inflammatory effects of hyaluronic acid, further exploration is needed to understand its specific mechanisms and clinical applications. As research on hyaluronic acid deepens and ongoing clinical studies and safety monitoring continue, it may offer new solutions for the treatment of inflammatory diseases in the future. This could provide patients with additional treatment options and opportunities to improve their quality of life.

AUTHOR CONTRIBUTION STATEMENT

All authors listed have significantly contributed to the development and the writing of this article.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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