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Review Article

Context-dependent roles of 11β-HSD1 in bone and skeletal muscle diseases

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Abstract: Bone and skeletal muscles are vital to human health, and diseases related to these tissues can place significant stress on patients, families, and society. The key enzyme regulating glucocorticoid metabolism, 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), is encoded by the *HSD11B1* gene and can convert inactive cortisone into active cortisol. Recent studies have shown that 11β-HSD1 is a key enzyme in the pathogenesis of bone and skeletal muscle, with its function being strictly context-dependent. 11β-HSD1 inhibits osteoblast differentiation and activates osteoclast formation, contributing to glucocorticoid-induced osteoporosis (GIOP). 11β-HSD1 accelerates skeletal muscle atrophy by disrupting the stability of muscle proteins. It plays a dual role in anti-inflammation and bone protection, participating in polyarthritis; 11β-HSD1 also contributes to bone loss and anti-inflammation in rheumatoid arthritis (RA) through multiple pathways. Clarifying the context-specific mechanisms of 11β-HSD1 in bone and skeletal muscle diseases is critical for clinical translation. This review systematically summarizes the role of 11β-HSD1 in bone and skeletal muscle diseases, outlines its potential as a disease-specific therapeutic target, and provides new insights for precise treatment of these diseases.

Keywords: 11β-HSD1, glucocorticoids, osteoporosis, polyarthritis, rheumatoid arthritis, skeletal muscle atrophy

Introduction

Bones and skeletal muscles are crucial for human health. Diseases related to these tissues, including osteoporosis, polyarthritis, rheumatoid arthritis, and muscle atrophy, are highly prevalent worldwide, imposing a significant economic burden on patients, families, and society [1-3]. In the western world about one-fifth of men and one-third of women aged 50 years and over will sustain at least one fragility fracture during their remaining lifetime. In the entire world itself there are 9 million fractures per annum alone due to osteoporosis [1]. Therefore, it is urgently necessary to elucidate new mechanisms of bone and skeletal muscle diseases, and it is of great significance to develop new therapeutic strategies and effective drugs based on these new pathogenic mechanisms.

It is well known that osteoporosis is related to disorders in glucocorticoid metabolism. Abnormal local activation or inactivation of glucocorticoids leads to bone remodeling, disruption of muscle protein homeostasis, and inflammatory responses, which are important factors in the progression of musculoskeletal diseases. *HSD11B1* is a gene encoding 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which is responsible for converting inactive cortisone into active cortisol and is an important regulator of glucocorticoid metabolism [4]. This enzyme directly regulates the local bioavailability of glucocorticoid in bone and skeletal muscle tissues, making it a potential key mediator of

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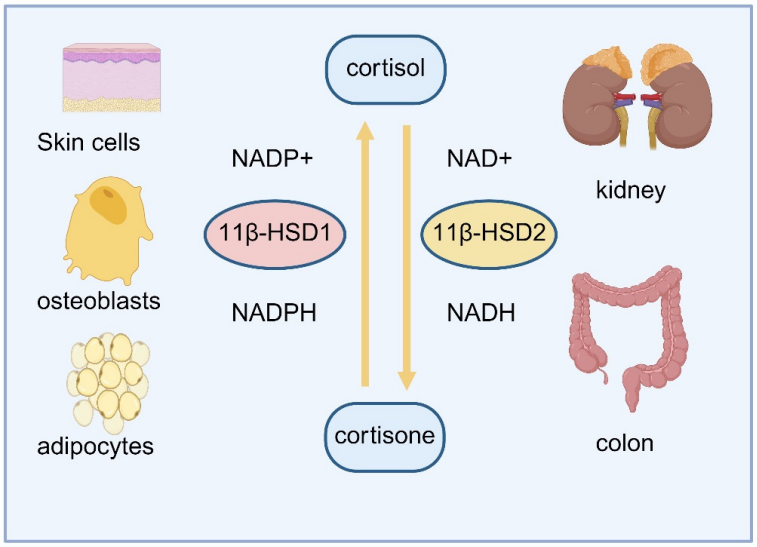

Figure 1. Glucocorticoids in the human body undergo interconversion between activated and inactivated forms via 11β-HSD1 and 11β-HSD2. 11β-HSD1 is prominently expressed in skin cells, adipocytes, and osteoblasts. 11β-HSD2 is predominantly localized in the kidney and colon. Their effect on glucocorticoids is contingent upon the presence of NADPH/NADP+ and NAD+/NADH in the surrounding milieu.

the above disorders. However, the specific mechanisms by which 11β-HSD1 regulates skeletal and muscle diseases remain unclear. This article mainly discusses the functional differences and molecular mechanisms of 11β-HSD1 in osteoporosis, polyarthritis, rheumatoid arthritis, and skeletal muscle atrophy, providing new molecular targets for the above diseases.

11β-HSD1: molecular structure and function

Gene structure and localization

In humans, the *HSD11B1* gene is located in the 1q32.2 region of chromosome 1, with its locus spanning from 209,686,178 bp to 209,734,949 bp. The gene contains several exons and introns, which produce functional specific mRNA through complex transcription regulation. In mice, the *HSD11B1* gene is located on chromosome 1, which has certain site conservation. This conservation provides a genetic basis for studying gene function by using a mouse model.

Expression and distribution of 11β-HSDs

11β-HSD1 is a microsomal enzyme expressed on the luminal surface of the endoplasmic reticulum, encoded by *HSD11B1* [5, 6]. So far, three subtypes of 11β-HSD have been identified in different species (11β-HSD1, 11β-HSD2, and 11β-HSD3) [7-9]. However, in humans and rodents, only 11β-HSD1 and 11 β-HSD2 are considered key regulators of the interconversion between active and inactive glucocorticoids [10-12]. They regulate the tissue-level bioavailability of glucocorticoids, thereby participating in various physiological and pathological effects [13-16]. **Figure 1** illustrates the tissue distribution and catalytic function differences of the two isoforms of 11β-hydroxysteroid dehydrogenase (11β-HSD) in vivo. 11β-HSD1 is predominantly distributed in cells related to metabolism and bone tissue, such as skin cells [17], osteoblasts [18], and adipocytes [19]. Using NADPH as a cofactor, 11β-HSD1 catalyzes the conversion of inactive cortisone into active cortisol, thereby enhancing the potency of local glucocorticoid effects. This process is crucial for regulating bone metabolism, fat deposition, and skin barrier function. In contrast, 11β-HSD2 is primarily expressed in epithelial tissues such as the kidneys and colon [20]. Using NAD^+ as a cofactor, 11β-HSD2 catalyzes the conversion of active cortisol into inactive cortisone, thereby protecting these tissues from excessive inhibition by high concentrations of glucocorticoids. For example, this process helps maintain the homeostasis of water and salt balance in the kidneys [21, 22].

Species-specific differences in 11β-HSD1 localization have been observed, particularly in rodents. For example, in mice, the expression of liver 11β-HSD1 is the highest in the perivenous region around the central vein of the liver. The expression of mesenchymal fibroblasts in lung tissue is the highest, while in the adrenal gland, it is only expressed in the glomerulus and medulla [23]. Additionally, the 11β-HSD isozymes were expressed in human synovial tissue. Synovial fibroblasts were the main cells expressing 11β-HSD1, and synovial macropha-

ges were the main cells expressing 11β-HSD2 [24, 25]. The cell type-specific distribution pattern of 11β-HSD may be related to the regulation of local glucocorticoid activity in joint tissues.

Unlike 11β-HSD1, the gene encoding 11β-HSD2 is located on chromosome 16 in humans and on chromosome 8 in rodents [26]. 11β-HSD2 expression is more limited than that of 11β-HSD1, mostly localized in the kidneys, adrenal glands, and colon, with moderate levels in the liver and gonads [26, 27]. This human tissue-specific pattern aligns with 11β-HSD2's primary role in glucocorticoid inactivation, particularly in renal tissues [28].

Enzymatic activity and functional interaction of 11β-HSD1 and 11β-HSD2

As 11β-HSD1 has a bidirectional enzyme function and can be used as a reductase or an oxidase, but it mainly acts as a reductase in vivo, converting inactive corticosteroids (e.g., cortisone) into cortisol [29]. Mechanically, this reaction reduces the keto group in cortisone C11 to a hydroxyl group, thus dramatically transforming the hormone into one with a higher affinity for glucocorticoid receptors. Importantly, the affinity of unmodified cortisone for GR is extremely low, so 11β-HSD1-mediated transformation is necessary to activate glucocorticoid signal transduction in target tissues [7].

The reductase activity of 11β-HSD1 depends on its binding to hexose-6-phosphate dehydrogenase (H6PDH) and inositol hexaphosphate. H6PDH and inositol hexaphosphate maintain the reduction ability of 11β-HSD1. Specifically, H6PDH produces nicotinamide adenine dinucleotide phosphate (NADPH), which is a necessary cofactor for the activity of 11β-HSD1 reductase, and keeps the local NADPH/NADP+ ratio high to allow the enzyme to work efficiently in the reduction direction [6, 30].

As an NAD-dependent oxidase, 11β-HSD2 only converts active glucocorticoids such as cortisol into inactive glucocorticoids such as cortisone [31]. This reaction can reduce the concentration of circulating hormones and cortisol in specific tissues. Moreover, this process can protect the activity of mineralocorticoid receptors (MRs) from the false activation of cortisol. 11β-HSD2 also plays an important role in renal distal tubule cells, inactivating glucocorticoid, preventing cortisol from binding with MRs, and making MRs react specifically to its physiological ligand aldosterone [32].

11β-HSD1 and 11β-HSD2 have a close functional relationship because they serve as reciprocal sources of enzyme substrates [29, 33]. Specifically, the inactive glucocorticoid products (such as cortisone) of 11β-HSD2 are the substrates for catalytic reduction of 11β-HSD1, and the active products (e.g., cortisol) of 11β-HSD1 are the substrates for catalytic oxidation of 11β-HSD2. The interdependence of these substrates forms a regulatory loop, which closely regulates the bioavailability of local glucocorticoid to ensure that the local glucocorticoid signal in the target tissue is properly regulated. Although both 11β-HSD1 and 11β-HSD2 are important regulators of glucocorticoid metabolism, 11β-HSD1 has been the primary focus of research in skeletal and muscle disorders due to its predominant role in local glucocorticoid activation. The following section therefore focuses on the context-dependent functions of 11β-HSD1 in these tissues.

Pathogenic function of 11β-HSD1 in glucocorticoid-induced osteoporosis

According to the internationally recognized definition, osteoporosis is a systemic skeletal disorder characterized by low bone mass and deterioration of bone tissue microarchitecture. And these pathologies will increase bone fragility, thus increasing the risk of fracture [34, 35]. Osteoporosis can be categorized into glucocorticoid-induced osteoporosis (GIOP), environmental toxin-induced osteoporosis, and osteoporosis related to metabolic diseases [36-38]. Among these, GIOP is the most common form. Both oral and intravenous glucocorticoids require conversion to cortisol to exert their biological effects, and this conversion process is dependent on 11β-HSD1. Therefore, 11β-HSD1 is considered a pivotal mediator in the pathogenesis of GIOP.

11β-HSD1 is expressed in osteoblasts [39], osteoclasts [40], and bone marrow mesenchymal stem cells [41], and is involved in the pathogenesis of GIOP [42, 43]. Two key mechanisms underlying 11β-HSD1-mediated GIOP have been identified, as detailed below.

First, overexpression of 11β-HSD1 in osteoblasts may elevate local glucocorticoid activity, thereby inhibiting osteoblast differentiation [44, 45]. Fenton and colleagues [46] evaluated bone parameters in wild-type (WT) and 11β-HSD1 knockout (KO) mice following oral gavage of cortisol, using micro-computed tomography (micro-CT), submicron absorptiometry, and serum markers of bone metabolism. They found that WT mice treated with cortisol exhibited significant trabecular bone loss, characterized by a decrease in bone volume/tissue volume (BV/TV) ratio, trabecular thickness, and trabecular number. At the same time, the expression of osteoblast-specific marker genes, alkaline phosphatase (ALP) and osteocalcin (BGLAP), was significantly reduced. In contrast, 11β-HSD1 knockout mice treated with cortisol showed partial protection against the decrease in osteoblast numbers and serum levels of the N-terminal propeptide of type I procollagen (P1NP) and full protection against trabecular bone loss. These data demonstrate that 11β-HSD1 is a key mediator of GIOP, because 11β-HSD1 may inhibit glucocorticoid-induced anabolic bone formation and subsequently reduce bone volume by lowering osteoblast abundance.

However, another study on *HSD11B1* knock-in (KI) and knockout (KO) mice found that 11β-HSD1 expression was significantly increased in the osteoclasts of osteoporotic mice, while the bone mass of *11β-HSD1* KI mice was significantly reduced. Compared to WT controls, *11β-HSD1* KI mice exhibited elevated osteoclast numbers, while KO mice showed reduced osteoclast counts. In addition, the selective 11β-HSD1 inhibitor BVT-2733 also inhibited osteoclast generation in a dose-dependent manner. Mechanistically, 11β-HSD1 was found to promote the maturation of osteoclasts by reducing the release of platelet-derived growth factor-BB (PDGF-BB) and inhibiting bone formation associated with the proliferation of H-type endothelial cells (CD31hiEmcnhi). Transcriptome sequencing analysis showed that the components of the Hippo signaling pathway were significantly enriched in osteoclasts isolated from 11β-HSD1 KI mice. This pathway can regulate the effect of 11β-HSD1 on osteoclasts. YAP plays a key regulatory role in the Hippo signaling pathway, and its expression level is high in osteoclasts. Immunofluorescence and Western blotting showed that 11β-HSD1 activated the Hippo signaling pathway, thus upregulating the expression of core protein YAP and promoting the generation and maturation of osteoclasts.

In summary, 11β-HSD1 inhibits bone formation by increasing the local activation of glucocorticoids around osteoblasts. Overexpression of 11β-HSD1 can accelerate the differentiation and maturation of osteoclasts through the Hippo signaling pathway by increasing YAP protein, thereby promoting osteoporosis. In addition, 11β-HSD1 can also inhibit osteogenesis by reducing osteoclast precursor cells, decreasing PDGF-BB secretion, and suppressing H-type angiogenesis.

The bone-protective effects of HSD11B1 in polyarthritis

Chronic polyarthritis refers to a group of diseases characterized by involving four or more joints, persistent inflammatory reaction or degenerative changes, and a disease course of more than 6 weeks. Its etiology is often complex and unclear, with pathogenesis involving multiple factors, including genetics, immunity, environment, infection, and metabolism [47-49]. Among these, immune dysregulation and inflammatory responses represent the common core mechanisms underlying most chronic inflammatory polyarthritis conditions. Recent studies demonstrate that 11β-HSD1 plays a role in modulating inflammation and bone metabolism associated with polyarthritis by mitigating synovial inflammation and providing bone-protective effects.

Fibroblast-like synoviocytes (FLS) are the main functional synoviocytes among the cell drivers of polyarthritis because these cells produce pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) to degrade cartilage. Wei and colleagues [50] examined the expression of inflammatory factors in synovial fibroblasts of SD rat knees stimulated by IL-1β. They found that 24 hours after IL-1β stimulation, the expression levels of tumor necrosis factor-α and IL-1β in cultured cells without cortisol were significantly higher than those in the cortisol-treated group, indicating that cortisol has an anti-inflammatory effect on IL-1β-induced inflammation. PF915275 (a selective 11β-HSD1 inhibitor) can

reverse cortisol-mediated anti-inflammatory effects.

Hardy and colleagues [51] generated a transgenic mouse model of arthritis by crossing TNF-transgenic (TNF-tg) mice (which exhibit spontaneous inflammatory arthritis) with global 11β-HSD1 knockout (11β-KO) mice, resulting in TNF-tg mice lacking 11β-HSD1 (TNF-tg$^{11\beta KO}$). Compared to wild-type (WT), 11β-KO, and TNF-tg littermates, TNF-tg$^{11\beta KO}$ mice displayed significantly increased forepaw edema and deformity. Histological and immunological analyses examination showed that TNF-tg$^{11\beta KO}$ mice had exacerbated synovial inflammation and enhanced M1 macrophage polarization - both of which are associated with increased tissue damage in polyarthritis. Furthermore, the expression of osteoblast-specific markers, including procollagen type I N-terminal propeptide (P1NP), runt-related transcription factor 2 (Runx2), and osteoprotegerin (Tnfrsf11b), was reduced in TNF-tg$^{11\beta KO}$ mice. Thus, this study demonstrated that 11β-HSD1 plays an essential protective role in mitigating synovitis, joint destruction, and systemic bone loss in polyarthritis models. Fenton and colleagues [52] found that TNF-tg mice exhibited lower expression levels of the osteoblast markers P1NP and osteocalcin (BGLAP) compared to TNF-tg$^{11\beta KO}$ mice following cortisol treatment. In TNF-tg mice treated with cortisol, the serum concentration of type I collagen cross-linked C-terminal peptide (CTX-1) decreased significantly, which is a marker of osteoclast-mediated bone resorption. Therefore, oral corticosteroids with therapeutic doses can inhibit osteoblast-driven bone formation and osteoclast-mediated bone resorption in inflammatory arthritis. Histomorphometric analysis further revealed that TNF-tg mice (with intact 11β-HSD1) had increased trabecular bone density and total bone volume compared to TNF-tg$^{11\beta KO}$ mice. Collectively, these data indicate that 11β-HSD1 primarily exerts its bone-protective effects in arthritis by reducing osteoclast-mediated bone resorption. **Figure 2** illustrates the differential effects of 11β-HSD1 deficiency on bone metabolism under inflammatory and non-inflammatory conditions, highlighting its context-dependent role in regulating bone mass and turnover.

Pathogenic function of 11β-HSD1 in rheumatoid arthritis (RA)

Research indicates that 11β-HSD1 modulates pathological behavior and bone remodeling processes in synovial fibroblasts of rheumatoid arthritis (RA) through multidimensional regulation of local active glucocorticoid levels: Hardy and colleagues [53] found that 11β-HSD1 induced Dickkopf-1 (DKK1) in synovial fibroblasts isolated from RA patients. DKK1 is an important regulator of bone remodeling; it can directly inhibit the differentiation of osteoblasts and indirectly promote the production of osteoclasts by reducing the expression of osteoprotegerin, thus causing bone loss unique to RA. Specifically, TNF-α and IL-1β can increase the expression and activity of 11β-HSD1 in synovial fibroblasts, locally increase the production of inactive steroids to active glucocorticoids, and then directly lead to the synthesis of DKK1. Glycyrrhetinic acid (GE), an inhibitor of 11β-HSD1, prevented the induction of DKK1 by corticosterone and also inhibited the sensitization of corticosterone to DKK1 after TNF-α pretreatment, demonstrating that 11β-HSD1 was the main mediator of indirect regulation of DKK1 by inflammatory cytokines.

Although 11β-HSD1 promotes bone loss in RA, studies indicate that 11β-HSD1 can suppress inflammatory responses in synovium macrophages [54]. Specifically, 11β-HSD1 suppresses inflammatory responses in M1 macrophages by activating glucocorticoids, reducing secretion of TNF-α and IL-6, and upregulating expression of the anti-inflammatory factor CD163. Additionally, 11β-HSD1 catalyzes the conversion of the androgen precursor androstenedione (A4) into testosterone (T), which further generates dihydrotestosterone (DHT). DHT inhibits synovial fibroblast activity, reduces inflammatory cytokine secretion, and alleviates synovial inflammation and tissue damage.

The main function of 11β-HSD1 is to catalyze the conversion of cortisol to cortisone so as to adjust the bioavailability of local glucocorticoids, but bioinformatics analysis shows that the cortisol level of RA patients is lower than that of healthy controls [55]. In RA patients, the levels of 11β-HSD1 and NR3C1 (glucocorticoid receptor, GR) increased significantly in synovial

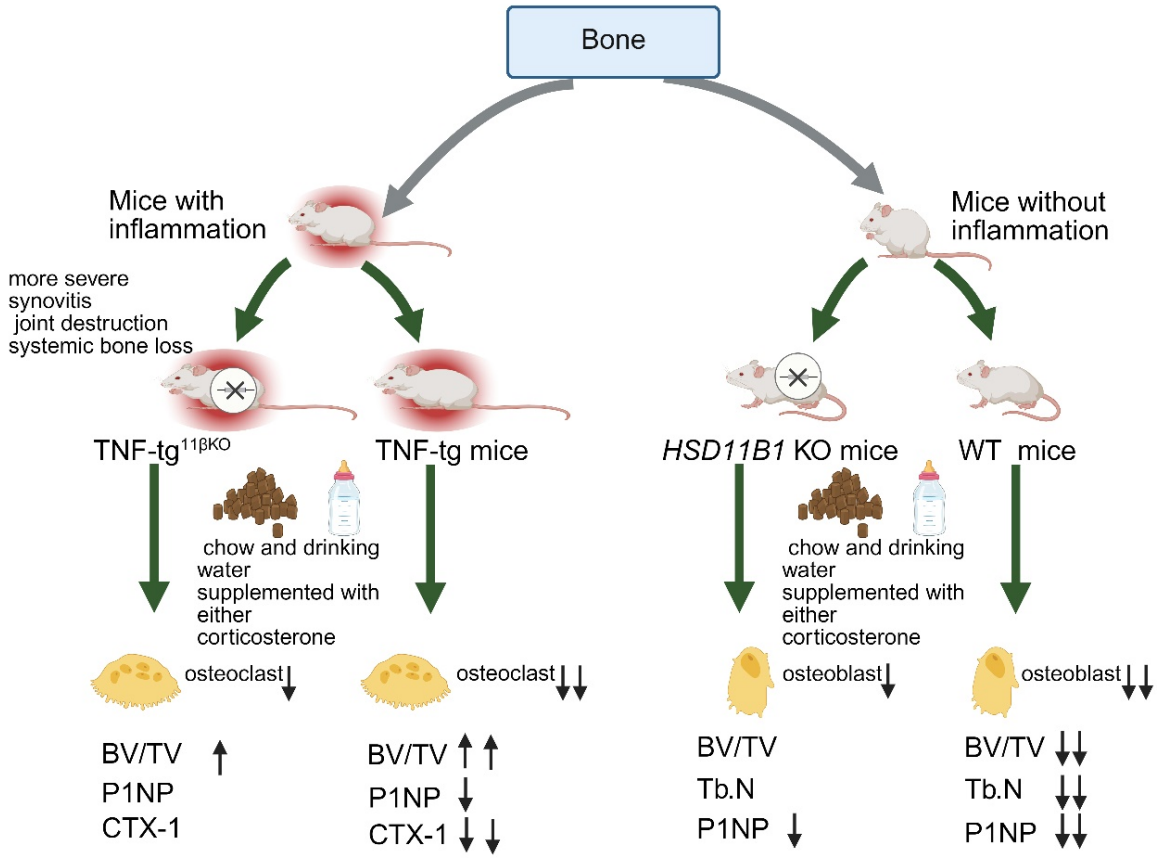

Figure 2. 11β-HSD1 affects bone metabolism in both inflammatory and non-inflammatory mouse models. In the non-inflammatory mouse model, the number of osteoblasts and P1NP levels were significantly reduced, while the bone trabecular volume to tissue volume ratio (BV/TV) and bone trabecular number (Tb.N) were reduced in WT mice administered corticosterone compared to 11β-HSD1-KO mice. In the inflammatory mouse model, TNF-tg mice receiving corticosterone exhibited a more pronounced increase in BV/TV, a reduction in the osteoblast marker P1NP, the osteoclast marker CTX-1, and a more significant decrease in osteoclast numbers compared to TNF-tg$^{11\beta KO}$ mice.

tissue, but the glucocorticoid receptor signaling pathway remained functionally impaired. It is possible that other regulatory factors in the RA joint microenvironment will interfere with the normal operation of the 11β-HSD1-glucocorticoid axis. The activity of 11β-HSD1 in RA patients treated with anti-TNF-α decreased obviously [56], indicating that pro-inflammatory cytokines may contribute to the pathogenesis of rheumatoid arthritis by regulating 11β-HSD1 activity and also providing a certain clinical basis for HSD11B1-targeted therapy for rheumatoid arthritis.

It should be noted that the pathological process of the musculoskeletal system does not exist only in isolated injuries of bones and joint tissues. As a core component of this system, skeletal muscle frequently exhibits structural and functional imbalances that are intertwined with the development of bone diseases (e.g., chronic inflammation-mediated bone-muscle coupling injuries [57, 58], systemic musculoskeletal adverse reactions induced by glucocorticoid therapy [59, 60]). As a key regulator of local glucocorticoid activity, 11β-HSD1 has a context-dependent function in bone and joint diseases and has similar functional characteristics in the pathological process of skeletal muscle-related diseases. For example, 11β-HSD1 promotes skeletal muscle atrophy in the presence of high levels of hormones and plays a protective role in an inflammatory microenvironment.

The dual regulatory role of HSD11B1 in skeletal muscle disorders

Skeletal muscle atrophy is a common condition, primarily characterized by a decline in

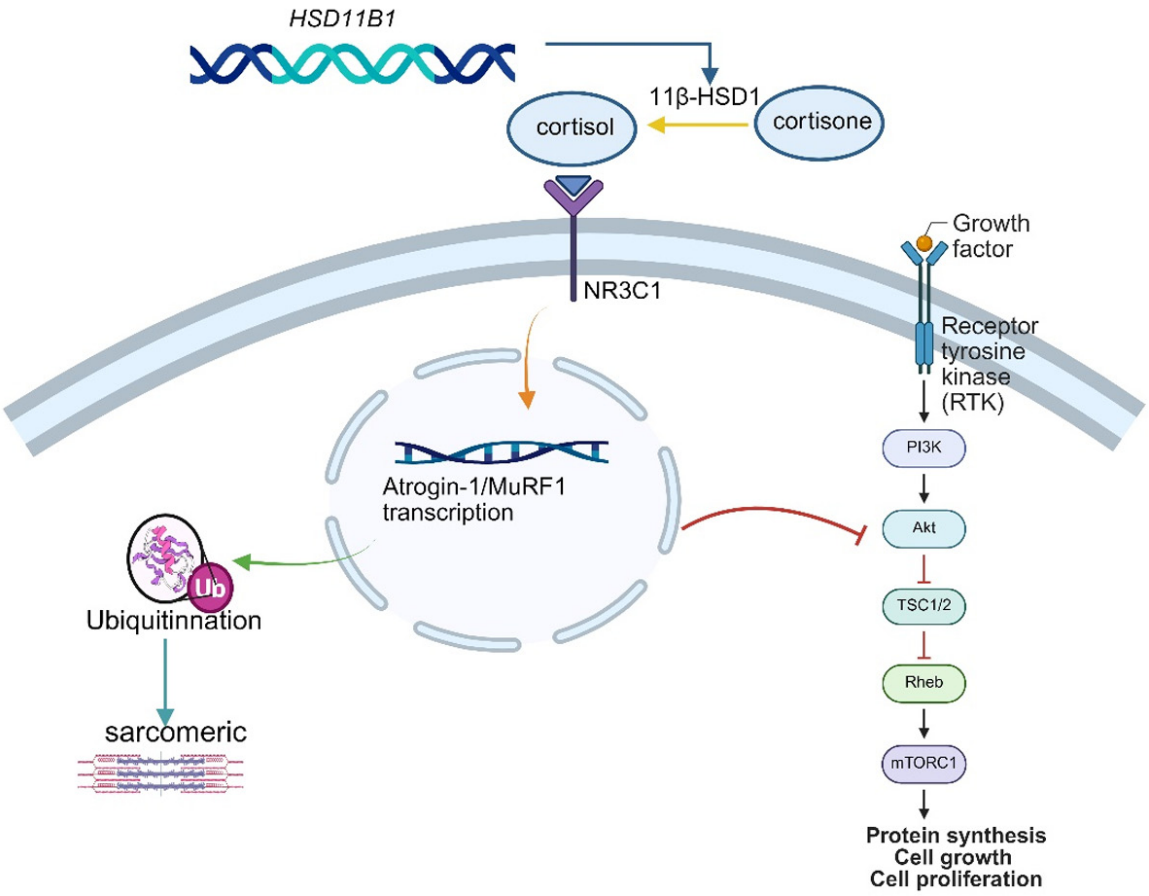

Figure 3. *HSD11B1* regulates 11β-HSD1 to convert inactive cortisone into active cortisol, which activates the glucocorticoid receptor (NR3C1) and induces Atrogin-1/MuRF1 transcription. These ubiquitin ligases accelerate myosin protein ubiquitination and degradation while simultaneously inhibiting the PI3K/AKT-mTOR pathway to block protein synthesis, ultimately exacerbating skeletal muscle atrophy.

muscle mass, strength, and function, seriously affecting patients' ability to live and quality of life. Skeletal muscle atrophy is influenced by various pathological factors, mainly including protein metabolism disorders, cytokine-mediated degeneration, and metabolic/epigenetic abnormalities [61-65]. The expression of *HSD11B1* in human skeletal muscle is high, and the age-related increase in female skeletal muscle is more obvious than that in men. This explains the higher incidence of glucocorticoid-related adverse reactions in women [66]. Schluessel and colleagues [67] found that 11β-HSD1 promoted the production of cortisol by regulating the activity of its encoded 11β-HSD1 enzyme in 33 elderly patients with sarcopenia (≥60 years old). Increased cortisol further boosts the transcription of two major ubiquitin ligases, FBXO32 (Atrogin-1) and MuRF1 (TRIM63), which accelerate the degradation of myofibrils, resulting in the loss of muscle mass. **Figure 3** illustrates how 11β-HSD1 destroys the internal balance of skeletal muscle protein. Specifically, the endogenous expression of 11β-HSD1 in skeletal muscle tissue is regulated by 11β-HSD1, which converts inactive cortisone into bioactive cortisol. After binding to the glucocorticoid receptor (NR3C1/GR), cortisol induces a conformational change in the receptor, causing it to dissociate from chaperone proteins such as heat shock proteins in the cytoplasm. After that, the activated NR3C1 was translocated into the nucleus and combined with glucocorticoid response elements (GREs) to start the transcription of muscle-specific ubiquitin ligases FBXO32 (Atrogin-1) and TRIM63 (MuRF1). These ligases accelerate the ubiquitination and degradation of sarcomere proteins (including myosin). At the same time, the increase of Atrogin-1 and MuRF1 inhibits

the downstream mTOR pathway that drives protein synthesis by suppressing the PI3K/AKT signaling pathway [68]. The dual effects of 11β-HSD1 in accelerating skeletal muscle degradation and hindering protein synthesis create a vicious cycle that leads to skeletal muscle atrophy. In particular, the role of *HSD11B1* in skeletal muscle is not unidirectional, and its role in muscle homeostasis is strictly regulated by the microenvironment. Although 11β-HSD1 is a driver of skeletal muscle atrophy, it protects the balance of muscle anabolism and catabolism from being disrupted by pro-inflammatory factors. For example, compared to TNF-tg mice, TNF-tg$^{11\beta KO}$ mice exhibited significantly elevated expression of TRIM63 and Mstn (myostatin gene), which are the catabolic markers induced by endogenous glucocorticoids [69, 70].

Therefore, when exogenous glucocorticoids are sufficient (long-term hormone therapy, sarcopenia in the elderly), 11β-HSD1 promotes muscle atrophy by activating NR3C1-FBXO32/TRIM63. On the contrary, 11β-HSD1 may protect against skeletal muscle atrophy in an inflammatory microenvironment (chronic inflammation caused by TNF-α) by inhibiting catabolism mediated by endogenous glucocorticoids.

Context-dependent pathogenic mechanisms of 11β-HSD1 in bone and skeletal muscle disorders

Differential regulation of 11β-HSD1 by the pathological microenvironments

The pathological microenvironments of bone and skeletal muscle diseases are different. For example, Polyarthritis is characterized by local chronic inflammation, and inflammatory cytokines (e.g., TNF-α, IL-1β) upregulate 11β-HSD1 expression, thereby inducing local glucocorticoid production and suppressing the inflammatory response. On the contrary, in osteoporosis caused by estrogen deficiency or excessive exogenous hormones (especially GIOP), the upregulation of 11β-HSD1 lacks effective anti-inflammatory targets and instead exerts a 'pathogenic effect' by activating osteoclast signaling pathways and inhibiting stem cell osteogenic differentiation.

Cell-specific expression and functional differentiation of 11β-HSD1

11β-HSD1 mainly produces glucocorticoid to play an anti-inflammatory role in synovial cells and articular chondrocytes; 11β-HSD1 inhibits the activation of osteoclasts in an inflammatory microenvironment but promotes osteoclast formation through the Hippo signaling pathway under hormonal imbalance. Moreover, 11β-HSD1 mainly affects tissue repair by regulating the balance between osteogenic and adipogenic differentiation of bone marrow mesenchymal stem cells [41].

The influence of glucocorticoid concentration and duration of action

The concentration of glucocorticoid and its action time can regulate the function of 11β-HSD1: in polyarthritis, 11β-HSD1 plays a local short-term role in treatment or presence of physiological low-concentration of glucocorticoid, mainly playing an anti-inflammatory role; in osteoporosis, however, abnormal local accumulation of glucocorticoids may occur (e.g., age-related endogenous GC elevation, exogenous hormone excess). The continuous activation of 11β-HSD1 will lead to the increase of activated GC level, which will further inhibit the function of osteoblasts and promote the activation of osteoclasts [39, 46, 71]. Acute inflammation is exacerbated in the absence or inhibition of 11β-HSD1, yet in certain chronic inflammatory contexts such as obesity or diabetes, 11β-HSD1 deficiency/inhibition proves beneficial by reducing inflammation [72]. This temporal difference also contributes to the functional differentiation of 11β-HSD1 across various diseases.

Research status and challenges

In summary, 11β-HSD1 is a regulator of skeletal and skeletal muscle homeostasis. **Figure 4** summarizes the different mechanisms by which 11β-HSD1 is involved in the pathogenesis of bone and skeletal muscle. 11β-HSD1, as a key regulator of local glucocorticoid (GC) activity, plays a crucial mediating role in musculoskeletal disorders. In glucocorticoid-induced osteoporosis, exogenous supraphysiological GCs amplify bone destruction via 11β-HSD1 by inhibiting osteoblast differentiation and promot-

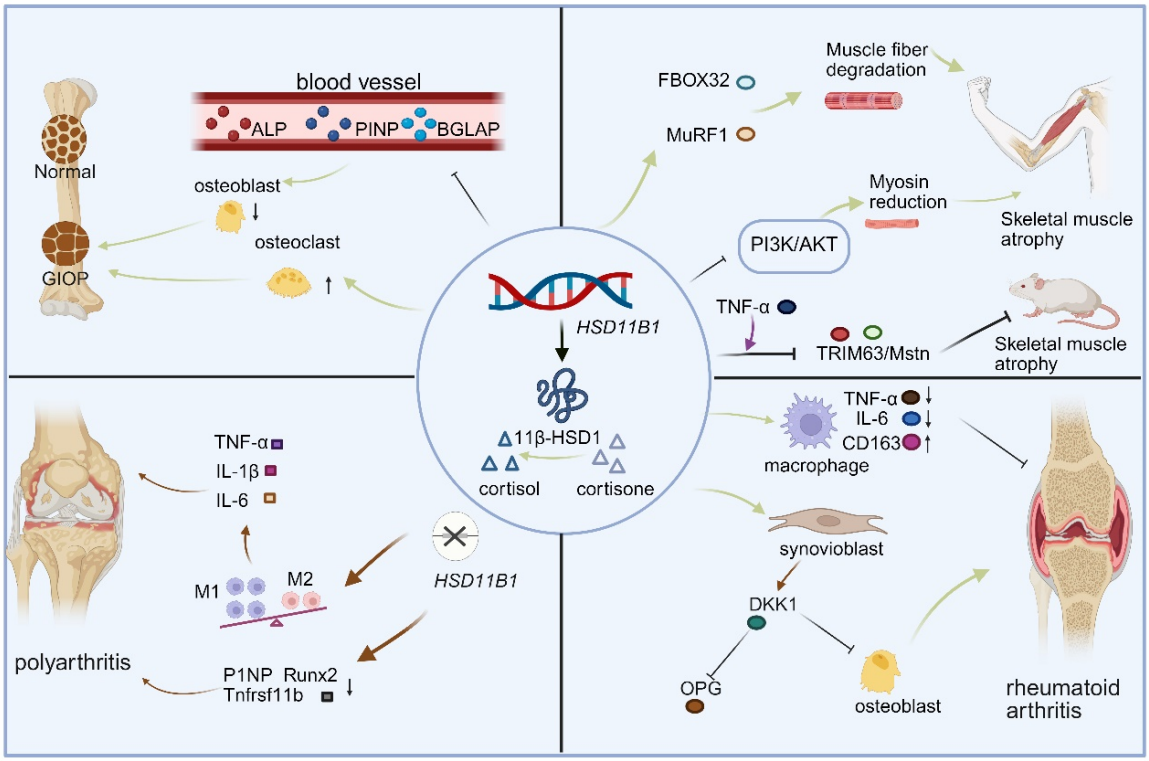

Figure 4. The Role of 11β-HSD1 in musculoskeletal disorders. 11β-HSD1 participates in inducing inducible GIOP by inhibiting osteoblast differentiation and promoting osteoclast formation. In 11β-HSD1 knockout mice, M1 polarization of synovial macrophages is increased. This leads to heightened secretion of inflammatory cytokines. At the same time, osteogenic markers are reduced. Collectively, these changes exacerbate inflammation and tissue damage associated with polyarthritis. In rheumatoid arthritis, 11β-HSD1 primarily inhibits osteoblast differentiation and promotes bone loss in RA by regulating synovial fibroblast secretion of DKK1. Additionally, 11β-HSD1 modulates macrophage inflammatory factor secretion via glucocorticoids, thereby improving inflammatory responses in RA. In skeletal muscle diseases, 11β-HSD1 regulates skeletal muscle fiber synthesis and degradation through FBOX32, MuRF1, and the PI3K/AKT signaling pathway; under TNF-α stimulation, 11β-HSD1 exerts a bone-protective effect by inhibiting TRIM63/Mstn in mice.

ing osteoclast generation, thus causing bone loss. In polyarthritis, knockdown of 11β-HSD1 induces M1 macrophage polarization and increased secretion of inflammatory cytokines, while simultaneously reducing osteoblast markers, thereby promoting tissue damage and synovial inflammation. In RA, 11β-HSD1 inhibits osteoblast differentiation by inducing synovial fibroblasts to secrete Dkk1, which downregulates the expression of osteoprotegerin. Additionally, it inhibits synovial hyperplasia by suppressing macrophage secretion of inflammatory cytokines TNF-α and IL-6 while promoting secretion of the anti-inflammatory factor CD163. In skeletal muscle atrophy, 11β-HSD1 accelerates the degradation of myofibrils through the NR3C1-FBXO32/MuRF1 pathway, promoting muscle wasting under long-term hormone therapy and exogenous GC-rich environments; in chronic inflammation mediated by TNF-α, 11β-HSD1 exerts a protective effect by inhibiting the expression of catabolic markers (TRIM63/MSTN). At the same time, 11β-HSD1 inhibits muscle protein synthesis by blocking the PI3K/AKT signaling pathway.

Glucocorticoids are widely used in clinical treatment, such as for type 2 diabetes, cardiovascular disease, metabolic syndrome, hypertension, non-alcoholic fatty liver disease, and Alzheimer's disease [73-77]. 11β-HSD1's role as the enzyme involved in generating active GC locally makes its modulators of great interest to be investigated preclinically and clinically [78]. A diverse panel of 11β-HSD1 inhibitors - including MK-0916 [79], MK-0736 [80], ABT-384 [81], INCB13739 [82], RO5093151 [83-85], and AZD4017 [86] - has been devel-

oped. These findings confirm that 11β-HSD1 is a viable therapeutic target for treating multiple diseases.

However, there are still many limitations and problems in the current research. Most studies are conducted through cell and animal experiments, lacking research on complex human diseases. Current research mainly focuses on the effect of 11β-HSD1 on glucocorticoid metabolism pathways, and the specific pathogenic mechanism of 11β-HSD1 in diseases has not yet been fully elucidated. Moreover, there are still many difficulties and challenges in developing efficient, specific, and safe 11β-HSD1 inhibitors or gene therapies.

Conclusion

In summary, 11β-HSD1 plays a crucial role in the development and progression of bone and skeletal muscle diseases. 11β-HSD1 is involved in the metabolic processes of bone and skeletal muscle cells by affecting the concentrations of endogenous and exogenous glucocorticoids, thereby contributing to the onset of diseases such as osteoporosis, rheumatoid arthritis, and muscle atrophy. Abnormal expression of 11β-HSD1 is closely related to disease progression, providing new insights into the pathogenesis of bone and skeletal muscle diseases.

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Disclosure of conflict of interest

All authors made a significant contribution to the work reported, either in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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