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Review article

Stromal cell-derived factor-1 (CXCL12) and its role in bone and muscle biology

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ABSTRACT

Musculoskeletal disorders are the leading cause of disability worldwide; two of the most prevalent of which are osteoporosis and sarcopenia. Each affect millions in the aging population across the world and the associated morbidity and mortality contributes to billions of dollars in annual healthcare cost. Thus, it is important to better understand the underlying pathologic mechanisms of the disease process. Regulatory chemokine, CXCL12, and its receptor, CXCR4, are recognized to be essential in the recruitment, localization, maintenance, development and differentiation of progenitor stem cells of the musculoskeletal system. CXCL12 signaling results in the development and functional ability of osteoblasts, osteoclasts, satellite cells and myoblasts critical to maintaining musculoskeletal homeostasis. Interestingly, one suggested pathologic mechanism of osteoporosis and sarcopenia is a decline in the regenerative capacity of musculoskeletal progenitor stem cells. Thus, because CXCL12 is critical to progenitor function, a disruption in the CXCL12 signaling axis might play a distinct role in these pathological processes. Therefore, in this article, we perform a review of CXCL12, its physiologic and pathologic function in bone and muscle, and potential targets for therapeutic development.

1. Introduction

Musculoskeletal disorders are the leading cause of disability worldwide in aging population [1]. Two of the most prevalent conditions are osteoporosis and sarcopenia. They are often seen together because bone and muscle interact mechanically and chemically [2]. For example, bone affects muscle through osteocalcin, a marker of bone formation, acting directly on skeletal muscle correlating with muscle strength, while myokines, produced by the muscle, can stimulate bone formation [2–4]. Therefore, targeting one may attenuate the other and vice versa.

Osteoporosis is estimated to effect more than 200 million people worldwide with one in three women, and one in five men, expected to experience an osteoporotic fracture after the age fifty [5]. Sarcopenia additionally effects millions of individuals and often the two are seen together in an aged population [6]. Aging is accompanied by musculoskeletal degradation and leads to comorbidities such as poor mobility, frailty, depression, cognitive impairment, falls and poor sleep quality [1]. The increased morbidity and mortality associated contributes to billions of dollars in annual healthcare cost [2]. Therefore, it is important to better understand underlying mechanisms contributing to the disease process which could be targets for therapeutic intervention. One area of research important in achieving this goal focuses on cellular communicators in the molecular environment of bone and muscle tissue [2]. The musculoskeletal system exists in a homeostatic balance of regenerative and degenerative forces that rely heavily on a cellular network composed of regulatory molecules and their receptors. With age, this homeostatic balance disrupts which leads to degenerative changes [7,8].

Aging is associated with elevated serum concentration of inflammatory cytokines which has pleiotropic effects on cellular functions, such as the decrease in viability of MSC to regenerate and differentiate [9,10]. One cytokine in particular, stromal derived factor-1 (CXCL12), is crucial to BMSC recruitment, survival, and engraftment in the bone and muscle. Therefore, the effect of age-related inflammation on CXCL12 levels might contribute to the pathologic changes of

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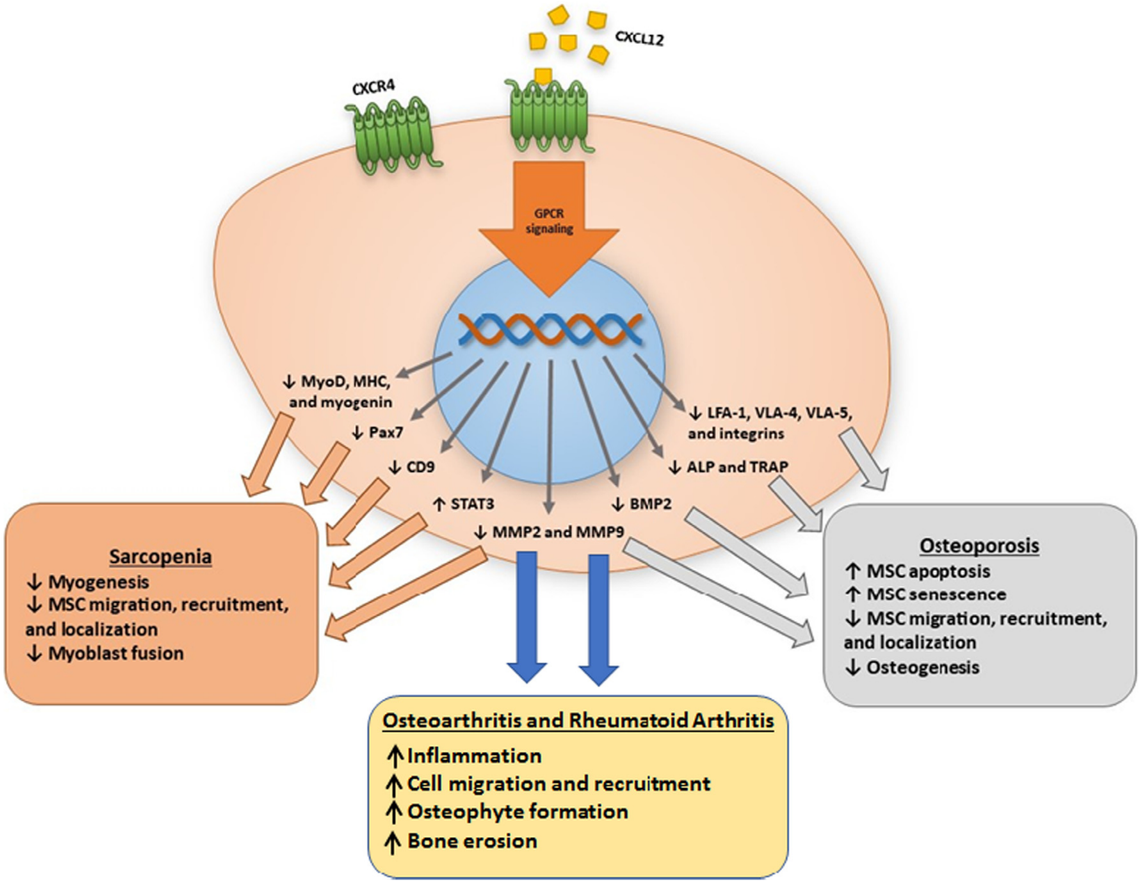

Fig. 1. Schematic diagram showing CXCL121 role in bone and muscle pathophysiology.

osteoporosis and sarcopenia. The molecule stromal derived factor-1, CXCL12 or CXCL12, is recognized as one of the important regulators in the musculoskeletal microenvironment [11–13]. CXCL12 is a small chemotactic signaling protein that acts mainly through specific G-coupled protein receptor (GCPR), CXCR4, promoting downstream effects required to maintain tissue integrity and to recruit new building blocks for repair and regrowth [14]. Specifically, CXCL12 is involved in recruitment, survival, and maturation of progenitor stem cells. Further understanding of CXCL12 role could provide new strategies for therapeutic intervention, thus, in this review article; we will discuss CXCL12, its physiologic and pathologic function in bone and muscle (Fig. 1), and possible targets for therapeutic development in pathological condition.

2. CXCL12 signaling and receptors

CXCL12 is a chemokine; a small signaling protein secreted by cells that dictate migration and activation of other cells [15]. Chemokines are differentiated from other cytokines by their size and structure. They are small, approximately 8–10 kDa, and form specific 3D configurations based on highly conserved cysteine residues which categorizes them into four subfamilies: CXC, CC, CX_3C, and C [15]. Signaling is mediated through trans-membrane G-coupled protein receptors (GCPR) expressed in many organ systems throughout the body [16]. There are approximately 20 known chemokine receptors divided into 4 subfamilies and upon binding the receptor-ligand complex undergoes conformational change resulting in downstream effects through the release of signal transducers G-alpha subunit, beta/gamma subunit, and phosphatidylinositol 3 kinase [17]. De-sensitization and down-regulation of receptors will occur with continued binding by endocytosis and receptor recycling [18]. Receptor recycling and down-regulation affects the signaling environment twofold. One, it decreases surface receptors available for binding, and two, it decreases available chemokine ligand through endocytic degradation [18]. This becomes important because aged individuals have chronically elevated cytokine levels which can lead to dysfunctional receptor-ligand dependent signaling.

CXCL12 belongs to the CXC family; originally isolated from murine stromal cells and known for its role in recruiting and activating leukocyte precursors [15,19]. Subsequent research has identified CXCL12 isoforms in human and other lower level vertebrates and allows CXCL12 to stands out among the chemokine family due to several unique characteristics [20]. First, the encoding gene is located on chromosome 10, a separate chromosome than other chemokines in its family, and the derived gene product is highly conserved across CXCL12 isoforms with greater than a 95% correspondence between counterparts [15,21]. Additionally, while most chemokines bind in a non-specific manner, CXCL12 is specific to seven-transmembrane G-coupled protein receptor CXCR4. Like CXCL12, CXCR4 is highly conserved and CXCL12 is its cognate agonist ligand, however, ubiquitin has recently been recognized as a non-cognate ligand [22,23]. Additionally, CXCL12 has been found to interact with an atypical 7-transmembrane chemokine receptor, CXCR7 [24,25]. While related to the GCPR member it lacks the ability to normally bind to G proteins – hence it was reclassified as an atypical cytokine receptor, ACKR3 [25,26]. CXCR7 binds CXCL12 with high affinity and signals through the β-arrestin2 signaling [25,26]. Though limited signaling function, CXCR7 binds CXCL12 with high affinity and may play a role as a decoy receptor binding free CXCL12 and affecting the CXCL12 microenvironment [27]. Therefore, the main physiologic function of CXCL12 is through CXCR4 [28].

Gene splicing produces six different variants of CXCL12. CXCL12-α and CXCL12-β are the two most abundant and are identical except for the additional 4 amino acids at the C-terminus of CXCL12-β [21].

Notably, these additional amino acids facilitate glycosaminoglycan-dependent stabilization in vascular tissues such as the bone marrow. The increased number of AA increases the stability of CXCL12-β, and therefore, its effectiveness in bone marrow remodeling when compared to CXCL12-α [29]. This finding makes it important in bone homeostasis and this, along with CXCL12/CXCR4 conserved genetic nature, supports a physiologic role distinct from other chemokines; making CXCL12 an exciting topic of targeted research [23].

3. CXCL12 bone homeostasis

The biologic role of the CXCL12/CXCR4 axis has advanced since its discovery and supports CXCL12 as key regulator in embryonic development, physiologic, and pathologic processes [15]. Genetic knockout experiments revealed it is vital role in the development of multiple organ systems and mice lacking CXCL12 or CXCR4 were non-viable secondary to abnormalities in vasculogenesis, cardiogenesis, myelopoiesis, and neurogenesis [8,15,30,31]. CXCL12 is highly expressed throughout the bone marrow and is particularly important in the musculoskeletal system through cell localization. Hematopoietic and mesenchymal progenitor cells, essential for bone homeostasis, require CXCL12 for localization, retention, survival, and early development [12,32]. Progenitor cells are recruited to niches in the bone marrow where they mature to the primary cells of bone forming (osteoblast) and bone resorption (osteoclasts).

Osteoclasts (Oc) originate from the monocyte-macrophage lineage of hematopoietic progenitor stem cells (HPSC), recruited from the bone marrow or the peripheral circulation [33]. Maturation to Oc is regulated by receptor activator of NF-kB ligand (RANKL) and Osteoprotegerin (OPG). RANKL binds RANK receptor on Oc precursor and the receptor-ligand complex stimulates maturation; while OPG, a soluble RANKL decoy receptor, acts in opposition by binding and decreasing free RANKL levels [34]. Mature Oc fuse into large multinucleated cells that dissolve bone through secretion of hydrogen ions and collagenases. CXCL12 main role in this process is the recruitment of pre-Oc cells. CXCR4 is highly expressed on pre-Oc cell lines and upon interaction with CXCL12 they are recruited into specific bone marrow niches for Oc development [12]. A study of pre-Oc development found CXCL12 promoted chemotactic recruitment of pre-Oc cells through CXCR4 interaction and following recruitment, RANKL promoted maturation into Oc. Further analysis found RANKL alone did not promote recruitment and in addition, levels of receptor CXCR4 were downregulated as Oc cells matured [35]. Together, these findings suggest that CXCL12 works in a complementary fashion to RANKL through cell recruitment but as maturation begins to take place; CXCL12 is not involved. CXCL12 also acts indirectly through regulation of matrix metalloprotease (MMP) [35]. MMPs are required for transmigration of pre-Oc from circulation to marrow and exposure to CXCL12 revealed upregulated levels of MMP-9 in pre-Oc cells [36]. Likewise, CXCL12 and CXCR4 interaction stimulated additional molecules required for transmigration including integrin LFA-1, VLA-4, and VLA-5 [37]. These findings support CXCL12 role in Oc development and because osteoporosis involves increased bone resorption it is reasonable to believe that CXCL12 might play a role.

Osteoblasts, the principle cell of bone formation, originate from mesenchymal stem cells (MSC). Similar to Oc, MSCs are recruited to their target location through a microenvironment of chemical signals including CXCL12 and its receptor CXCR4. MSCs are multipotent stem cells implemented in the differentiation of bone, cartilage, fat, tendon, and muscle. Therefore, MSCs are particularly important because they are essential in the scaffolding that supports the different tissue groups of the musculoskeletal system [38–40]. Furthermore, as osteoblast precursors, they are the cornerstone of bone growth and remodeling. Osteoblast deposit collagen, osteocalcin, and catalyze mineralization of bone via alkaline phosphatase (ALP), while also influencing osteoclastic bone resorption through paracrine signaling and RANKL secretion. Finally, there is an interplay between MSC and HPSC, and MSC activity is believed to support the development of HPSCs the precursors of osteoclasts, blood products, and cells of the immune system [41–43]. CXCL12 impacts the migration, growth, survival, and differentiation of MSC. Migration is the downstream effect of CXCL12/CXCR4 binding on the surface of progenitor cells [44,45]. CXCL12 is highly expressed by vascular endothelial cells, immature Ob, and bone marrow stromal cells which serve as beacons for cell localization [12,34,46]. Loss of the CXCL12/CXCR4 interaction results in failure of chemotaxis and is illustrated in CXCL12/CXCR4 genetic knockout mice who lack development in many organ systems including the muscle and bone marrow [31,46]. The response of human MSC to 16 different chemokines and growth factors (GF) found that CXCL12 was one of three chemokines to reach significant chemotactic activity [47]. Additionally, flow cytometry showed the only CXC chemokine receptor present on MSCs was CXCR4, and it was found in high levels [47]. Therefore, while MSCs are under the influence of many GFs and chemokines, these studies support that CXCL12 has a significant role in migration of MSCs when compared to others.

Following chemotactic transmigration, immature MSCs must undergo osteogenic differentiation into osteoblasts for bone formation. CXCL12 is thought to be involved in this process as well, specifically, in the earlier stages of differentiation. It is known that immature MSCs secrete a greater amount of CXCL12 when compared to differentiated osteogenic cells [32,44]. Use of cell markers distinct to specific levels of pre-Ob differentiation allows for this comparison. One marker, ALP, is an enzyme required for bone mineralization and therefore, ALP expression can be used to identify differentiated osteogenic cells. Conversely, cell marker STRO-1, is known to immature MSCs [48]. When compared, cells expressing ALP exhibited decreased CXCL12 production compared to those expressing STRO-1 [32]. In support, Shi et al [49] found CXCL12 expression was increased in the perivascular regions of the bone marrow, whereas, near the bone's surface, an area of osteogenic mature cells, exhibit lower expression. Together these finding indicate CXCL12 works to recruit an immature, non-differentiated, MSC population in the deep perivascular areas of bone marrow when new growth is needed; yet, towards the end of osteogenic differentiation CXCL12 expression is downregulated [32]. In one experiment, MSCs were exposed to an osteogenic medium plus CXCL12 and compared with MSCs in an osteogenic medium alone. Cells in the CXCL12 medium demonstrated higher expression ALP supporting CXCL12 role in osteogenic differentiation [50]. Moreover, MSC proliferation studies showed that with higher levels of CXCL12 there was an increase in growth by total cell number in comparison to control. These cells showed increase resistance to apoptosis when exposed to apoptotic inducing cytokine IL-4 and decreased expression of pre-apoptotic surface cell marker annexin V [32]. Together, these finding suggest that CXCL12 is intricate in the early differentiation of pre-Ob MSC, but that its involvement decreases as cells advance in maturity. Therefore, if there is a disruption in CXCL12 cell signaling, decreased migration and differentiation may occur, and could predisposed to a decrease in number and viability of progenitor cells; a process observed in osteoporosis and sarcopenia [51,52].

4. CXCL12 in muscle

Musculoskeletal health not only depends on maintaining bone homeostasis, but also muscle homeostasis as the two are often connected and work synchronously [6]. Muscle is in a state dynamic homeostasis, a balance of regenerative and degenerative forces. Damage occurs regularly in normal muscle as a result of strong contraction in physical exercise, but repair typically follows. It is when regeneration cannot compensate for the damage, that pathological changes take place.

The regenerative stem cell of skeletal muscle is the satellite cell and its role as a myogenic precursor is well established [53]. Satellite cells are located between the surface of myofibril and the encasing basal lamina. They not only produce differentiated myoblasts, but also contain a self-restoring mechanism, where one daughter remains a satellite cell while the other differentiates into a myoblast [53]. In addition to satellite cells, non-muscle specific MSCs, also have myogenic potential and contribute to skeletal muscle growth [54]. Following pathologic or mechanical damage, there is upregulation of cytokines and growth factors that aid in the proliferation and differentiation of muscle precursors. CXCL12 is one of these molecules known to be upregulated in time of muscle damage [55]. CXCL12 role is not fully understood but research suggests it is highly involved in activation and mobilization of both satellite cells and MSCs.

Satellite cells and MSC are both individually influenced by CXCL12. One well established role is influencing stem cell migration to injured tissue and is seen through transmigration assays of isolated soleus myoblasts exposed to CXCL12. Exposed myoblast showed a statistically significant increase in migration when compared to non-exposed controls [56]. Intramuscular CXCL12 injection also increased muscle regeneration in the soleus; resulting in higher muscle mass, lower levels of fibrosis, better tissue architecture and expression of muscle markers when compared with untreated controls [56]. It is thought muscle regeneration may be mediated by an increase in myoblast migration through an increase in MMP enzyme activity [36,56]. To support this, MMP expression was measured during myoblast migration and showed an increase in MMP activity in the CXCL12 group. Even more importantly, when CXCR4 was silenced, myoblast migration was greatly decreased highlighting the significance of CXCL12/CXCR4 axis on myoblast migration and regeneration [56].

In addition to MMPs, adhesion proteins are recognized for their role in skeletal muscle regeneration [57]. One adhesion protein in particular, CD9, a tetraspanin transmembrane protein, is critical to skeletal muscle formation [58]. Mice lacking CD9 are unable to regenerate skeletal muscle and show formation of dystrophic myofibers [59]. Therefore, CXCL12 influence on adhesion protein levels could prove significant [57]. Brzoska et al [60] found there was indeed a relationship, and CXCL12 exposure increased CD9 expression both in vivo, during wildtype and Pax7$^{-/-}$ muscle regeneration, and in vitro MSC myoblast culture. Therefore, CXCL12, via CXCR4, up-regulates CD9 on both native satellite cell myoblasts and stem cells infiltrating injured muscle such as BM-MSCs and ESCs [60]. Additionally, and importantly, they found CXCL12 increased the ability of stem cells to fuse with the native myoblast, supporting a role in muscle regeneration. Other adhesion proteins such as FAK, a non-receptor tyrosine kinase, also have been increased by CXCL12. It might contribute to muscle regeneration through its involvement in anchoring integrins with actin cytoskeletons and increasing cell migration through extracellular matrix degradation via expression of MMP 2 and 9 [61]. Together these findings are noteworthy and may be used to enhance therapeutic fusion of transplanted stem cells in disease such as sarcopenia.

CXCL12 role in stem cell differentiation is not as well understood. Following stem cell recruitment differentiation from myoblast into skeletal muscle cells is seen through the expression of committed myogenic cell markers such as MyoD, MHC, and myogenin. There have been conflicting results in regard to CXCL12 role in stem cell differentiation [56,62,63]. Odemis et al [62] reported that CXCL12 exposure inhibited the differentiation of myoblasts as seen by decreased expression of mature myogenic markers MyoD, MHC, and myogenin [62]. A few years later, Melchionna et al. [63] reported the contrary, stating that CXCL12 exposure assisted in the differentiation of myoblasts and showed an increase in MHC concentration and myotube formation. Furthermore, silencing of CXCR4 inhibited the myogenic differentiation previously observed [63]. Later, Brzoska et al.'s [56] failed to support either finding seen in Odemis et al. [62] or Melchionna et al. [63]. They reported CXCL12 did not affect myoblast proliferation and only slightly inhibited myotube formation and in addition there was no observed change in the level of myogenic regulatory transcription factors [56]. The conflicting reports speak to the complexity of CXCL12 signaling and the need for further understanding of its role in myogenesis. These three studies focused on CXCL12 in satellite cell differentiation but CXCL12 role may be through other cells with myogenic potential, such as BM-MSC. A new study has shown that CXCR4 + BM-MSC when co-cultured in a satellite cell niche adopted myogenic identity through the expression of myogenic regulatory transcription factors and adhesion proteins express on satellite cells. Furthermore, the addition of CXCL12 greatly enhanced this process [64].

5. CXCL12 in osteoporosis

Aging is an inevitable risk factors for degeneration of the musculoskeletal system as peak bone mass is reached early in life followed by gradual decrease in bone quality as we age [5]. In addition, increased age leads to premature senescence of mesenchymal progenitor cells which hamper differentiation process [51,52]. As it is well known, CXCL12 is essential to mesenchymal stem cell migration and development; processes involved endochondral and interosseous bone formation, and therefore loss of these cells to might predispose to osteoporosis [65]. Our group previously co-related relation between circulating plasma CXCL12 levels and bone mineral density (BMD). In over 1500 patients results, our group found circulating plasma CXCL12 levels were inversely related to bone mineral density (BMD) in both men and women and that increased age was associated with elevated plasma levels of CXCL12 [66]. Yet, despite lower BMD, there was no association with osteoporotic fractures. These findings are interesting because seems to contradict the established notion that CXCL12 is involved in osteogenesis [67,68]. Since, CXCL12 is needed for recruitment, management, and establishment of bone precursors, the expected outcome was that higher CXCL12 levels led to increased, rather than decreased bone density. Our group [66] purposed several viewpoints as to why there might be such a discrepancy.

First, the elevation of CXCL12 was observed in the plasma and not in the bone marrow. Therefore, despite an elevated plasma level, it does not imply that bone marrow levels are also high. In fact, in murine and human bone marrow interstitial fluid, total SDF1 levels declined with age [52,69]. Increased inflammation leads to the premature senescence of MSC and chronic senescent cells secret pro-inflammatory cytokines and proteases which might degrade CXCL12 [70]. Such cells, referred to as "senescence-associated secretory phenotype" (SASP), have been associated with increased mortality and chronic disease like osteoporosis. Therefore, an increase SASP cells could decrease SDF1 levels in the BM [9]. Another thought is chronic inflammation might deplete bone marrow MSC storage because MSC migrate to areas injury. If there is injury in other parts of the body, MSC will migrate from the BM to such areas with increased inflammatory signals, ultimately depleting the level in the BM. In addition, elevation in plasma CXCL12 might not truly represent the operational level CXCL12. In other words, total CXCL12 might be elevated, but functional CXCL12, known to drive osteogenesis and MSC development, might be misrepresented on assays. Increased age is associated with increased proteolytic processing and therefore functional CXCL12 might be rendered non-functional [71]. Yet, despite the proteolytic change in functionality, CXCL12 molecules are still be able to targeted by antibodies used in ELISA testing to measure CXCL12 concentrations [72]. Therefore, plasma CXCL12 measured via ELISA may inflate the level of CXCL12. Decreased BMD in this population may also be due to a disruption in the osteogenic potential of bone marrow MSC in the elderly population. An analogous situation seen in endothelial and hematopoietic precursor cells where there is an age-related decrease in CXCR4 expression resulting in abnormal cell functioning and tissue repair [73,74]. Therefore, if a similar down-regulation takes place on bone marrow MSCs then osteogenic potential could be disrupted. Supporting this, Guang et al. [52] found that CXCR4 mRNA and protein expression declined with age in murine bone marrow MSCs. CXCR4 mRNA expression decreased by 45% and 68% at 15–18 months and 20–23 months when compared to mice at 3–6 months [52]. Furthermore, they reported a 4.8x and 6.2x increases in ALP and OCN markers of osteogenic differentiation in young mice compared to elderly mice and levels of CXCL12 were found to be decreased in the aged population [52]. Together these findings support the hypothesis that down-regulation of CXCR4 negatively influences the ability to maintain the bone in an elder population.

CXCL12 is also linked with osteoclast recruitment; therefore, increased plasma levels could increase bone breakdown and decrease BMD, increasing the risk for osteoporosis [12,36]. One pathway is through estrogen activity. Increased osteoclast activity in post-menopausal women is one of the most well-known risk factors for osteoporosis. Recently, research has linked a relationship with estrogen and CXCL12 that might contribute to the increased osteoclast activity. Ucer et al. [75] reported that estrogen attenuates the expression of CXCL12 in MSC. TRAP+ expression, a marker of osteoclast activity, was attenuated in cultures exposed to an CXCL12 antibody and additionally, recombinant CXCL12 stimulated osteoclast formation in cultures [75]. Together these findings suggest the loss of estrogen results in decreased inhibition of CXCL12 induced osteoclast activity. CXCL12 and osteoclasts may also work in a concentration dependent manner as demonstrated by Wright et al. [12]. High levels of CXCL12 showed an inhibitory effect of on osteoclast differentiation when compared to lower levels [12]. Therefore, while it seems logical to equate increased CXCL12 levels, to increased osteoclast activity, and therefore bone resorption, the process is complex and not well understood.

Our published data demonstrated that CXCL12 expression is decreased in the aged BM environment of both mice and humans [76]. Such an age-related decrease may play a role in the development of pathological conditions due the differentiation potential of MSC. We also reported that miRNA-141-3p, has a major impact on CXCL12 levels in the BM. miRNAs are small non-coding RNAs that can modify expression of certain molecules such as CXCL12. We found that miRNA-141-3p inhibited CXCL12, BMP-2, and RUNX-2 in both human and mouse bone marrow MSCs suggesting anti-osteogenic properties [76]. MiRNA-141 are found to be up-regulated with increased age and can contribute to the premature senescence of cells and thought to be due to increased oxidative stress associate with aging [77,78]. Together ours data suggest the down-regulation of CXCL12, via miRNA-141-3p, seen in aging can contribute to the bone related pathology.

6. CXCL12 in sarcopenia

Sarcopenia is an age related progressive and generalized loss of muscle mass associated with impaired muscular function [2]. It effects activities of daily living and contributes to increased morbidity and mortality through increased frailty and fall risk. As aging occurs sarcopenia and osteoporosis often overlap because bone and muscle are interconnected mechanically, chemically, and metabolically [3,79]. As a result, the term osteo-sarcopenia has been proposed to describe those with concurrent disease [2,80,81]. CXCL12 has been implemented in both of these processes due to its effect on muscle satellite cells and MSCs. Similar to osteoporosis, sarcopenia, accompanies a population of increasing age and as a result stem cell functionality is progressively decreased [82,83]. One mechanism involved is the modulation of STAT3 signaling by CXCL12. STAT-3 is a transcription factor that mediates cytokine and growth factor signaling and has been reported to promote satellite cell progression into a myogenic lineage. It is activated by Interleukin-6, an inflammatory molecule elevated in damaged, senile muscle cells. As described previously satellite cells have the potential to produce differentiated myoblasts, but also contain a self-restoring mechanism [53]. Chronic stimulation of STAT3 by IL-6 is reported to favor the myogenic lineage over satellite cell self-renewal [84]. Therefore, if chronic stimulation continues, it may deplete the pool of satellite cells and result in decreased regenerative ability. Yet, in contrast, inhibition of STAT-3 results in increased regenerative ability and muscle repair. Satellite cells cultured with CXCL12 displayed no detection of STAT3 expression a result indicating that CXCL12 abolished STAT3 signaling in muscle satellite cells. Therefore, CXCL12 could reduce constitutive activation of STAT3 and diminish the development of sarcopenia in these patients through maintenance of satellite cell self-renewal.

The same study found that CXCL12 influenced Pax-7 expression on muscle satellite fibers [85]. Pax-7 is well known to be critical to muscle fiber development. Studies of mice with knockout $Pax7^{-/-}$ reported reduced growth and marked muscle wasting together with a complete absence of functional satellite cells [86]. Therefore, increased levels of Pax-7 expression would be beneficial to muscle regeneration. To support this, two groups of mice were compared in response to muscle injury. One group was administered CXCL12 prior to injury while the other group was not. Interestingly, the group exposed to CXCL12 showed regeneration with a significantly higher PAX7 level than the wild-type group [85]. In addition, MyoD, a myogenic regulatory factor essential for myogenic differentiation, was also increased in the CXCL12 group [85]. Together these results support that CXCL12 is critical to maintain of muscle regenerative ability. Thus, levels of CXCL12 with age may be a contributing factor loss of muscle regeneration.

CXCL12 modification by miRNAs may also play a role in muscle homeostasis. MiRNAs are known be involved in skeletal muscle development, proliferation, differentiation and age-related pathology [78,87]. As mentioned previously miRNAs are increased in age populations secondary to increased chronic inflammation and oxidative stressors. Increased levels of miRNAs can result in the down-regulation of CXCL12 as seen in bone marrow stromal cells of mice and humans [76]. Concurrently, Kowalski et al. [64] showed that CXCL12 increased the myogenic commitment of interstitial bone marrow MSC and skeletal muscle regeneration. Together this data suggests that miRNA down-regulation of CXCL12 may decrease the regenerative ability of skeletal muscles and may contribute to the development of sarcopenia, yet, to our knowledge, there are no known studies making a direct connection. The fat/bone axis of aged patients described previously may play a role in sarcopenia patients. Because MSCs have myogenic potential a similar microenvironment could contribute to increase fat build up in the muscles.

7. CXCL12 regulation in inflammatory disease (osteoarthritis and rheumatoid arthritis)

Just as aging is associated with elevated serum concentration of inflammatory cytokines, chronic inflammatory conditions of the musculoskeletal system, such as osteoarthritis (OA) and rheumatoid arthritis (RA), also exhibit increased concentration of inflammatory factors. OA is the most common form of arthritis and affect millions of people worldwide. It is a degenerative joint disease, in which abnormal regulation of oxidative and inflammatory molecules leads to cartilage degradation, synovial inflammation, subchondral bone thickening, osteophyte formation, and ultimately joint failure [88]. RA is thought to be autoimmune in nature but the underlying mechanism is not fully understood [89]. It is characterized by inflammation of the synovial membrane that results in hyperplasia and neoangiogenesis of the synovium. The ensuing hypertrophic synovium, or pannus, releases inflammatory mediators that lead to the devastation of surround bone and cartilage in the involved joint [89,90]. Though OA and RA have different onset and pathophysiological mechanisms, studies have shown CXCL12 plays a common role in the disease's signaling pathways [91–95].

Within the synovium of patients with OA and RA, it has been reported that CXCL12 levels are increased by 3.75 fold in OA patients and 10.71 fold in RA patients when compared to control [96,97]. The amplified CXCL12 gradient increases recruitment of CXCR4+ inflammatory cells into the joint space. This leads to further joint destruction through CXCL12 mediated expression of damaging proteins, such as MMP-1,3,9, and 13 [97–99]. In further support, removal of the synovium, via synovectomy, decreases CXCL12 levels and thus MMP-9 and MMP-13 in patients with OA and RA [99]. Moreover, patients with anti-cyclic citrullinated peptide (anti-CCP) positive rheumatoid arthritis where found to have higher expression of CXCL12 than those patients with anti-CCP negative RA which correlated with a higher level of joint destruction [95]. In OA, CXCL12 also has been shown to be associated with osteophyte formation and bone erosion, two cardinal features of the disease, through its effects on stem cell homing and differentiation [100,101]. These studies assist in displaying the importance of CXCL12 in the musculoskeletal system as a whole. OA and RA are two significant diseases that inhibit millions of people worldwide, and thus, they remain at the forefront of musculoskeletal research. Therefore, the breadth of information regarding CXCL12′s function in arthritic pathophysiology is immense, and to cover the topic thoroughly, would go beyond the scope of this review. Yet, it is important to reference these topics as arthritic processes are often seen in conjunction with osteoporosis and sarcopenia.

8. Therapeutic application

CXCL12 influence in the stem cell recruitment, localization, maintenance, and development in the musculoskeletal system makes it an exciting topic in tissue engineering and stem cell therapy. MSC have been used in clinical studies to repair and regenerate damaged bone and have showing promising results [102]. Concurrently, the pathological mechanisms behind age associated degenerative diseases, including osteoporosis and sarcopenia, have been connected to dysfunction of stem cell viability and differentiation [51,52,84]. Therefore, the application of CXCL12 as a potential target in improving regenerative stem cell therapy in these diseases may prove beneficial. Therapeutic strategies involving CXCL12 have emerged to provide more effective treatment options and include the use of multipotent stem/progenitor cells and biomaterials through the manipulations of musculoskeletal signaling pathways.

Transplantation of bone marrow MSCs into tissue hold great promise for stem cell regeneration therapy. Yet, widespread commercial use is limited due to drawbacks including malignant transformation, insufficient culture systems to provide adequate MSC population, and controlling cell fate following application [103]. One major challenge is failure of the donor cell to survive long enough to incorporate into tissue. Poor survival of transplanted cells is thought to be due to forces including hypoxia, free radical oxidation, and lack of proper nutrients resulting in cellular apoptosis. CXCL12 is an attractive topic in tissue engineering because it has displayed the ability to positively impact donor cell fate after administration. Interestingly, MSCs exposed to high levels of CXCL12 displayed an increased capacity for cellular growth, protection against apoptosis, and increased survival of transplanted MSC [32,104]. Moreover, Yin et al [105] found that following CXCL12 administration degradation of the mitochondrial membrane and subsequent release of cytochrome *c*, both potent triggers of apoptosis, were significantly inhibited. These findings indicate how CXCL12 can be used to enhance current stem cell treatment and tangible advances include the development of genetically engineered MSC that conditionally express CXCL12 [104]. When transplanted engineered MSCs prevented apoptosis and showed increased survival during in vitro analysis.

CXCL12 also indirectly improves stem cell survival through increased angiogenesis [106]. Increased vascularization improves tissue oxygenation, decreases free radical formation, while removing waste and supplying nutrients; all processes linked to increased MSC death. Therefore, improving vascularization increases the survival of MSC and is vital to the development of bone and muscle. Local expression of CXCL12, released in areas of ischemic injury, can accelerate revascularization in vivo through a VEGF/eNOS-related pathway [107]. One interesting therapeutic application is through reactive oxygen species (ROS) sensitive nanoparticles filled with CXCL12. When exposed to high levels of ROS, such as ischemic or injured tissues, the nanoparticles are triggered to release high levels of CXCL12 which has shown to improve re-vascularization in mouse models [108]. Because osteoporosis and sarcopenia are associated with decreased MSC viability, and viability is tied to increased inflammation and oxidative stress, this could have therapeutic potential in bone and muscle damage.

In addition to increased cell survival, CXCL12 determines cell fate through collaboration with musculoskeletal cell regulators while enhancing localization of transplanted cells. BMP-2 has been assessed in many clinical trials for its function in bone formation because of its well-established role in osteogenesis [109–112]. However, reports have shown the level of BMP-2 required for therapy is associated with harmful side effects such as ectopic bone formation [113]. Therefore, efforts have been made to remedy associated side effects of BMP-2 therapy and one promising approach has been CXCL12 enhancement of BMP-2 induced osteogenesis. Co-administration of CXCL12 with recombinant BMP2 provides a synergistic effect, allowing lower levels of BMP-2 to be used while still achieving optimal bone induction. An interaction that negates the unwanted consequences of high levels of BMP-2 therapy. Our group previously co-administration CXCL12 with 0.5 μg BMP-2 resulted in an equivalent level of bone formation as 5.0 μg BMP-2 without side effects [114]. CXCL12 augmentation of BMP-2 function is further enhanced indirectly through CXCL12 role in MSC localization. A recent study illustrated CXCL12 ability to localize using CXCL12 and BMP-2 loaded microspheres in repair of rat cranial defects [115]. The microspheres were designed to induce a sequential and continuous release of CXCL12 followed by BMP-2. Shen et al. [115] hypothesized the stepwise release would first recruit MSC to the site of injury through CXCL12, and subsequently, BMP-2 release would induce MSC bone formation. Results indicated step-wise release increased bone regeneration, completely bridging the site of injury, when compared to simultaneous release. These findings suggest that CXCL12 homing increases the number MSC available for osteogenic differentiation; if more cells are recruited, more cells undergo differentiation, and the result is enhanced bone formation. Importantly, BMP-2 potency is still improved by CXCL12 because CXCL12 is continuously released allowing for their synergistic relationship.

CXCL12 embedded microspheres are an example of biomaterials developed to enhance musculoskeletal repair. Implantation of microspheres or membranes laden with signaling molecules allow cell recruitment and repair to take place at a specific site of injury [116]. It utilizes the idea of guided bone regeneration, where signaling molecules, like CXCL12, promote bone growth via interacting with human stem cells [117]. Highlighting CXCL12 addition to this field, Ji et al. [118] used CXCL12 enriched PCL/gelatin membranes in repair of rat cranial defects. Results demonstrated the CXCL12 embedded membrane led to a 6-fold increase in total bone formation when compared to bare membrane controls [118]. These findings are significant because the use of guided bone regeneration and biomaterials allow a bone engineering mechanism that enhances the body's own regeneration capacity to fill osseous defects without the use of transplanted stem cells, thus, avoiding the potential side effects of stem cell transplantation like malignant transformation [119]. CXCL12 cell localization ability therefore helps advance a biomaterials and guided bone regeneration as a promising field in localized lesions. Yet, in regard to osteoporosis and sarcopenia, such therapies may not be as applicable. These diseases are associated with more generalized, diffuse, tissue damage and would be more susceptible to more systemic treatments.

Pretreatment of CXCL12 in cells also leads to the up-regulation of CD9 and MMPs crucial to developing muscle and bone. CD9 is an adhesion protein found to enhance fusion of satellite cell myoblasts and MSCs in skeletal muscle regeneration [60]. This idea has been utilized in experiments and pretreatment of stem cells with CXCL12 leads to increased fusion with myoblasts in vitro, a process that could be applied to stem cell engraftment into damaged tissues. Similar to CXCL12 increase of CD9, CXCL12 also up-regulates MMPs affecting both muscle and bone through migration and development of myoblast precursors and osteoclasts [36]. Therefore, pretreatment may also increase engraftment potential through enhanced migration of myoblast in damaged muscles [56]. This has been demonstrated by local delivery of CXCL12 in a severe rotator cuff injury model. Results showed, muscles treated with CXCL12 had significantly reduced levels of inflammatory molecules while also increased levels of MSC when compared to controls [120].

CXCR4 dependent increased osteoclast activity may also be an interest of therapeutic target. CXCR4 is highly expressed on pre-Oc and are recruited to target sites following the binding of CXCL12. There they can undergo Oc maturation and contribute to bone resorption [36]. Therefore, blocking CXCR4 could theoretically decrease osteoclast activity and reduce bone loss. One CXCR4 antagonist is AMD3100 and has been studied for as potential target for osteoporosis therapy because it can decrease osteoclast recruitment. A postmenopausal model of osteoporosis, mice that had undergone oophorectomy, looked at bone loss in mice treated with AMD3100 compared to a control [121]. The AMD3100 group showed decreased bone loss on micro CT compared to control, thought to be due to a reduction of osteoclast number onto bone surfaces. These findings might be a potential alternative treatment for osteoporosis as effects are more systemic. In contrast to CXCR4 inhibitor, an osteoporotic rat model showed that CXCR4 overexpression improved stem cell migration in vitro [122]. MSCs were found to migrate towards CXCL12 significantly slower in osteoporotic mice and aged mice compared to younger mice. When CXCR4 was overexpressed, migration rate towards CXCL12 improved significantly, suggesting that CXCR4 overexpression could be used to increase MSC migration in osteoporosis fracture to improve fracture healing [122]. It is well known that osteoporotic patients have poor facture healing rate.

Another important therapeutic target related to CXCL12 is controlling its proteolytic breakdown [123]. CXCL12 possesses a very short half-life, and its N-terminus is cleaved by dipeptidyl peptidase 4 (DPP4) within minutes of its release [104,124]. The produced cleaved CXCL12 does not signal through CXCR4 but retains most of the CXCR7-mediated signaling [125,126]. While scientific literature generally overlooks cleaved CXCL12 contribution to CXCL12 biological activity, our group recently showed that contrary to intact CXCL12, cleaved CXCL12 inhibits MSCs ability to migrate or differentiate into osteoblasts and induces senescence of MSCs [127]. Complicating this problem, commercially available antibodies cannot differentiate between intact and cleaved CXCL12, and usually both are quantified as total levels of CXCL12 [72]. Cleaved CXCL12 acting as an antagonist to intact CXCL12 could explain the reported contradicting effects of CXCL12 on both osteoclast and myoblast differentiation. Since DPP4 enzyme inhibitors are commonly used in the clinic as anti-diabetic drugs, it is essential to characterize any beneficial or side effects they might have on bone and muscle in aged population.

MicroRNAs have gained recognition for their role in regulating CXCL12 levels in an age dependent manner. miRNAs, specifically, miRNA-141-3p, are found to be up-regulated with increased age and can contribute to the premature senescence of stem cells, decreased levels of CXCL12, BMP-2, and RUNX-2 [76]. This is important because both osteoporosis and sarcopenia are age related diseases, and therefore, up-regulation of these micro molecules could be contributing to degenerative loss of bone and muscle. In theory, antagonists to miRNA-141 could be used a therapeutic agent in relation to age related musculoskeletal disorders and warrants future research.

9. Conclusion

Research has validated the CXCL12/CXCR4 axis is fundamentally integrated in the development and maintenance of the musculoskeletal system through the recruitment of multipotent MSCs for bone and muscle regeneration. Furthermore, experiments have linked alterations in the CXCL12 axis to increasing age and various mechanisms involved in the pathology of osteoporosis and sarcopenia including MSC migration, angiogenesis, inflammation, and apoptosis. In addition, novel studies have recognized a significant inverse relationship between plasma CXCL12 and BMD in the aged population. Therefore, CXCL12 role in the development of age-related disease is conceivable, yet, the complexity of pathways involved suggests there are many contributing factors and a cause and effect relationship cannot be established, but merits further research. There is good evidence that CXCL12 has advanced the development of therapeutic modalities applicable to bone and muscle repair. Currently, use of CXCL12 is aimed at enhancing acute, localized, injury repair which is helpful in patients with age related diseases because of their increased risk of injury. Yet, due to the diffuse degeneration associated in these disease processes, further research is needed in potential systemic applications, such as miRNA and CXCR4 modification. Moreover, additional in vivo and human models are needed to better understand CXCL12 relation to osteoporosis and sarcopenia as the majority of studies are now performed in vitro and in murine models.

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Declaration of Competing Interest

The authors also declare that there is no other conflict of interest regarding the publication of this manuscript.

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