The role of PGRN in musculoskeletal development and disease

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1. ABSTRACT

Progranulin (PGRN) is a growth factor that has been implicated in wound healing, inflammation, infection, tumorigenesis, and is most known for its neuroprotective and proliferative properties in neurodegenerative disease. This pleiotropic growth factor has been found to be a key player and regulator of a diverse spectrum of multi-systemic functions. Its critical anti-inflammatory role in rheumatoid arthritis and other inflammatory disease models has allowed for the propulsion of research to establish its significance in musculoskeletal diseases, including inflammatory conditions involving bone and cartilage pathology. In this review, we aim to elaborate on the emerging role of PGRN in the musculoskeletal system, reviewing its particular mechanisms described in various musculoskeletal diseases, with special focus on osteoarthritis and inflammatory joint disease pathomechanisms and potential therapeutic applications of PGRN and its derivatives in these and other musculoskeletal diseases.

2. INTRODUCTION

The “isolation and characterization of a novel class of leukocyte peptides with possible cytokine-like activities called granulins” were first researched in 1990 (1). “Granulins” were initially found in inflammatory cells and bone marrow. Within the following two years the intact structure was coming into a clearer view by presenting the structural composition of its domains (2). Progranulin (PGRN), a 593-amino-acid autocrine growth factor, also known as GP88 (3), granulin epithelin precursor (GEP) (4), PC-cell-derived growth factor (PCDFG) (5), proepithelin (6), and acrogranin (7), contains seven-and-a-half repeats of a cysteine-rich motif (CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6CX5–6C) in the order P–G–F–B–A–C–D–E, where A–G are full repeats and P is the half-motif.

PGRN is heavily glycosylated and appears as a ~90-kDa protein, and when secreted undergoes proteolysis, leading to the release of its constituent peptides, the
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Figure 1. A Diagram depicting the structure of PGRN. TNFR binding domains and Sortilin binding motif are indicated.

Granulins (8). It consists of a subdomain shared by small toxins, protease inhibitors as well as the EGF-like protein modules (9). PGRN is digested into 6-kDa GRN peptides by many proteinases, including matrix metalloproteinase 9, 12, and 14, elastase, and proteinase 3, and ADAMTS-7 (10).

It has been known to interact with ADAMTS7, ADAMTS 12 (11), COMP, Perlecain (12), HDL/apo A–I (13), TLR 9 (14), Sortilin (15), and its most significant anti-inflammatory functions can be attributed to its direct inhibition of TNFa through interaction with TNFR1 and especially TNFR2 (16). (Reference protein interaction chart from “cubic of I review” (17)) (Figure 1).

Due to the pleiotropic nature of PRGN, it is highly expressed in a broad range of cells including, epithelial cells (18), neurons (19), and macrophages (20), immune cells (21), chondrocytes, adipose tissue (22), hematopoietic cells, including neural stem cells (23), skeletal muscle (24), endothelial cells (25), as well as lung parenchyma, where it has been known to counter the pneumotoxic effects of LPS induced ARDS (26). PGRN has also been implicated in a wide variety of biological processes, including wound healing (27), embryo development (28), morphogenesis (29), and cancer (30). PRGN overexpression has been found to be associated with cholangiocarcinoma (31), sarcoma (32), glioblastoma (33) and both ovarian and breast cancer (19). PGRN knockout models however, have presented with rheumatoid arthritis, osteoarthritis, and frontotemporal lobar degeneration (FTLD) (34), implicating its intricate protective role in various diseases of inflammatory etiology (35).

Progranulin’s role and function have been indeed, widely studied throughout the systems, with implications of its anti-inflammatory properties in rheumatoid arthritis (36), cardiovascular pathology, mainly atherosclerosis (20), autoimmune disorders, and it has also been found that PGRN may act as a prognostic marker in breast cancer (37). It influences the prevention of muscle-atrophy (38), and its neurotrophic and neuro-protective characteristics have been vastly researched in neurodegenerative diseases including frontotemporal dementia (39) (Figure 2). However, its protective, growth-promoting characteristics are of particular interest and significance in osteoarthritis and articular disease models (40).

Recently, it has been identified as a factor stimulating chondrogenesis, and is considered an important regulator of cartilage formation and function (41). PGRN is known to selectively interact with the COMP epidermal growth factor repeat domain. Progranul overexpression can stimulate chondrocyte proliferation, which is then enhanced by COMP (42). Progranul’s ability to influence chondrocyte differentiation is mediated through the extracellular regulation of the kinase (Erk) 1/2 signaling pathway and Jun B transcription factor (43). Its chondroprotective nature manifests in its ability to directly bind to ADAMTS-7 and ADAMTS-12 and inhibit their degradation of COMP (44).

Progranulin with its specific binding and key regulation of the TNFαs signaling pathway, through binding to TNFR receptors, competitively inhibits TNFα-induced ADAMTS-7 and ADAMTS-12 expression, and prevents COMP degradation by ADAMTS-7 and ADAMTS-12 through direct protein–protein interactions. Also, it has been well established that PGRN activates ERK and PI3K/ AKT pathways in several types of cells, such as chondrocytes (43).

In this review, we will present an updated review of the functions of PGRN in the musculoskeletal system by looking at its effects in osteo-degenerative and inflammatory pathology and other select musculoskeletal diseases presented in the literature.

3. FUNCTION OF PGRN IN THE MUSCULOSKELETAL SYSTEM

3.1. PGRN in chondrocyte and cartilage metabolism

PGRN plays a definitive role in regulating the equilibrium of the ECM by protecting functionally intact cartilage and preventing the degradation of its integral components (45). This function is considered to be vital in determining articular disease progression of both inflammatory and degenerative etiology, and constitutes a “balancing mechanism”, the curtailing of which provides a preventative method for the progression of chondrodegradative and osteoarthritic changes of articular surfaces. PGRN is a key signaling molecule at the onset of the pro-inflammatory cascade which prevents the degradation of COMP by inhibiting TNFα-induced ADAMTS-7 and ADAMTS-12 expression and cleavage of COMP (11), acting thereof, to entirely disrupt the breakdown of the pathology-stricken cartilage matrix. Also, PGRN directly binds to the cartilage oligomeric matrix protein (COMP), thereby exuding its salvaging role of this essential collagen-binding, structurally stabilizing component of the ECM (42, 46), and simultaneously prevents its degradation which otherwise would have led to the morphological and clinical exacerbation of arthrosis (47).
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In a previous study, it has been established that ADAMTS-7 overexpression leads to increased expression of TNF and metalloproteinases which promotes the breakdown of the ECM and consequent OA. Through signaling by NFκB, this patho-mechanism is further enhanced by TNF’s direct induction of ADAMTS-7 expression, which constitutes a positive feedback loop contributing to accelerated degeneration of cartilage and osteoarthritic transformation of the joint (48, 49). PGRN has the ability to intervene in this process as the dominant and rate limiting mediator by acting directly on TNF receptor signaling to inhibit this biofeedback mechanism altogether.

The significant chondroprotective role of PGRN is further substantiated by evidence showing that the overexpression of PGRN stimulates the proliferation of chondrocytes and this stimulation is enhanced in turn by the effects of COMP (42). A preliminary in vitro study of cartilage explant cultures of human chondrocytes has shown that both PGRN and the PGRN engineered derivative, Attstrin (50), were effective in inhibiting the release of TNFα-induced inflammatory and catabolic mediators, including MMP13, RUNX2, COX-2, and iNOS, in human osteoarthritis chondrocytes, and in exuding its chondro-proliferative effects and stimulating the anabolic metabolism, including the synthesis of ECM integrating components, such as Collagen 2 and Aggrecan (Zhao and Richbourgh et al. unpublished data).

PGRN exhibits its chondro-regenerative characteristics by acting as a downstream molecule of bone morphogenetic protein 2 (BMP-2) in cartilage repair (47). Also, PGRN activates chondrocyte differentiation through Erk1/2 signaling and JunB transcription factor is one of key downstream molecules of PGRN in chondrocyte differentiation (43). The intricate interplay of these stimulatory and promoting mechanisms of PGRN as well as its anti-inflammatory properties inarguably makes it an essential regulator of cartilage metabolism, the presence of which maintains the integrity of the structural matrix and at the onset of osteo-degenerative processes, could act as a preventative agent for the progression of disease.

3.2. PGRN in bone formation and bone remodeling

PGRN’s role in the process of bone development and healing by means of endochondral ossification indisputably lies in its regulatory function of chondrogenesis, however, its most noteworthy properties can be found in its ability to induce osteoblastogenesis. PGRN assists in the initiation of the process of bone healing and development by, at least in part, triggering the proliferation of osteoblasts, creating the trabecular matrix for structurally integral bone (1).

Progranulin is induced by bone morphogenic protein 2 (BMP-2) and is required for BMP-2 mediated ectopic bone formation (51). BMP-2 is a growth factor that has been shown to induce bone formation, and has been used clinically to treat bone fractures (51). In the presence of high levels of TNF-α induced by a local or systemic inflammatory process, it has been established that bone formation and regeneration are decelerated and impaired by inhibiting BMP-2 signaling (52, 53). It is also known that the process of bone resorption is signaled via TNFR1 (54). Hence, PGRN’s known interaction with both TNFR 1/2 may serve as an important regulator in bone metabolism, allowing for stimulation of osteoblastogenesis and bone formation as a downstream mediator of BMP-2 signaling, and the prevention of osteoclastogenesis and bone resorption through inhibiting TNF/TNFR signalin (51). PGRN is also important for endochondral ossification in bone regeneration and repair. A recent study has shown that PGRN increased cartilaginous callus formation in bone de novo synthesis by means of TNF signaling (51). In addition
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to the already mentioned anti-inflammatory properties of the PGRN-TNF receptor interaction, and its known regulation of rheumatoid arthritis (50). PGRN binds to TNFR2 to stimulate PGRN-mediated endochondral ossification (51).

PGRN has also been studied in the process of bone remodeling and has been found to prevent osteoclastogenesis, dramatically influencing the regeneration of bone in osteolysis models. Its significant effects on the regeneration of iatrogenically induced osteolytic lesions, presents its novel regeneration enhancing role by stimulating osteoblastic synthesis of new bone trabeculae (Zhao et al. unpublished data). The focus of these findings provides a promising potential therapeutic target in arthroplasty implant failure and aseptic loosening caused by implant-induced osteolysis and can be an eventual therapeutic target in complex cases of osteosynthesis including high-energy comminuted fractures with bone fragment loss.

PGRN’s osteoregenerative properties can also be applied to osteoporosis and osteopenia models constituting PGRN’s influence on both qualitative and quantitative structural bone loss. There is substantial evidence confirming the correlation of PGRN with estrogen and progesterone. Serum concentration levels of PGRN were noted to be augmented with increased circulating levels of estrogen and progesterone (55). Confirmatory findings have been presented in a study clearly depicting the up-regulation of PGRN by exogenously administered estrogen in the hypothalamus of newborn mice (56). Estrogen is a key regulator of bone mineral density and the direct positive feedback loop that it participates in with PGRN could provide a postulation to identify the mechanism by which PGRN maintains and enhances bone integrity. There has been a recent study providing substantial evidence that there is a direct and positive correlation between endogenous PGRN levels and the qualitative integrity of bone. Recent investigations have allowed for the visualization of PGRN’s role in the development of osteoporosis. A PGRN knockout ovarietomized mouse model has presented with increased osteoclastic activity, trabecular bone frailty and regions of demineralization conferring the osteoporotic phenotype (Tang et al. unpublished data).

PGRN’s influence on Vitamin D 25-OH metabolism is also worthy of note and has been studied in an obesity patient model (BMI>30). It has been found that osteopenic obese patients presented with higher circulating levels of IL-17, IL-6, TNFα and IL-4 and lower concentrations of IL-13, IL-10, and PGRN. Through a direct positive correlation, measured concentrations of IL-13, IL-10 and 25-OH vitamin D were increased and the concentration of TNFα and IL-17 were decreased, by raising the concentration of PGRN (57). The patients presented with a marked improvement of bone status by steadily increasing PGRN levels, hence further confirming PGRN’s vital function in osteoblastogenesis.

3.3. PGRN in skeletal muscle pathology

PGRN’s implications in the musculoskeletal system, also include its role as a critical mediator in skeletal muscle differentiation. PGRN is part of a regulatory feedback loop along with MyoD and JunB, where MyoD causes PGRN expression which is able to inhibit myotube formation, suppressing the process of myogenesis and in turn repressing JunB. By influencing myogenic differentiation, PGRN poses itself as a critical factor in regulating disease processes affecting functional muscular capacity (58). A PGRN mutation has also been found to correlate with several neuromuscular diseases, including amyotrophic lateral sclerosis and spinal muscular atrophy, in which denervation produces atrophy of myocytes with an abnormal quantity and functional ability of myogenic progenitor cells (MPC) (59).

It has been shown that PGRN is detectable within skeletal muscle tissue and is differentially expressed during the fusion of myoblasts to myotubes. MyoD, a muscle-specific transcription factor, regulates this differential expression of PGRN. Current research has shown that regulation of myogenesis is, at least partially, mediated by the transcription factor JunB (58). Murine studies have shown that PGRN promotes myotube hypertrophy by way of the PI3K/Akt/mTOR pathway (38).

Significantly, it was discovered that PGRN, JunB, and MyoD transcription factor form a regulatory loop, which acts in concert in the course of myogenesis. This regulatory feedback loop, in which MyoD induces PGRN expression, inducing JunB, appears to inhibit MyoD. MyoD induces PGRN, by binding to the specific sites within the 50-flanking regulatory region of the gene encoding PGRN. The action of PGRN, then, partially depends on JunB, since the silencing of JunB reverses the inhibitory effect of PGRN. Thus, PGRN as a MyoD- inducible growth factor acts as a novel regulator of myogenic differentiation. PGRN has the ability to inhibit myotube formation in vitro and has modulatory effects on muscle tissue development in vivo. The elucidation of PGRN’s role and molecular events involved in myogenic differentiation will better our understanding of normal muscle development and the pathogenesis of muscular diseases (58).

PGRN also acts in concert with IGF signaling exhibiting its myotrophic properties. Numerous in vivo and in vitro studies have demonstrated the critical role Insulin-like growth factor 1 (IGF-1), a signaling factor, plays in the regulation of postnatal muscle growth (60). In skeletal muscle, IGF-1 serves in a plethora of functions. Most notably, it stimulates myoblastic proliferation, regulating myoblastic differentiation, and promoting protein synthesis (61). The liver is the principal source of circulating IGF-1, however, several reports have also demonstrated the importance of locally produced IGF-1 in muscle growth. PGRN has the ability to circumvent IGF-1 signaling to stimulate muscle growth through myoblastic hypertrophy. PGRN can be used to mediate an adaptive strategy for sustaining partial muscle growth via the PI3K/Akt/mTOR pathway in the absence of IGF-1 signaling (38).
4. PGRN POTENTIAL THERAPEUTIC ROLE IN OSTEOARTHRITIS AND OTHER MUSCULOSKELETAL DISEASES

Progranulin’s main therapeutic properties are entailed in its role as a TNFR ligand and competitive inhibitor of one of the most critical immunological cascades which is responsible for the inductive patho-mechanism of a broad range of inflammatory diseases, including rheumatoid arthritis, ulcerative colitis and other inflammatory bowel diseases, ankylosing spondylitis, psoriasis, including pathologies spanning the cardiovascular system such as ischaemia-reperfusion injury (62), myocarditis, with the resultant progression of congestive heart failure (63) and can even be proposed as a potential target therapy in graft versus host disease, which has been shown to be triggered by TNFR1 mediated induction of TNFa (64).

Through its binding to TNFR1/2, via F-A-C GRN domains, as opposed to sole targeting of TNFα, as effectuated by current therapeutic inhibitors, such as adalimumab (Humira) (65, 66), Etanercept (Enbrel) (67, 68), infliximab (Remicade) (69, 70), it can intervene through selective receptor affinity, especially TNFR2 (71), and may simultaneously regulate and effectuate a broader range of therapeutic functions. The discernment of this binding specificity was recently established, by in turn, identifying the TNFR1 and TNFR2 binding domains required for interaction with PGRN. TNFR1 has been shown to bind with PGRN through its CDR2 and CRD3 domain, whereas, TNFR2 similarly strongly exhibits affinity for both of these binding domains (Jian et al, 2013). It has been shown that TNFα binding occurs through interaction with the CDR2 and CRD3 domains of TNFR (16). However, established binding specificity of PGRN through specific targeting of TNFR1 and 2, regulates a broader spectrum of functions especially imperative for targeting inflammatory processes in for instance, rheumatoid and osteoarthritis, and can specifically, as presented, target the induction of chondrocyte proliferation and bone regeneration presenting a potential for the enactment of complex therapeutic functions and may serve as a preventative measure for the progression of osteoarthritis at the onset of disease.

Worthy of note is PGRN’s interaction at the neutrophilic level which reduces the synthesis of ROS and regulates the oxidative burst response to the release of TNFα (62). The high expression of PGRN in the cytoplasm of neutrophils converted into GRNs by neutrophil- released elastase (10), accounts for PGRN’s significant role in the regulatory mechanism of acute inflammation processes. The later activated granulins promote the release of inflammatory cytokines, including IL-8 expression in epithelial cells to summon further recruitment of neutrophils and other mediatory cells to the inflammation site (72). The counter-regulatory mechanism of this promotion of inflammation can be found at the level of SLPI binding with PGRN thus inactivating PGRN conversion to GRNs by elastase (6).

It has been also established that PGRN plays a key regulatory role in acute (73) and chronic inflammatory processes involving the musculoskeletal system (17), and could play a role in the treatment of auto-immune and inflammatory conditions presenting with musculoskeletal manifestations. For instance, through its recently established expression in the endothelial cell and its induction of endothelial cell migration and proliferation mediating angiogenesis (25), and the coincidental presence of anti-PGRN antibodies found in autoimmune diseases such as granulomatosis and polyangiitis (45), it can be postulated that the administration of PGRN in such cases, may exhibit anti-inflammatory effects and prevent the exacerbation of clinical musculoskeletal and systemic symptoms of these and other auto-immune disorders.

Recently, the potentiation of the efficacy of PGRN’s therapeutic effects has been obtained by creating the engineered construct Attstrin, the antagonist of TNFα signaling, which selectively interacts with TNFR1/TNFR2, and consequently antagonizes TNFα and TNF/TNFR signaling (41). The application of this PGRN-derivative can act in a myriad of clinical conditions whose patho-mechanism involves upregulation and a disproportion of TNFα signaling and its resultant induction of inflammatory processes, including but not limited to neuro-degenerative and inflammatory diseases, Crohn’s disease (74), IBD (75), and ulcerative colitis (76), asthma (77), dermatitis and psoriasis (78), and rheumatoid arthritis (79). Attstrin’s effects have been studied in rheumatoid arthritis (50) and dermatitis models (27), and its clear signaling interception and competitive inhibition of TNFα via TNFR1/2 binding proposes it as a highly promising therapeutic target for the prevention of inflammatory diseases affecting the musculoskeletal system. In addition, the presented chondro-proliferative and osteo-regenerative effects of PGRN, present a clear therapeutic implication for the use of Attstrin and other effective PGRN recombinant derivatives, in OA and other conditions requiring the induction of bone remodeling and repair.

5. CONCLUSION

The application of PGRN’s functions in the processes of chondrocyte regeneration and bone de-novo synthesis propose a relevant potential clinical therapeutic alternative. Considering its broad range of biological functions as a multi-factorial progenitor growth hormone, the precise identification of its binding domains and the therapeutic implementation of a biologically specific and effective engineered molecule could provide a pharmaceutical alternative to the current available treatment options in rheumatoid arthritis, osteoarthritis, osteomyelitis, and may possibly constitute an alternative to proposed therapies accelerating fracture healing, such as parathyroid hormone-related peptide (PTHrP) (80), and also the recently proposed deferoxamine (81).

PGRN targets both cartilage and bone metabolism and its chondroprotective role in the cartilage degradative cascade, stimulation of chondrocyte
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Figure 3. A proposed model for explaining the role of PGRN in the musculoskeletal system. PGRN plays a chondroprotective role in the metabolic cascade of cartilage degradation, promotes chondrocyte proliferation, via binding to TNFR2 receptor binding which acts as a downstream mediator of BMP-2 signaling and triggers osteoblastogenesis and bone regeneration. In cartilage, PGRN exhibits a particular affinity for the TNFR2 receptor, binds via the F-A-C domain and activates BMP-2 signaling stimulating chondrocyte function and proliferation. TNFR 1 binding to PGRN’s F-A-C domain prevents the activation of the NF-KB pathway by TNFa assisting in the chondro-protective process, thus, inhibiting the degradation of COMP by ADAMTS-7. The positive biofeedback loop between TNFa and ADAMTS 7 is indicated in the figure, and PGRN directly tampers with this biofeedback mechanism. In bone metabolism, TNFR2 receptors are of particular importance, where PGRN/TNFR interaction may mediate BMP-2 induction of de-novo osteogenesis.

proliferation, via binding to TNFR2 receptors, along with induction of osteoblastogenesis and bone regeneration constitute key therapeutic goals in OA treatment, prevention, and prophylaxis. In cartilage, these functions are executed by PGRN’s particular affinity for the TNFR2 receptor, and the binding that occurs via the F-A-C domain activates ERK 1/2 signaling thus promoting chondrocyte metabolism and proliferation. TNFR 1 binding to PGRN’s F-A-C domain prevents the activation of the NF-KB pathway by TNFa and the resultant chondroprotective inhibition of the degradation of COMP by ADAMTS-7. PGRN directly regulates the positive biofeedback loop which exists between TNFa and ADAMTS 7. The PGRN/TNFR2, in turn, induces the process of osteoregeneration, where PGRN is a downstream molecule of BMP-2. Targeting of the F-A-C domain is fundamental in the treatment of OA- and rheumatoid arthritis-related arthroses and chondral pathology, which allows for an effectuation of the highly specific functions without influencing the occurrence of potential side-effects, related to its properties as a pleiotrophic growth hormone (Figure 3).

The highly specific properties of Attstrin, for instance, which encompass the targeting of the F-A-C domains and the implementation of their therapeutic function, may provide the achievement of the curative and preventative effects at the level of chondrocyte metabolism and the process of osteoregeneration through TNFR signaling and the prevention of degradation of cartilage and its ECM structural components, and the mediation of BMP2 signaling pathways, respectively. Clinical trials which correlate and contrast the effects of current available treatment options such as methotrexate – TNFa inhibitor combination therapy (82), and target TNFR inhibitors, i.e. Attstrin, could allow for a differentiation of therapeutic effectiveness on many levels.

6. ACKNOWLEDGMENTS

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**Abbreviations:** PGRN, progranulin; TNF, tumor necrosis factor; ECM, Extracellular Matrix; TNFR, tumor necrosis factor receptors; COMP, cartilage oligomeric matrix protein; ADAMTS, A Disintegrin And Metalloproteinase with Thrombospondin Motifs; MMP, matrix metalloproteinase; PEPI, proepithelin; PCDGF, GP88/PC-cell derived growth factor

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