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Review article

Progranulin: A key player in autoimmune diseases

Jinlong Jian [a], Guangfei Li [a,b], Aubryanna Hettinghouse [a], Chuanju Liu [a,c,*]

[a] Department of Orthopedics Surgery, New York University School of Medicine, New York, NY 10003, United States
[b] Department of Orthopedics, The Second Affiliated Hospital of Soochow University, Suzhou 215004, China
[c] Department of Cell Biology, New York University School of Medicine, New York, NY 10016, United States

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ABSTRACT

Autoimmune disease encompasses an array of conditions with a variety of presentations and the involvement of multiple organs. Though the etiologies of many autoimmune conditions are unclear, uncontrolled inflammatory immune response is believed to be a major cause of disease development and progression. Progranulin (PGRN), an anti-inflammatory molecule with therapeutic effect in inflammatory arthritis, was identified as an endogenous antagonist of TNFα by competitively binding to TNFR. PGRN exerts its anti-inflammatory activity through multiple pathways, including induction of T_{reg} differentiation and IL-10 expression and inhibition of chemokine release from macrophages. In addition, the protective role of PGRN has also been demonstrated in osteoarthritis, inflammatory bowel disease, and psoriasis. Intriguingly, PGRN was reported to contribute to development of insulin resistance in high-fat diet induced diabetes. Emerging evidences indicate that PGRN may also be associated with various autoimmune diseases, including systemic lupus erythematous, systemic sclerosis, multiple sclerosis and Sjogren's syndrome. This review summarizes recent studies of PGRN as a novel target molecule in the field of autoimmune disease, and provides updated information to inspire future studies.

Contents

1. Introduction

Inflammation is a normal protective response to pathogen exposure, cell injuries and stress in human and animal physiology. However, dysregulation of the magnitude and duration of inflammatory reaction leads to tissue damage. Cytokines, a group of small proteins that are released from leukocytes or stromal cells, are major mediators in the initiation of inflammatory response. Among these cytokines, tumor-necrosis-factor α (TNF-α) is at the peak of the inflammatory cascade, and increased levels of TNF correlate with inflammation in various diseases, including rheumatoid arthritis, systemic lupus erythematosus, and contact dermatitis.

* Corresponding author at: Rm 1608, Hospital Joint Diseases, New York University School of Medicine, 301 East 17th Street, New York, NY 10003, United States.
E-mail address: chuanju.liu@nyumc.org (C. Liu).

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Blockade of TNF by its specific antibodies or soluble receptors has been accepted as an effective biological treatment approach for multiple autoimmune and inflammatory diseases, in particular rheumatoid arthritis.

Negative regulatory mechanisms have evolved to limit inflammatory response. For instance, regulatory T cells (T_{reg}), a subpopulation of T cells, are immunosuppressive and function to suppress self-reactivity under healthy conditions. IL-10 is an anti-inflammatory cytokine and mice deficient in IL-10 develop many types of autoimmune disorders spontaneously. Progranulin (PGRN), also known as granulin–epithelin precursor (GEP) [1], proepithelin (PEPI) [2,3], acrogranin [4], and GP88/PC-cell derived growth factor (PCDGF) [5], is a 593-amino-acid secretory growth factor which was originally identified as a growth factor involved in the promotion of epithelial cell proliferation and wound healing [6]. PGRN is also important in regulating inflammation, at least in part, by directly binding to tumor-necrosis-factor receptors (TNFR) and counteracting the TNF-mediated inflammatory signaling pathway [7]. PGRN contains seven-and-a-half cysteine-rich motifs [8], and it can be degraded by various proteinases, including matrix metalloproteinase (MMP) 9, 12, and 14, ADAMTS-7, elastase, and Proteinase-3 [5,9–12]. Importantly, the degraded fragments of PGRN, or GRNs, are pro-inflammatory and may neutralize intact PGRN's anti-inflammatory activities [5].

Since its initial discovery, PGRN has been revealed to be an important molecule in a wide variety of disease processes. PGRN level is considered a prognostic biomarker for many forms of cancer as PGRN overexpression associated with cancer cell proliferation and migration [13–15]. *GRN* gene mutations cause frontotemporal lobular dementia [16,17]. PGRN functions as an important neurotropic factor, and its insufficiency is associated with many other neurodegenerative diseases, such as Parkinson's disease, Creutzfeldt-Jakob disease, motor neuron disease, and Alzheimer's disease [18–21]. PGRN has been extensively reviewed as a growth factor and neurotropic factor. This review paper instead focuses on recent updates of PGRN's role in autoimmune diseases.

PGRN binds to TNFR1 with binding affinity comparable to that of TNFα, and binds to TNFR2 with much higher affinity than TNFα [7]. Granulin F, A, C domains mediate the interaction between PGRN and TNFR [7]. A PGRN-derived engineered molecule, called Atsttrin, containing half units of GRNs F, A, and C and their linker regions, also showed clear binding to TNFR1/2 and effective inhibition of TNF-induced inflammation [7]. Subsequent studies indicated that PGRN bound to the CRD2 and CRD3 domains of TNFR1/2 [22]. Increasing evidences specify that TNFR1 and TNFR2 mediate different signaling pathways and play distinct roles in various pathophysiological conditions [23,24]. TNFR1 signaling induces the apoptotic pathway while TNFR2 signaling triggers cell survival signaling [24]. PGRN not only blocks the TNF-induced inflammatory pathway by competitively binding to TNFR1, but also binds to TNFR2 to promote cell proliferation. In addition to TNFR, death receptor 3 (DR3), the highest homolog of TNFR1, was also isolated as a PGRN and Atsttrin binding receptor in a protein-protein interaction screen between PGRN and all TNFR superfamily members [25]. PGRN and Atsttrin inhibit the binding of DR3 to TL1A, the only known ligand of DR3. Similar to TNF/TNFR1, TL1A/DR3 is also involved in the process of various inflammatory disorders [26,27]. In addition to binding to TNFR1/2 and DR3, PGRN induces T_{reg} populations and IL-10 production [7,28,29] and inhibits chemokine release [30]. In this review, we start with a recent update of the anti-inflammatory function of PGRN in RA, osteoarthritis (OA), inflammatory bowel diseases (IBD), and psoriasis. We will also summarize relevant findings from additional autoimmune diseases in which PGRN may function as a contributory factor. Lastly, we will discuss the exciting discovery of a PGRN autoantibody and its clinical relevance to autoimmune diseases.

2. Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a systemic autoimmune disorder that primarily affects the joints, with the wrists and hands most commonly affected. Patients of RA present with swollen, warm, and painful joints. Although the cause of RA is still unclear, it is believed that TNF-α driven inflammation plays a critical role, and TNF inhibitors are regarded as the most effective treatments for RA [31].

Recently, PGRN was found to be an endogenous antagonist of TNFα through competitively binding to TNFR [7]. Under a collagen-induced arthritis (CIA) model, PGRN null ($PGRN^{-/-}$) mice exhibit a higher incidence of arthritis and a more severe phenotype [7], however, administration of recombinant PGRN protein inhibits disease progression in these PGRN-deficient mice. These data demonstrate that the loss of PGRN expression *in vivo* results in hyper-susceptibility to collagen-induced arthritis, a well-accepted model of inflammatory arthritis, which can be reversed by the administration of recombinant PGRN.

Deletion of one or both copies of the *GRN* gene in TNF-transgenic (TNF-Tg) mice, which develop an inflammatory arthritis phenotype spontaneously [32,33], significantly accelerates the onset of arthritis [7]. Pathologically, TNF-Tg mice with deletion of one or both alleles of PGRN exhibit significantly increased synovitis, pannus formation, destruction of the ankle joints, and loss of cartilage matrix [7]. In a collagen-induced arthritis model of RA, treatment of PGRN-deficient TNF-Tg mice with recombinant PGRN protein resulted in an interruption of disease progression and a dramatically reduced arthritis clinical score. Interestingly, at 7 days following the cessation of PGRN treatment, signs of arthritis relapsed. Taken together, these data suggest that PGRN exerts its anti-inflammatory effects through the inhibition of TNF/TNFR signaling *in vivo*. Importantly, PGRN-derived Atsttrin was shown to be even more effective than PGRN in preventing inflammation in several inflammatory arthritis models [7].

Recently, the clinical relevance of PGRN in RA has been reported by several groups [34–36]. Research teams consistently report elevated serum levels of PGRN in RA patients, as compared to healthy controls, independent of sex and age [34,35]. Interestingly, the balance between PGRN and TNF seems to be important in RA progression, as the ratio of PGRN/TNF is closely correlated with RA stages [34]. Moreover, PGRN levels in synovial fluid are also significantly higher in RA patients than in OA patients [33,34]. Immunohistological analysis of synovial tissue from patients with RA has confirmed significant upregulation of PGRN in infiltrating inflammatory cells, especially in the sublining layer [35]. The immunosuppressive activity of PGRN is exemplified through PGRN's stimulatory effect on T_{reg} cell population [7,28]. A recent study has also reported that both PGRN level and human B regulatory (B_{reg}) cell population were significantly higher in RA patients. However, the number of B_{reg} cells was not correlated to PGRN level [36], suggesting that PGRN and B_{reg} cell population may be independently altered in RA.

3. Osteoarthritis

Osteoarthritis (OA), the most common joint disease, is a slow-progressing degenerative disease characterized by cartilage loss. Originally, mechanical wear and tear was considered paramount in OA etiology. However, increasing evidence indicates that growth factors and cytokines are strongly implicated in initiating and aggravating OA lesions [37]. PGRN was isolated as one such growth factor in a genome-wide screen for genes differentially expressed

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