The role of progranulin (PGRN) in the modulation of anti-inflammatory response in asthma

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Abstract

Asthma is one of the most common chronic diseases. Epidemiological studies show that asthma will develop among around 40% of children under six years old with symptoms of bronchial obstruction. Diagnosis of asthma is complicated, especially in the paediatric population. As a result, a lot of research is being carried out to establish the pathophysiology and to find new biomarkers of this disease. Progranulin (PGRN) is a recently discovered growth factor with many biological functions. PGRN has anti-inflammatory properties because it inhibits neutrophil degranulation and blocks tumor necrosis factor α (TNF-α) transmission. The underlying mechanisms are still being researched, but TNF-α is considered to be a cytokine responsible for neutrophilic inflammation in the airways and bronchial hyperresponsiveness. Therefore, PGRN, by lowering TNF-α concentration and stimulating regulatory T-cell (Treg) proliferation, relieves symptoms of bronchial inflammatory diseases. This article attempts to verify the current knowledge about basic pathophysiological mechanisms in asthma. We also summarise the most recent research advances in the role of PGRN in the respiratory system.

Key words: *progranulin, PGRN, paediatric asthma, TNF-α, biomarker.*

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Introduction

Over the last few decades, a significant increase in the incidence of bronchial asthma has been observed. The World Health Organisation (WHO) estimates that 235 million people are affected by asthma worldwide. It is also the most common non-infectious disease in the paediatric population [1]. According to the Global Initiative for Asthma (GINA) 2017 report, asthma is a disease with many variations (heterogeneous), usually characterised by chronic airway inflammation. It is defined by a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, which vary over time and in intensity, together with variable expiratory airflow limitation [2]. Currently, most data concerning asthma prevalence in the paediatric population worldwide come from the ISAAC study (International Study on Asthma and Allergies in Childhood). More than 100 clinical centres from over 50 countries participated in the ISAAC study, which included children aged 6-7 and 13-14 years. The incidence of asthma varied greatly across the globe and ranged from 1% (China) to 32.6% (New Zealand) in the population of 6-7-year-olds and from 2.4% (India) to 37.6% (Costa Rica) among children 13-14 years old. After seven years, the study was repeated and the further increase in the prevalence of asthma among children was noted, especially in the younger group and among children in developing countries [3]. The disease can occur at any age; however, late onset is rare and medical history generally confirms the presence of the first asthmatic symptoms in early childhood [4]. The majority of patients (80%) develop their first symptoms by the age of five years: approximately 50% by the age of two years and 30% in the first year of life [5]. Diagnosis of asthma in this age group is complicated because many children present with symptoms of bronchial obstruction in the first years of life, most often during the respiratory infections. Epidemiological studies show that asthma will develop in around 40% of children under six years old with symptoms of bronchial obstruction [6].

Therefore, asthma should be diagnosed among the youngest children. Suitable treatment usually allows the control of symptoms of mild and moderate asthma, whereas a severe form of asthma can be resistant to treatment with inhaled glucocorticosteroids (GCS), long-acting β-agonists (LABA) and anti-leukotriene drugs (anti-LT). Over the past few years many research studies have focused on the pathophysiology of different phenotypes of asthma, attempting to identify potential therapeutic targets. Biomarkers are qualitative or quantitative indicators of some biological state or condition, correlating with the disease's presence, its severity, pathophysiology, progress, and response to treatment. Therefore, assessment of biomarkers may be an effective tool to establish proper diagnosis and determine the most effective treatment, minimalising future adverse clinical consequences [7]. The most thoroughly examined biomarkers of airway inflammation include: fraction of exhaled nitric oxide (FeNO), exhaled breath condensate (EBC), induced sputum analysis, level of blood eosinophils, immunoglobulin E (IgE) level, and periostin concentration. They may be useful in medical practice, but they do not reflect the entire clinical picture [8, 9]. As the understanding of the pathophysiological processes and immunology concerning asthma increases, attempts have been made over the last few years to identify a new biomarker. One of the recent discoveries is progranulin (PGRN), a protein of anti-inflammatory and immunomodulatory activity. Recent reports confirm a positive correlation between PGRN concentration and pulmonary function among asthmatic patients. The exact mechanism of action of PGRN has not yet been fully understood. Nevertheless, PGRN level has been proposed to be a new index of asthma severity [10]. Biomarkers among asthmatic patients have not yet reached the precision of e.g. glycated haemoglobin (HbA$_{1c}$) in diabetes monitoring; however, several indicators helpful in defining phenotypes and endotypes of asthma have been identified. These indicators may be a useful tool in predicting patient characteristics and response to specific therapy.

Classification, aetiology, and pathogenesis

In light of current knowledge, asthma is a heterogeneous disease, which consists of various, overlapping phenotypes. Therefore, the therapeutic strategy must be determined by asthma subtype. Many research studies have attempted to categorise patients according to the asthma phenotype, in order to improve response to treatment. The asthma phenotype was determined by the underlying pathophysiological process in the airways [11]. The phenotype describes the clinical, physiological, morphological, and biochemical characteristics of the disease, as well as response to specific therapy. In 2006 Anderson introduced the term endotype of asthma, which correlates the clinical picture with the pathophysiology [12, 13]. There are two main types of asthma: allergic and non-allergic. Childhood and late-onset asthma are also distinguished. Other asthma phenotypes are related to obesity, smoking, allergic bronchopulmonary aspergillosis, aspirin-induced asthma, and exercise-induced bronchoconstriction [14]. The categorisation of asthma due to its severity and level of control is the most useful in clinical practice. Asthma may be divided into eosinophilic, neutrophilic, and non-cellular asthma, given the dominant inflammatory cells in the bronchial wall. On a molecular basis, Type 2-high and Type 2-low airway inflammation in asthma are distinguished, according to the level of T-helper 2 (Th2) cell airway inflammation [15]. The Th2 cell subpopulation secretes interleukin (IL) 4, IL-5, and IL-13. In the classic theory of allergy, Th2 lymphocytes stimulate the humoral response, in particular IgE synthesis. This process is mediated by IL-4 and IL-13, which are necessary for class switching of immunoglobulins produced by B lymphocytes. Because or while IL-5 stimulates the differentiation and activation of eosinophils, eosinophilia is also present in the Th2 lymphocyte-mediated immune response [16]. T-helper 1 (Th1) lymphocytes produce IL-2, interferon γ (IFN-γ), and transforming growth factor β. Both Th1 and Th2 lymphocytes produce IL-3, IL-6, IL-10, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Th1 lymphocytes produce TNF-α in greater amounts than other cytokines [17]. An important role is also attributed to the T regulatory lymphocytes (Treg), which secrete TGF-β and IL-10 and act as antagonists to Th2 lymphocytes [15]. They are necessary in maintaining the immune tolerance towards own antigens, and in suppressing an inadequate response of the body to extrinsic antigens [18, 19]. Decreased levels of Treg lymphocytes in the peripheral blood were observed among patients with asthma [20, 21]. Recent studies have linked the disease development with the deficiency of type 1 Treg cells with the Foxp3 + CD25 + CD4 + and Foxp3 + CD25 + CD8 + phenotype. Acting in contrast to Tregs, T helper 17 cells (Th17) secrete IL-17, which regulates the expression of proinflammatory cytokines, recruits inflammatory cells (mainly neutrophils), and therefore contributes to the development of bronchial hyperresponsiveness in asthma [21]. Cytokines that are produced by Th17 cells are resistant to steroid therapy. Therefore, asthma associated with the predominant neutrophilic inflammation is considered to be steroid-resistant. Furthermore, associations between TNF-α and Th17 lymphocytes were observed; elevated levels of TNF-α were found among patients with Th17-lymphocyte-associated asthma in both lung tissue and serum [22]. TGF-β plays a dual role in asthma development. On the one hand, its anti-inflammatory activity promotes the formation of Treg cells. On the other hand, TGF-β alongside IL-6 induces IL-17 expression in naive T lymphocytes leading the formation of Th17 cells. Studies on pathomechanisms of asthma led to the development of targeted therapy, such as anti-IgE antibodies (omalizumab) or anti-IL-5 antibodies

(mepolizumab). Therefore, further promising clinical trials are being carried out using antibodies directed against other cytokines involved in asthma development [2].

Progranulin – biological role

PGRN, also known as acrogranin, proepithelin, GP88, granulin/epithelin precursor (GEP), or PC cell-derived growth factor (PCDGF), performs many biological functions and is highly expressed in mammalian cells, including the airway epithelial cells [23]. Many studies proved the anti-inflammatory role of PGRN. It is a pleiotropic protein that plays an important role within the human body by participating in cell development, cell cycle control, embryogenesis, angiogenesis, neoplasia, wound healing, inflammatory processes, and modulation of autoimmune processes [24-28]. PGRN is encoded by the GRN gene, located on chromosome 17q21.32, which contains 12 exons and results in three isoforms. It is a protein consisting of 593 amino acids with a molecular weight of 68.5 kDa. It usually migrates around 88 kDa in Western Blot analysis due to several glycosylation sites [29]. Full-length PGRN consists of the secretory *N*-terminal signal peptide of 17 amino acids and contains 7 cysteine-rich domains (granulins), held by disulphide bonds. It can be degraded by various proteinases, including metalloproteinases (MMP) 9, 12, and 14, ADAMTS-7, neutrophil elastase, and proteinase 3. Importantly, granulins formed in the PGRN degradation process have pro-inflammatory properties and can neutralise the anti-inflammatory action of PGRN [30, 31]. For example, granulin B stimulates the expression of IL-8 in epithelial cells, resulting in an increase of phagocytosis and bactericidal properties of neutrophils [31]. Some molecules inhibit PGRN degradation; secretory leukocyte protease inhibitor (SLPI) directly binds to PGRN and blocks its proteolysis by neutrophil elastase. Similar properties are shown by high-density lipoproteins (HDL) or apolipoprotein A1 (APOA1) [32]. Considering the great number of processes that are mediated by PGRN, there is no evidence to support the existence of a unique PGRN receptor. PGRN is a secreted glycoprotein (internalised mainly via endocytosis); however, it also acts at nuclear and cytoplasmic levels. So far, over 20 proteins that bind to PGRN have been described. The most detailed descriptions in the literature concern binding of PGRN to the membrane tumor necrosis factor receptor 1/2 (TNFR1/2), as well as sortilin. Sortilin mediates extracellular PGRN uptake and regulates its concentration in the central nervous system (CNS) [33, 34]. PGRN is a neurotrophic factor [35]. It has been proven that PGRN gene mutations resulting in partial loss of PGRN protein are involved in the pathogenesis of frontotemporal lobar degeneration (FTLD) [36]. Studies conducted by Tang *et al*. suggest that PGRN binds to TNFR1 with a similar affinity and to TNFR2 with a much higher affinity than TNF-α [25]. Further research

has shown that PGRN binds to the cysteine-rich domains 2 and 3 of TNFR1/2 [37]. Many studies suggest that TNFR1 and TNFR2 exert pleiotropic effects via various signalling pathways [38]. Domains of PGRN: granulin F, A, and C, as well as the cross-linking region, have been identified to bond with TNFR1/2. As a result, a novel molecule Atsttrin was derived, which consists half of F, A, and C granulins and the cross-linking region. Therefore, Atsttrin blocks TNF-α-TNFR1/2 signalling by interacting selectively with TNFR1/2 [25]. Furthermore, death receptor 3 (DR3), with highest homology to TNFR1 binds to PGRN and Atsttrin, inhibiting the binding of DR3 with tumor necrosis factor-like protein 1A (TL1A). The TL1A/DR3 complex is involved in the pathogenesis of various inflammatory disorders [39]. PGRN promotes proliferation of Treg cells and IL-10 secretion, which mediate a state of immunological self-tolerance [25, 40]. There are also studies suggesting PGRN inhibits expression and release of chemokines CXCL9 and CXCL10 in a TNFR1-dependent manner [41]. In brief, PGRN can act either as a growth factor, an anti-inflammatory agent, or an adipokine, and the pro- or anti-inflammatory function of PGRN might depend on the target tissue [29].

Mechanisms of bronchial hyperreactivity

One of the asthma's hallmarks is bronchial hyperresponsiveness (BHR), where an excessive bronchospasm is caused by various specific and nonspecific stimuli. Such reaction is not elicited among healthy people [42]. The pathomechanism of this phenomenon is not fully understood, but it is known to be different in various asthma phenotypes. The importance of airway epithelium is emphasised. Epithelial cells are known to secrete inflammatory cytokines, as well as bronchoconstriction and bronchodilation factors. Inflammatory processes accompanying asthma develop due to mast cells, eosinophils, neutrophils, Th2 lymphocytes, and cytokines. The role of IgE must be highlighted because IgE has a high affinity to high-affinity IgE receptor (FcεRI), which is present on the surface of basophils and mastocytes. Bonding of IgE with its receptor initiates an inflammatory cascade with subsequent release of proinflammatory mediators (histamine, IL-4, IL-5, and IL-13, leukotrienes, and prostaglandins) and contributes to the development of acute and chronic respiratory diseases and BHR. Late phase reaction is enhanced by IL-9, a growth factor for mast cells and IgE-releasing factor, which is produced by T-lymphocytes, eosinophils, and mast cells. Furthermore, IL-9 contributes to airway inflammation, mucus production, and airway hyperresponsiveness. Likewise, IL-13 stimulates IgE and eosinophil production, mucus secretion, expression of cell adhesion molecules, and chemokines, as well as directly inducing airway smooth muscle contraction (*in vitro*). Airway epithelial cells may also produce proin-

flammatory cytokines, such as IL-1, IL-6, IL-8, TNF-α, and GM-CSF [43-45]. Current research suggests that TNF-α is produced in significant quantities in the respiratory system of asthmatic patients and may potentially be involved in the development of bronchial hyperresponsiveness by directly altering the properties of airway smooth muscle (ASM). The underlying mechanisms are still largely unknown, but recent studies suggest that most biological effects of TNF-α on ASM are mediated by the p55 receptor or TNFR1, which causes alteration of calcium (Ca^{2+}) homeostasis in ASM. Therefore, TNF-α signalling pathway appears to be a new potential mechanism responsible for BHR [45-47].

The role of progranulin in respiratory diseases

PGRN exerts its anti-inflammatory effect by interacting selectively with TNFR1/2 and blocking TNF-α-TNFR1/2 signalling, thus inhibiting neutrophil degranulation [25]. Therefore, PGRN plays a role in TNF-α-associated inflammatory diseases, including respiratory diseases [10, 48]. Ungurs *et al.* in their study examined human sputum among patients with chronic obstructive pulmonary disease (COPD) and found higher serum concentration of PGRN to be an indicator of low-grade neutrophilic inflammation [48]. Another study conducted by Park *et al.*, composed of 475 patients with asthma and a control group of 35 healthy people, showed that serum PGRN is a significant indicator of neutrophilic airway inflammation and thus one of the asthma severity markers. Furthermore, patients with asthma were evaluated considering the asthma severity classification by the GINA, and serum concentration of PGRN correlated negatively with the intensity of bronchial obstruction. In comparison to the control group, significantly lower PGRN levels were noted among asthmatic patients. Furthermore, a relationship between low PGRN concentration and risk of severe asthma was also demonstrated. It was concluded that PGRN probably acts as an inhibitor of neutrophil inflammation in the airways [10]. Published in 2017, Chiba *et al.* study examined intranasal administration of Atsttrin in mice (BALB/c) and showed significantly inhibited bronchial hyperresponsiveness [49]. Based on the literature review presented above, PGRN is a promising object of research, both as a potential marker of asthma severity and as a possible new therapeutic target for asthma.

The authors declare no conflict of interest.

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