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PROGRANULIN: IS IT A NEW ADIPOCYTOKINE AT THE CROSSROADS OF OBESITY, METABOLIC SYNDROME AND CANCER?

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Abstract

Progranulin (PGRN) stimulates the proliferation and survival of several cancer cell types. Obesity increases the risk for metabolic as well as cardiovascular diseases, and is linked to an increased incidence and aggressiveness of various cancers. Prepubertal morbid obese (MO) children and those with metabolic syndrome (MetS) (MO+MetS) were included in our studies. World Health Organization age- and sex-dependent body mass index percentile tables were used for the classification of obesity. MetS criteria were defined. Anthropometric measurements, blood pressure values, lipid and glucose metabolism–related parameters, obesity-related adipocytokines were determined. Statistical evaluations were performed. Our studies have pointed out an increasing trend going from MO towards MO+MetS group in terms of PGRN. Elevated PGRN can contribute to tumour microenvironment; stimulate growth, invasion and

metastasis of cancer cells. Children with MetS have the tendency of developing chronic diseases such as cancer in their future lives. Obesity, a major public health problem, increases the risks for many severe chronic diseases. Elevated PGRN levels may promote tumor growth, serve as a potential clinical biomarker in cancer and be associated with the increased cancer risk in children with MetS. As a new molecule, PGRN may provide a new intervention target for molecular treatment options.

Keywords

Children, Progranulin, Obesity, Metabolic Syndrome, Cancer

1. Introduction

Obesity is characterized with an excessive adipose tissue accumulation. An abnormal quantity of adipose tissue leads to impaired secretion of numerous molecules (Szydlo, Kiczmer, Swietochowska, & Ostrowska, 2016)(Booth, Magnuson, Fouts, & Foster, 2015). Obesity is also known as a low-grade inflammatory disease. In recent years, the potential mechanisms as well as links between obesity, and some severe chronic diseases such as cardiovascular diseases, diabetes, asthma as well as liver diseases have been investigated (Senevirathne, Katulanda & Dhanapala, 2015) (Donma, 2015) (Donma, 2016). Obesity also alters the profile of regulatory T cells (Donma et al., 2015). Metabolic syndrome (MetS) is characterized by central obesity, insulin resistance (IR), glucose intolerance, dyslipidemia and hypertension (Lee, & Mattson, 2014). Obesity is recognized as the second highest risk for cancer (Venniyoor, 2017). Therefore, effective approaches towards controlling obesity are in progress (Shamsiya, Manjunatha & Manonmani, 2016).

There are some certain ambiguities related to the mechanism of carcinogenesis. There exist controversies on the matter whether it is caused by metabolic derangements, inflammation or some other genetic susceptibilities (Venniyoor, 2017) (Schleinitz, 2015). Proposed mechanisms are not limited to glucose intolerance, IR, oxidative stress, and inflammation (Booth et al., 2015). Adipose stem cells, altered by obesity, have been shown to impact cancer progression through the increased recruitment to the tumor site and increased production of cytokines and growth factors (Strong, Burow, Gimble, & Bunnell, 2015) (Perez, 2016) (San Martin, & Galvez, 2011) (Cignarelli et al., 2012). Adipose tissue secretes many physiologically important molecules including adipocytokines (Schleinitz, 2015). Various adipose tissue-secreted factors are suggested to play roles in obesity-related carcinogenesis. Of them, increased

concentrations of those known as classical adipocytokines such as leptin, tumor necrosis factor-α (TNF-α), interleukin-6, resistin exert pro-carcinogenic whereas adiponectin exerts anti-carcinogenic effects. The involvement of recently introduced molecules such as apelin, endotrophin, omentin, visfatin, nesfatin, vaspin, chemerin in MetS and tumorigenesis has also been investigated. Each of them is suggested to be used as a biological marker for clinical conditions such as obesity, MetS, diabetes mellitus (DM), pancreatitis, or cancers of stomach, lung, colon, breast, liver or endometrium (Cabia, Andrade, Carreira, Casanueva, & Crujeiras, 2016) (Szydlo et al., 2016) (Booth et al., 2015) (Wieser, Moschen, & Tilg, 2012). It is reported that most adipocytokines enhance cell survival, tumor cell proliferation, migration and invasion. Therefore, they promote cancer cell progression. They favor inflammatory as well as anti-apoptotic pathways, and thus prompt cancer metastasis. These properties as well as many others are also confined to progranulin (PGRN), which is described as a well-known growth and survival factor. However, this newly introduced molecule has not been reviewed in a detailed manner.

2. Progranulin: Biological and pathological processes

Progranulin, as a molecule at the interface of neurodegenerative and metabolic diseases, is involved in multiple biological and pathological processes as in the case of minerals (Table 1) (Abella et al., 2017) (Donma, Donma, Michalke, Halbach & Nischwitz, 2012) (Nguyen, Nguyen, Martens, Mitic, & Farese, 2013).

Table 1: *Biological and pathological processes in which progranulin is involved*

Biological	Pathological
Cell growth	Obesity
Cell proliferation	Tumorigenesis
Embryogenesis	Inflammation
Wound healing	Infection
Immunity	Insulin resistance
Angiogenesis	Neurodegeneration
Vascularization	Neuronal ceroid lipofuscinoisis

Progranulin also regulates energy balance and may modulate processes involved in atherosclerosis. Paradoxically, PGRN appears to suppress neuroinflammation and neuronal death in the central nervous system as well as atherosclerosis. However, it acts as a proinflammatory molecule in the context of diet-induced obesity (Nguyen et al., 2013).

Actually, PGRN serves as a major anti-inflammatory molecule in some diseases however, it may also promote the development of certain diseases (Jian et al., 2016) (Figure 1).

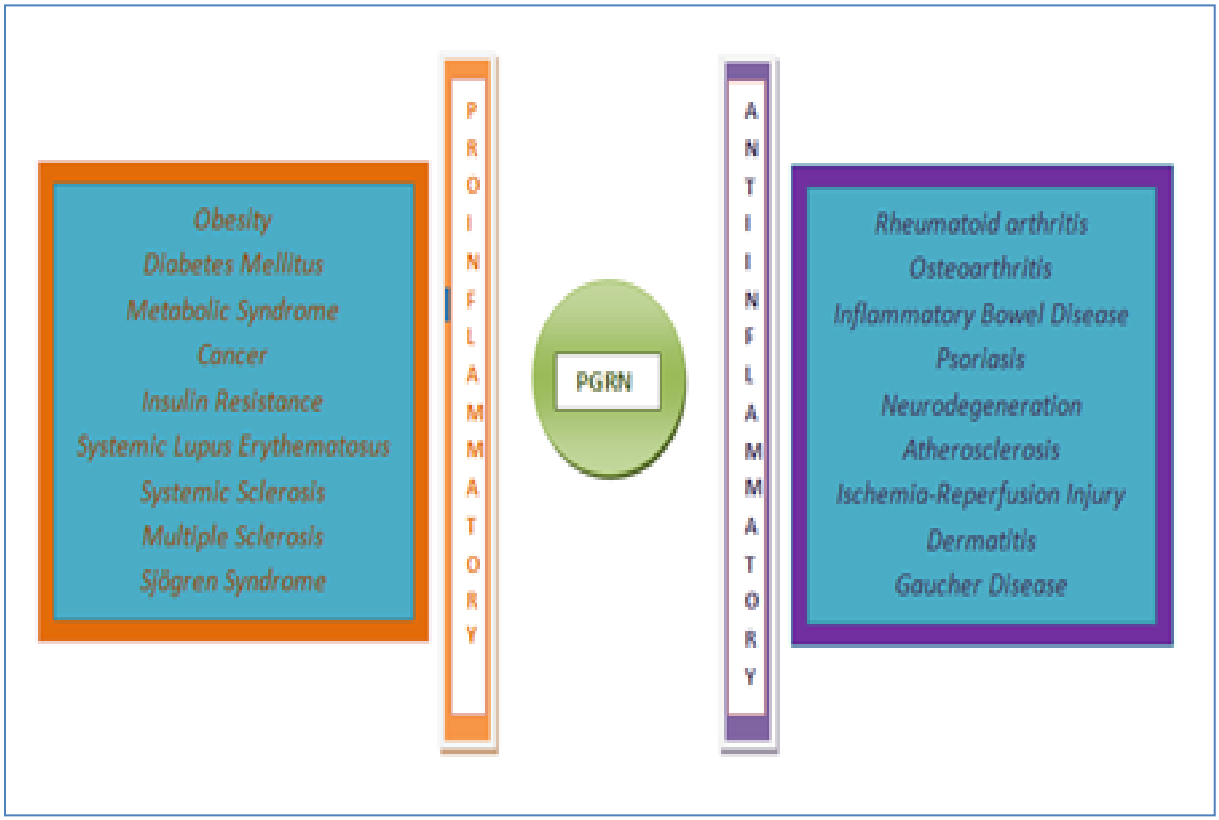

Figure 1: *Progranulin paradox*

TNF-α impairs endothelium-dependent vasorelaxation. Progranulin is an antagonist of TNF-α receptor type 1. The vascular effect of PGRN seems to be a promising therapeutic target. Progranulin also possesses protective effects in ischemia-perfusion injury. The effects of PGRN on insulin sensitivity as well as its role in carcinogenesis are also important issues to be considered (Beltowski, 2017).

3. Progranulin and Neurodegenerative Diseases

Mutations in the gene encoding PGRN are suggested to be linked to frontotemporal dementia. Progranulin deficiency may have pleiotropic effects on neural circuit development and maintenance, stress response, innate immunity and ageing. This may lead to new therapeutic approaches for neurodegeneration (Kao, McKay, Singh, Brunet & Huang, 2017).

4. Progranulin and Infections

Recently, it has been discovered that therapeutic administration of PGRN improved mortality in severe bacterial pneumonia. Its role in pulmonary immunity is suggested and also it is stated that treatment with PGRN may be a viable therapy for bacterial pneumonia (Zou et al., 2017). Progranulin is suggested to play a central role in host defense during sepsis by promoting macrophage recruitment. Progranulin-mediated protection against sepsis was found to be closely linked to improved peritoneal macrophage recruitment. This may open new opportunities to host-directed therapeutic strategy that manipulate host immune response in the treatment of sepsis (Song et al., 2016).

Progranulin is implicated in infection, immunity and host defense. Increased PGRN production and association between PGRN levels and viral loads in patients with chronic HBV infection, suggest a functional role of PGRN in the pathogenesis of HBV infection (Gong et al., 2016)

5. Progranulin and Asthma

Although the exact mechanism of anti-inflammatory action of PGRN remains unknown, serum PGRN may be an indicator of severe asthma with airflow limitation, because serum PGRN levels were found to be significantly lower in the asthma group than in healthy group. Higher PGRN levels were associated with a lower risk of severe asthma (Park et al., 2016).

6. Progranulin, Obesity and Metabolic Syndrome

Progranulin is a multifunctional protein with neuroprotective and anti-inflammatory activities. On the other hand, increased PGRN concentrations are observed in obesity and involved in the pathogenesis of obesity-associated IR (Korolczuk, & Bełtowski, 2017). Progranulin causes adipose IR via induced autophagy resulting from activated oxidative stress and endoplasmic reticulum stress (Guo et al., 2017).

Increased PGRN levels were reported in obese individuals with DM. This suggests that PGRN and metabolic diseases are linked (Youn et al., 2009). In such diseases, PGRN acts as a pro-inflammatory adipocytokine. There are reports informing that PGRN level may be a useful biomarker for inflammation and DM related to obesity (Nguyen et al., 2013) (Nicoletto, & Canani, 2015) (Shafaei, Marjani & Khoshnia, 2016).

It is pointed out that further studies are needed to determine if measuring PGRN levels appear to be a useful biomarker also in MetS. This problem has already been solved in a scientific research project study carried out on prepubertal children with morbid obesity as well as MetS (NKUBAP.00.20.AR.14.16). Obesity classification was performed using World Health Organization age- and sex-dependent body mass index percentile tables. MetS criteria were defined based upon anthropometric measurements, blood pressure values, lipid and glucose metabolism–related parameters. Concentrations of obesity-related adipocytokines were determined. Data were evaluated statistically. An increasing trend has been observed going from morbid obesity to MetS (Figure 2).

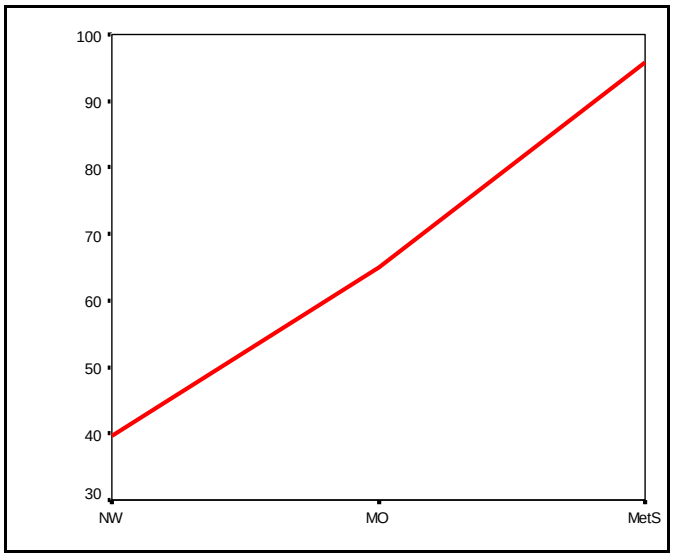

Figure 2: *Progranulin pattern in morbid obesity and metabolic syndrome*

A very recent report states that PGRN may be associated with the increased risk of cancer in those with MetS (Korolczuk, & Bełtowski, 2017). Actually, MetS components are found to be strongly associated with increased risk of developing primary liver cancer or cirrhosis (Nderitu et al., 2017). Decreased adiponectin may be a determinant risk factor for colorectal cancer in MetS patients (Divella et al., 2017). Overweight and obesity, acting through both inflammation and other mechanisms, likely explain the MetS-colorectal cancer connection (Harlid, Myte, & Van Guelpen, 2017). Metabolic syndrome was found to be significantly associated with aggressive prostate cancer (Di Francesco, & Tenaglia, 2017).

7. Progranulin and Cancer

Progranulin possesses growth-promoting properties. It not only promotes IR in obesity, but can also promote tumor growth (Bateman, & Bennett, 2009) (Ong, & Bateman, 2003). The

potential links between obesity and cancer needs further explanation. Mostly, this is made by way of stem cells. It has been suggested that the responsiveness of colonic stem cells to anti-inflammatory adipocytokine adiponectin in diet-induced obesity is impaired and may contribute to the stem cell accumulation observed in obesity. This indicates that obesity promotes colonic stem cell expansion during cancer initiation (DeClercq, McMurray, & Chapkin, 2015).

Progranulin plays an important role in activation of colorectal cancer fibroblasts, which may be considered as a target for the treatment of this cancer (Wang et al., 2017). Progranulin also promotes tumorigenesis of cervical cancer via PI3K/Akt/mTOR signaling pathway. Inhibition of this signaling may be targeted during the treatment of cervical cancer (Feng et al., 2016).

In recent reports, the growth and survival factor PGRN has been introduced as a critical regulator of transformation in several cancers such as breast cancer, glioblastomas, leukemias, genitourinary cancers, hepatocellular carcinomas and advanced biliary tract carcinoma (Tanimoto et al., 2016) (Kim et al., 2016). Elevated serum PGRN concentrations are associated with poor diagnosis in patients with malignant lymphomas (Yamamoto et al., 2017). It is also demonstrated that suppression of PGRN expression inhibits bladder cancer growth and sensitizes cancer cells to cisplatin (Buraschi et al., 2016).

Elevated PGRN levels may promote tumor growth, serve as a potential clinical biomarker in cancer and be associated with the increased cancer risk in children with MetS. As a new molecule, PGRN may provide a new intervention target for molecular treatment options.

8. Conclusion

Progranulin promises hope as a biomarker for rheumatoid arthritis, systemic lupus erythematosus, inflammatory diseases, metabolic diseases, cardiovascular risk, neurodegenerative diseases such as Alzheimer's disease, frontotemporal lobe degeneration, bipolar disorder, diabetic microangiopathy, and several types of cancer (Szydlo et al., 2016) (Jian, Li, Hettinghouse, & Liu, 2016) (Nguyen et al., 2013) (Pickering-Brown, 2007) ((Lee & Mattson, 2014). The discovery of its derived engineered peptide attstrin has pointed out its potential use as therapeutic agent in rheumatoid arthritis, osteoarthritis, bone regeneration, dermatitis and Gaucher disease (Abella et al., 2017).

Progranulin possesses both disease-causing as well as therapeutic effects. This growth and survival factor may constitute a target for therapeutic interventions against tumors and also

may serve as a biomarker for various cancers. Much more elevated PGRN concentrations observed in MetS in comparison with the values detected during morbid obesity may be the predictor of future carcinogenic state.

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