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Reg Family Proteins Function and Effects on Human Disease

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Abstract:

The Reg family all contain C-type lectin domains, which have various functions, including anti-inflammatory, antibacterial, anti-apoptotic and immunomodulatory functions. It plays a role in the liver, intestines, pancreas, lungs and nervous system. Researchers have identified 18 Reg genes and have a potential positive effect on diabetes, infections, diseases, cancer and other diseases, but cannot be used in clinical treatment. This paper first introduce the discovery process and main characteristics of reg gene proteins, and then discuss their function and current role in disease. This article provides a brief summary for those who want to understand the reg gene protein. This article has compiled the characteristics, functions, and current effects on disease of the reg gene family for the convenience of those who wish to understand them However, as a drug, reg gene protein is not mature enough, and its specificity of expression in different organs still needs to be further studied, as well as its administration dose, administration time and side effects as a drug, a large number of experiments are needed to study, which will be the direction of future research.

Keywords: Reg family proteins; C-type lectin domains; clinical application challenges.

1. Introduction

The regenerating gene (Reg) family can be categorized into four distinct groups(Reg1, Reg2, Reg3 and Reg4)based on their diverse structural characteristics and functional attributes [1]. In rodents, Reg family includes Reg1, Reg 2, Reg3α, Reg3β, Reg3γ, Reg3δ and Reg4, but Reg family which in human being, they are REG1A, REG1B, REG3α,REG3γ, and REG4 [2]. There are some similarities between the two groups, such as REG3α is 62–67% similar to murine Reg3α and Reg3γ [2]. Reg family both have the C-type lectin domain, therefore able to bind to sugars and recognize carbohydrate structures on the surface of pathogens. From the discovery of the new gene by Yamnoto et al in 1984, which was named Reg1 in 1997, to the cloning and determination of 18 reg families in recent years [3]. The REG protein family has a variety of functions including anti-inflammatory, antibacterial, anti-apoptosis, immunomodulatory effects and other functions [4]. Because REG protein family is involved in the proliferation and differentiation of cells in the pancreas, liver and other organs, they have potential and positive effects

on diabetes infections diseases cancer, etc [5]. For example REG3 can promote the proliferation of pancreatic beta cells and release more insulin. In addition, Reg3 protein is an effective membranous antibacterial defense protein, which is critical to the integrity of the intestinal barrier. researchers used INGAP-P in Reg3δfor the treatment of diabetes, which is currently in clinical study. In this study, patients with type 1 and type 2 diabetes (T2D) received 600 mg/d INGAP-P treatment respectively, after continuous treatment for 90 days, the level of C-peptide in the serum of patients with type 1 and T2D was significantly higher than that of the control group, and the control of blood glucose level was also significantly better. REGIIIα protein could serve as a potential treatment for diabetes.

In recent years, although scientists have found several reg family genes in rodents and humans, and measured data such as gene size, they have found a positive impact on human organs, but the substantial help in clinical medicine still needs more research. Based on the literature on reg family gene proteins, this paper will summarize the discovery process of reg genes and their currently known functions, such as the role of reg1 in islet proliferation and the promotion of growth and recovery of gastric mucosa. It will also discuss the current effects of several reg gene proteins on diabetes, cancer, inflammation and the development trend of reg family genes in treatment. This will be of some help to readers who want to understand Reg family proteins.

2. The Discovery Process Of REG Proteins

In 1984, Yamaoto et al. discovered a new gene encoding a 165-amino acid protein while screening the cDNA library of the regenerated islet In their experiments. They injected 90 percent of depancreatization and niacinamide into mice and found that expression of the gene increased in regenerated islets one month after partial pancreatectomy and reached a maximum three months after the operation. The increased expression of this new gene was associated with a decrease in urinary glucose levels over time and was later found to be activated in mice treated with extreme sulfoglucose. Therefore, they hypothesized that the expression of this new gene would affect the replication and regeneration of islet b cells, thereby promoting the role of insulin in diabetes.

Reg1 was discovered by different people and named by different names. De Caro A et al in pancreatic stone protein (PSP), which is also known as lithosthathine because of its potential role in inhibiting the formation of pancreatic stones Reg1, PSP, PTP, P19 and lithostathine all refer to the same gene or gene product. In humans, Reg1 gene is 3kb in size and contains six foreign and five endosomes [6]. Reg 1 can also be expressed in gastric enterochromaffin-like (ECL) cells because it is stimulated by gastrin.

Reg2 was detected only in the genome of mice, but it has not been detected in humans.The similarity between reg1 and reg2 in mice was 76% [2].

Reg genes in humans and mice were divided into three subgroups [7]. They are classified according to their different structure and chromosomal location [8]. Reg3 them also is divided into four subtypes (α, β, γ and δ), in mice Reg3α, Reg3β, Reg3γ, Reg3δ, and in humans has REG3α,REG3γ [2].REG3G has 65-66% homology with mouse Reg3a, Reg3b, and Reg3g [2]. All the genes of Reg 3 are 6 foreign sons, encoded into a protein with a length of 175 amino acids, and their mass is 16-17 kDA [9].

Reg4 was detected by Hartupee et al in 2001 and is clearly distinct from the other three subtypes [2]. Reg4 consists of seven exons, while in humans all reg proteins are located on the second chromosome (2p12), but the reg4 gene is located on chromosome 1 (1p11-3) [2]. In mice, reg4 is located on chromosome 3F3, while the other genes are on chromosome 6C3 [2]. Thus reg4 has the least similarity to the other genes. Table 1 shows the members of Reg family, length of amino acids and chromosome localization [3].

Table 1. Members of Reg family

Superfamily memeber	Species	Chromosome localization
Reg I	Mouse Reg I	6
	Rat Reg	4q33-q34
	Human Reg/PSP/PTP	2p12
Reg II	Mouse Reg	6
Reg III	Rat PAP	4q33-q34
	Rat peptide 23	4q33-q34
	Human HIP	2p12
	Bovine PTP	
Reg IV	uman Reg IV	1q12-q21

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Researchers have found 17 genes in various animals, most of which are highly similar, and they are expressed in various organs, and overexpressed in response to damage to their parts, causing positive effects in many ways.

3. The Function Of REG Proteins

The specific receptor of the Reg gene family has not been studied so far, and each gene protein pair may have an effect on a certain organ.

Reg1 is mainly expressed in intestinal chromosomal pigmented (ECL) cells and proteasome-secreting cells so that it promotes the growth and recovery of gastric mucosa. It also plays an important role in beta cell growth and regeneration

Reg1a is expressed in various organs and is particularly involved in the proliferation and differentiation of the digestive system. At the same time, studies have found that reg1a is also expressed in the central nervous system (CNS). In contrast, reg1a is strongly expressed in the infant brain but weakly expressed in the adult brain. So reg1-a may affect the germination and regeneration of neurons. This study suggests a potential effect of reg1a on Alzheimer's disease [10]. In primary Sjogren's syndrome, Reg1α is involved in the regeneration of salivary duct epithelial cells. However, antibodies to Reg1α were detected in the patient's serum, suggesting that Reg1α is also an autoantigen. These Reg1α autoantibody positive patients had significantly reduced salivary ability, and further studies suggested that reg1α-mediated autoimmunity may lead to the self-degeneration of salivary duct epithelial cells.

Reg2 is highly expressed in the islet and ductal epithelium of mice, it is an autoantigen of type 1 diabetes. Segment C of Reg2 is a calcium-dependent lectin like domain with high connexions, which has protective effect on beta cells of pancreatic islet. It is speculated that reg2 can protect beta cells while causing autoimmune damage. When the islet damage is relatively low, the immune system will not be activated with low or no expression of reg2. However, after the islet damage is aggravated, a large number of inflammatory factors will activate the immune system and promote the expression of reg2, which will cause the exacerbation of the disease [11].

REG3 protein is mainly expressed in the distal small intestine and is proteolytic by trypsin. Mice lacking the REG3 protein showed altered mucus distribution and increased bacterial contact with epithelial cells as well as elevated inflammatory markers in the ileum, suggesting that the REG3 protein plays an important role in regulating symbiotic relationships among gut microbes.

Reg4 protein has been found to be highly expressed in gastrointestinal cancer, breast cancer, ovarian cancer, prostate cancer, pancreatic cancer and other cancer diseases, which can significantly promote the proliferation, invasion and migration of tumor cells, resist apoptosis, and improve the degree of undifferentiation of tumor cells and the tolerance level of chemotherapy drugs [12]. Reg4 protein can promote the invasion and migration of tumor cells, and produce tolerance to drugs.Kadowaki et al. found that exogenous Reg4 protein can activate the phosphorylation of Erk1/2 molecule in gastric cancer cells, thus promoting cell proliferation. Reg4 can also induce the up-regulation of two cell invasion factors, MMP-7 and MMP-9, thereby promoting the invasion and metastasis of tumor cells.

4. The Current Effects On Disease

4.1 Diabetes

Diabetes is a chronic disease characterized by hyperglycemia, which is caused by the insufficiency of absolute or relative insulin secretion and the insufficiency of its utilization.The pathogenesis of diabetes is mainly due to the insensitive response of insulin receptors to insulin, which leads to the regulation of glucose metabolism. The high concentration of glucose in the body stimulates the islet beta cells to secrete a large amount of insulin compensatory, resulting in hyperinsulinemia. However, high insulin concentration can reduce the expression or sensitivity of insulin receptor on the cell surface, which leads to the decrease of sugar intake of peripheral cells. In the early and middle stages of diabetes mellitus, most broad-spectrum hypoglycemic drugs on the market can control blood sugar levels and reduce the damage caused by hyperglycemia by inhibiting or regulating the absorption and metabolism of sugar. In the later stage of diabetes, the islet beta cells are damaged and apoptotic due to exhaustion, and the islet tissue has insufficient self-repair and regeneration ability, resulting in absolutely insufficient insulin secretion, which will greatly accelerate the process of diabetes. Recent 10 years of research have shown that Reg protein has the function of protecting pancreatic β cells, resisting cell necrosis and apoptosis, and promoting tissue regeneration.

Reg2 has a significant protective effect on high-fat food-induced obesity mouse models. After 19 weeks of high-fat feeding, the number and area of islet cells and serum insulin levels of REG2-deficient mice were significantly reduced compared with those of wild-type mice. At the same time, REG2-deficient mice fed normal food began to develop abnormal glucose tolerance symptoms at 13-14 months, accompanied by a decrease in serum insulin levels. It can be concluded that Reg2 protein has a protective effect on islet cells in diabetic or elderly mice (with

decreased islet compensatory proliferation and regeneration capacity).Increased REG3A in humans improves glucose and lipid homeostasis in nutritional and genetic mouse models of obesity and type 2 diabetes. Overexpression of REG3A in the liver of mice showed improved glucose homeostasis, which reflected better insulin sensitivity in normal weight and obese states [13]. Reg3β is an anti-inflammatory factor that increases pancreatic resistance to inducers of acute pancreatitis [14]. the study of Reg3β protein, it was found that administration of recombinant Reg3β protein had a resistance to STZ-induced islet injury in mice. Tail intravenous administration of recombinant Reg3β protein can significantly reduce the blood glucose level, maintain body mass, alleviate the damage of islet tissue, and increase pancreatic insulin production in diabetic mice.

4.2 Cancer

Reg1α, Reg3α and Reg4 proteins are highly expressed in tumor cells, which have important effects on tumor development, treatment and prognosis.PAP is overexpressed in colorectal cancer [15]. Reg1 can be expressed in gastrointestinal chromatide-like (ECL) cells [16]. This suggests that Reg I acts as an autocrine or paracrine tumor inhibitor. Reg4, can regulate the proliferation of tumor cells through PI3K/Akt, PKA or PKC and Rho-like GTPase signaling pathways. The proliferation and growth of tumor cells were promoted by increasing the phosphorylation of EGFR. By up-regulating the expression of Bcl-2, Bcl-XL and survivin, the anti-apoptosis ability of tumor cells was improved. At the same time, Reg4 can also induce the up-regulation of two cell invasion factors, MMP-7 and MMP-9, thereby promoting the invasion and metastasis of tumor cells. It can be seen that Reg4 plays an important role in the development of tumor diseases. Therefore, taking Reg4 as the target and antagonizing Reg4 protein can inhibit multiple pathways of tumor disease development, thus inhibiting tumor growth, proliferation, drug resistance and metastasis.REG4 can serve as a biomarker for cancer tumorigenesis, subsequent progression, and poor prognosis, and may be a useful target for gene therapy [17].

4.3 Inflammation

Reg protein also plays a very important role in inflammation. inflammatory bowel disease (IBD) is one of the most serious diseases affecting human health. IBD includes ulcerative colitis (UC) and Crohn's disease (CD), both of which are immune-mediated intestinal mucosal damage and persistent chronic inflammation. Reg protein is also expressed in pseudomembranous colitis. These results suggest that Reg protein plays an important role in the injury and repair of intestinal inflammation. In addition, the high expression of Reg protein in liver can effectively resist the damage of hepatitis. The research group of the author also found that recombinant Reg3α and Reg4 proteins had anti-inflammatory and other protective effects in L-Ag-induced mouse pancreatitis model.

The regulation of Reg protein expression is closely related to some inflammatory factors such as IL-6, IL-22 and IFN-2. A large number of studies have shown that IL-6 and dexamethasone can induce Reg protein expression in a variety of cells. In inflammation, the inflammatory environment generated by tissue injury and cell necrosis will induce the expression of Reg protein, so that it can participate in tissue damage repair and play an anti-inflammatory role. However, the insufficient expression of endogenous Reg protein and the delayed expression time may not be enough to improve the condition of patients, and exogenous administration of REG protein is needed to achieve therapeutic effect. Therefore, the construction and modification of recombinant protein drugs based on Reg protein will have a great promotion effect on the treatment of major inflammatory diseases such as UC and pancreatitis.

The Reg protein family contains multiple protein molecular members, which play different functions in different diseases. With the deepening of the research on Reg protein, the development of drugs based on its function has emerged in an endless stream.

In conclusion,Reg protein has the function of protecting and promoting regeneration of tissues and cells damaged in various diseases. Among them, Reg3β has a good therapeutic effect on diabetes; Reg3α and Reg4 have obvious anti-inflammatory effects. Although Reg1α and Reg2 are autoantigens, they also play an important role in promoting tissue repair and regeneration.

5. Conclusion

The Reg family genes are divided into four groups. The Reg family which in human being, they are REG1A, REG1B, REG3α,REG3γ, and REG4. They have some similarities. Different reg gene proteins have different functions. For example, Reg3β have better therapeutic effects on diabetes. Reg3α and Reg4 have obvious anti-inflammatory effects. This article has compiled the characteristics, functions, and current effects on disease of the reg gene family for the convenience of those who wish to understand them However, as a drug, reg gene protein is not mature enough, and its specificity of expression in different organs still needs to be further studied, as well as its administration dose, administration time and side effects as a drug, a large number of experiments are needed to

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