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# Application of pancreatic regenerating protein in early warning and diagnosis of diabetes mellitus

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**Abstract**: Pancreatic regenerating (REG) protein belongs to the calcium-dependent lectin superfamily, and is encoded by a regenerating gene. As secreted growth factors with multiple functions, REG protein family plays a regulatory role in nutrient metabolism, anti-apoptosis, anti-fibrosis, anti-inflammation and antibacterial. Since 1979, REG protein family has been found to be associated with various diseases, such as diabetes, inflammation and cancer. Several subtypes of REG proteins are involved in different pathogenesis of diabetes. The purpose of this study is to review the origin, structural characteristics, distribution patterns of REG protein family and its pathogenesis and therapeutic regulation in different types of diabetes, and to explore the potential application value of REG protein family in the early warning, diagnosis, treatment and prognosis of diabetes, with a view to its wider application in the fields of therapeutic targets and biomarkers in the future.

**Keywords**: Pancreatic regenerating protein; Regeneration of islet beta cell; Diabetes mellitus; Diabetes of exocrine pancreas; Clinical early warning
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Pancreatic regenerating (REG) protein is primarily expressed in pancreatic tissue, synthesized and secreted by pancreatic acinar cells, and expressed at low levels in the gastrointestinal tract, brain tissue, and urinary system. An increase in the expression of REG protein can be observed *in situ* or ectopically when there is inflammatory damage to the tissue [1]. REG protein plays an anti-apoptotic and regenerative role in islet β-cells and nerve cells, as well as a proliferative, differentiative, and anti-infective role in the liver, pancreas, and gastrointestinal tract [2]. This article reviews the application value of the REG protein family in diabetes warning, diagnosis, and treatment.

## 1 Origin and Classification of the REG Protein Family

In 1979, De Care *et al.* first isolated a novel protein called pancreatic stone protein (PSP) from pancreatic stones of patients with chronic calcifying pancreatitis. A pH-dependent protein called pancreatic thread protein (PTP) was discovered in human pancreatic tissue and pancreatic juice. A pancreatic regeneration-related gene related to the regeneration, proliferation, and differentiation of islet β-cells was screened from a cDNA library of regenerated islet cells in rats with 90% of their pancreas removed, and was named the regenerating gene (*REG* gene). The small molecular weight (16,000) protein enCoded by the *REG* gene is called REG protein. Watanabe isolated the *REG* gene from human pancreatic tissue and found through sequencing analysis that PSP, PTP, and REG proteins may be products enCoded by the same *REG* gene, unifying their names as REG protein[3]. REG I, REGII, REGIII, and *REGIV* constitute a large

*REG* gene family, encoding different subtypes of REG proteins. Currently, the names of REG family members are mixed and not yet unified. This discussion summarizes and categorizes relevant terminology based on NCBI Genebank **[Table 1]** [4].

## 2 Structure and Function of REG Proteins

The REG protein family belongs to the calcium-dependent plant lectin superfamily, characterized by the presence of a C-type lectin domain (CTLD) that selectively binds to various ligands and carbohydrates to exert biological effects. REG family genes are highly homologous, and the protein structures are conserved, but different protein subtypes exhibit different characteristics and perform different functions.

The *REGI* gene is located on chromosome 2p12, with a full length of 2,922 bp, encoding 166 amino acids. The REGI protein has a signal peptide composed of 22 amino acids at the N-terminus, which has the function of cleaving protein chains. REGI protein has two subtypes, REGIα and REGIβ, with 87% homology. Human REGI protein contains an externally attached glycan, producing different isoforms, which may be related to protein localization and stability. The receptor of REG Iα is exostosin tumor-like 3 (EXTL3), which can mediate REG Iα protein to regulate the growth of nerve synapses. REGI protein has the biological effect of promoting the proliferation and regeneration of pancreatic cells (islet β cells), gastric epithelial cells, and gastric progenitor cells. Overexpression of REGI protein significantly attenuates the apoptotic effect of tumor necrosis factor-alpha (TNF-α) in pancreatic cells [5].

The *REGII* gene is only expressed in rodents, while the REGIII gene expresses four subtypes in rodents and two in humans, namely REGIIIα and REGIIIγ. Human REGIIIα protein is also known as hepatocarcinoma intestinal pancreatitis-associated protein or pancreatitis-associated protein. REGIIIα protein has no biological activity under normal physiological conditions, but exhibits antibacterial properties after trypsin hydrolysis. REGIIIγ protein, also known as pancreatitis-associated protein B, is similar to REGIIIα protein and has important clinical significance in early recognition of pancreatitis, assessment of disease severity, and prognosis [6-7]. The *REG IV* gene is expressed in both humans and rodents, but it has the lowest homology with the *REG* gene family. Unlike other *REG* genes with six exons, the *REG IV* gene has seven exons. The *REG IV* gene is located independently on chromosome 1p12 and is involved in tumorigenesis and development [8].

Multiple studies have suggested that the REG protein family in pancreatic exocrine cells significantly increases its expression under injury or inflammatory stimulation, binding to the pancreatic endocrine cell surface receptor EXTL3 through paracrine or autocrine forms, exerting effects such as promoting proliferation, resisting apoptosis, inducing differentiation, and anti-inflammatory and anti-infective actions [9].

**Tab. 1** List of REG family classifications

| Name/Gene ID | Aliases | Location | Translation Product (amino acid) |
|---|---|---|---|
| ***Homo sapiens*** **(human)** | | | |
| REGIα (REG1A) | PSP, PSPS, PSPS1, PTP, REG | 2p12 | 166 |
| REGIβ (REG1B) | PSPS2, REGH, REGL | 2p12 | 166 |
| REGIIIα (REG3A) | PAP, PAP1, REG3, REGIII, INGAP, HIP/PAP | 2p12 | 175 |
| REGIIIγ (REG3G) | PAP1B, UNQ429, LPPM429, REGIII | 2p12 | 175 |
| REGIV (REG4) | GISP, RELP | 1p12 | 158 |
| ***Mus musculus*** **(house mouse)** | | | |
| RegI (Reg1) | PSP, PTP | 6C3 | 165 |
| RegII (Reg2) | PSP, PTP, REG-2 | 6C3 | 173 |
| RegIIIα (Reg3a) | AV063448 | 6C3 | 175 |
| RegIIIβ (Reg3b) | HIP, Pap, PAP1, REG-III | 6C3 | 175 |
| RegIIIδ (Reg3d) | INGAP, Ingaprp | 6C3 | 175 |
| RegIIIγ (Reg3g) | AI449515 | 6C3 | 174 |
| RegIV (Reg4) | GISP, RELP, 2010002L15Rik | 3F2.2 | 157 |
| ***Rattus norvegicus*** **(Norway rat)** | | | |
| RegIα (Reg1a) | Reg, RGPI, Reg1, Rgp1, LITHOST, RATRGPI, RATLITHOST | 4q33 | 165 |
| RegIIIα (Reg3a) | Pap2, PapII | 4q33 | 174 |
| RegIIIβ (Reg3b) | Pap, Pap1 | 4q33 | 180 |
| RegIIIγ (Reg3g) | Pap3, PAPIII | 4q33 | 174 |
| RegIV (Reg4) | — | 2q34 | 157 |

## 3 The Relationship between REG Protein Family and Different Types of Diabetes

Diabetes is a metabolic disorder syndrome characterized primarily by hyperglycemia. In 2021, the International Diabetes Federation (IDF) reported that the number of adult diabetic patients globally was 537 million, and it is expected to reach 783 million by 2045 [10]. The number of diabetic patients in China has reached 140 million [11], ranking first in the world. This section provides an overview of the pathogenesis characteristics of different types of diabetes and the role of REG protein family in diabetes.

### *3.1 Type 1 Diabetes Mellitus (T1DM)*

The incidence of T1DM is increasing year by year, with nearly 2/3 of T1DM patients belonging to adult-onset cases. Its pathogenesis and clinical manifestations are highly heterogeneous, making early diagnosis and differential diagnosis more difficult, often leading to misdiagnosis as type 2 diabetes mellitus

(T2DM). Currently, there are four common mechanisms for T1DM.

First, insulin deficiency caused by autoimmune destruction, with the core pathological and physiological characteristics being immune-mediated islet β-cell injury and chronic inflammation leading to absolute insulin deficiency [12].

Second, insulin resistance. Some T1DM patients exhibit characteristics of "double diabetes". Patients with T1DM who have both metabolic disorders and autoimmune abnormalities often experience insulin resistance. The genetic characteristics of these "double diabetes" patients are highly similar to those of T1DM patients [13].

Third, obesity-related T1DM. The proportion of T1DM patients with overweight and obesity is increasing year by year. The risk of developing childhood and adolescent T1DM in the offspring of overweight or obese women is significantly higher. Overweight and obese T1DM patients are more likely to experience insulin resistance and other characteristics of "double diabetes" [14].

Forth, programmed death receptor-1 (PD-1) / programmed death ligands (PD-Ls) pathway theory. Activated immune T cells express the type I transmembrane glycoprotein PD-1. When PD-1 binds to its ligand PD-Ls, it inhibits T cell activation, reduces islet β-cell damage, and limits the development of T1DM. Lack of PD-Ls in the body can lead to increased activation of autoimmune T cells, increasing the susceptibility and risk of T1DM.

The four mechanisms described above illustrate different ways of damaging islet β-cells, suggesting that islet β-cells are a key factor in the development of T1DM. The REG protein family plays a certain biological role in the process of resistance to apoptosis and proliferation and regeneration of islet β-cells. In *REGI* gene knockout mice, the size of the islets was significantly reduced, and the number was significantly decreased. *REGI* gene overexpression increased islet beta cell regeneration in mice. The progression of diabetes in T1DM offspring mice carrying overexpressed *REGI* gene was significantly delayed. Endoplasmic reticulum stress is an important mechanism for islet beta cell damage. In the model induced by endoplasmic reticulum stress, REGI protein levels were upregulated; the serum REGIprotein level of diabetic patients caused by endoplasmic reticulum stress was also significantly increased [9]. REGII protein is unique to rodents, with autoimmune epitopes at its N-terminus, which induce islet beta cell damage and participate in the occurrence of T1DM. However, its C-terminus has a calcium-like lectin domain that protects the islets. When mouse insulinoma cells overexpress endogenous *REGII* gene, mitochondrial damage and endoplasmic reticulum stress in islet β-cells are inhibited. Specific knockout of the *REGII* gene leads to decreased insulin levels and impaired glucose tolerance in mice. REGII is involved in the pathogenesis of diabetes and regulates the proliferation and regeneration of islet β-cells.

Bariatric surgery is gradually being used in obese patients with T1DM to adjust the secretion and release of various intestinal hormones, helping to reduce insulin resistance, control blood sugar, reduce weight, and improve overall metabolism [15]. The main advantage of stem cell therapy (SCT) is to down-regulate immune rejection and promote the differentiation of stem cells into functional islet β-cells or β-like cells to treat T1DM [16]. Inducing the proliferation and regeneration of islet β-cells is another potential method for treating diabetes. The biological role of the REG family in the regeneration and proliferation of islet β-cells is expected to become a new target for the treatment of T1DM.

### *3.2 T2DM*

The survey in 2023 showed that the prevalence of T2DM globally is increasing at a rate of over 1.5% annually [17]. The pathogenesis of T2DM is complex, with eight previous pathophysiological abnormalities and four new mechanisms of pathogenesis, collectively forming the "twelve-part theory" [18]. This section will briefly describe the four new mechanisms.

Firstly, the activation of chronic inflammation, which mainly refers to metabolic inflammation in T2DM, is characterized by immune cell infiltration, abnormal production of cytokines, and activation of inflammatory signaling pathways. Cytokines such as IL-1β, TNF-α, and IL-6 have been proven to be key factors involved in the pathogenesis of pancreatic β-cell damage; signaling pathways such as c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and extracellular signal-regulated protein kinase 1/2 (ERK1/2) are related to the dysfunction and apoptosis of pancreatic β-cells. Therapeutic drugs targeting this pathway include glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, and anti-inflammatory drugs [19].

Secondly, immune dysfunction, characterized by reduced activity of natural killer cells (NK cells), leading to abnormal T-cell immune function, abnormal secretion of multiple cytokines and receptor levels, resulting in immune dysfunction in T2DM patients. Therapeutic drugs targeting this pathway include GLP-1 receptor agonists, SGLT-2 inhibitors, and immunomodulators [20].

Furthermore, intestinal flora imbalance has been proven to participate in the disease process of T2DM through various complex mechanisms. Currently, the short-chain fatty acid theory, bile acid theory, and endotoxin theory are widely recognized. Therapeutic drugs targeting this pathway include GLP-1 receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, α-glucosidase inhibitors, amylase analogs, and metformin [21].

Last, excessive deposition of pancreatic amyloid protein; in healthy individuals, the pancreas secretes islet amyloid polypeptide to help regulate blood sugar levels and gastric food volume. In pathological conditions, islet amyloid polypeptide transforms into amyloid fibrils that deposit and accumulate in the body, destroying islet

β-cells and islet structure [22]. The specific mechanism of amyloid polypeptide lesions is still unclear, and drug development targeting this pathway is a focus for the future.

Clinical studies have shown that REG Iα protein is closely related to T2DM and its complications. Except for patients with T1DM, serum REG Iα protein levels are also significantly elevated in patients with T2DM, suggesting that REG Iα protein can be used as a biomarker for pancreatic β-cell damage and regeneration. Yang *et al.* [23] reported that both newly diagnosed T2DM patients and long-term T2DM patients with multiple complications had upregulated serum REG Iα protein levels, and the increasing trend was associated with the duration of diabetes. The longer the duration of diabetes, the higher the serum REG Iα protein level, suggesting that serum REG Iα protein can help predict the progression of T2DM. Zhu *et al.* [24] found that compared with healthy controls and diabetic patients, diabetic kidney disease patients had higher serum REG Iα protein levels, and REG Iα protein was positively correlated with serum creatinine levels and negatively correlated with glomerular filtration rate, suggesting that REG Iα may be a potential indicator of renal insufficiency. Wang *et al.* [25] also confirmed that the REG Iα gene can be used as a biomarker to predict the risk of diabetic kidney disease.

REG Iα protein is a potential new biomarker for predicting the occurrence and development of T2DM and its complications, with clinical practical value.

### *3.3 Gestational Diabetes Mellitus and Special Types of Diabetes Mellitus*

In 2021, the International Diabetes Federation (IDF) reported that the global incidence of gestational diabetes mellitus (GDM) reached 16.7% [10]. Insulin resistance is the primary feature of GDM, and in the middle and late stages of pregnancy, maternal obesity and various hormones released by the placenta can cause varying degrees of insulin resistance, leading to GDM [26]. Serum REG Iα can be used as a potential novel biomarker for early detection of pregnancy-related diseases [27]. Zhu *et al.* [28] and Romana *et al.* [29] found that serum REG Iα levels are closely related to renal function in pregnant women and are potential biological indicators for assessing renal insufficiency in GDM pregnant women.

Diabetes of exocrine pancreas (DEP) belongs to special types of diabetes, mainly including post-pancreatitis diabetes, diabetes associated with pancreatic cancer, and diabetes related to cystic fibrosis [30]. The main pathogenesis of DEP includes pancreatic islet dysfunction and insulin secretion insufficiency, insulin resistance, reduced intestinal-derived incretin, intestinal flora disturbance, and genetic factors [31]. *REGI* is a biomarker for pancreatitis [32] and pancreatic cancer [33]. Although there are no direct studies exploring the relationship between the REG family and DEP, given the close relationship between the REG family and the causes of DEP, pancreatitis, and pancreatic cancer, it suggests that REG may have a certain association with DEP. The protective role of the REG family in pancreatic β-cells is also expected to provide new ideas and targets for the treatment of DEP.

## 4 Conclusion and Prospect

In summary, the REG protein family plays an important role in the field of diabetes, promoting the regeneration, proliferation, and differentiation of pancreatic β-cells as a cell regeneration factor. It is expected to provide new ideas and directions for targeted diabetes treatment in the future. REG Iα protein, a member of this family, is a novel biomarker for diabetes and diabetic complications, and has a clinical warning role in the risk of diabetic kidney disease. However, current research on REG family proteins is still not comprehensive and in-depth, and the signaling pathways and expression regulation methods are not yet unified. The causal relationship as a biomarker is still unclear and requires continuous research in molecular research and long-term, multicenter, prospective cohort studies.

**Conflicts of Interest** None

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· 学术前沿 ·

# 胰腺再生蛋白在糖尿病预警及诊疗中的应用价值

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**摘要**：胰腺再生(REG)蛋白是由再生基因编码的一组钙依赖性凝集素超家族蛋白。REG 蛋白家族作为具有多种功能的分泌型生长因子，在营养代谢、抗凋亡、抗纤维化和抗炎抗菌等方面起着调节作用。自 1979 年被首次发现至今，REG 蛋白家族被证实与糖尿病、炎症和肿瘤等多种疾病息息相关。REG 蛋白家族的多种亚型参与糖尿病的不同发病机制。本文旨在综述 REG 蛋白家族的起源、结构特征、分布模式、在各种类型糖尿病中的发病机制和治疗调控作用，探讨 REG 蛋白家族在糖尿病预警、诊断、治疗和预后方面的潜在临床应用价值，以期未来更广泛地应用于治疗靶标和生物标志物领域。

**关键词**：胰腺再生蛋白；胰岛 β 细胞再生；糖尿病；胰腺外分泌糖尿病；临床预警

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# Application of pancreatic regenerating protein in early warning and diagnosis of diabetes mellitus

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**Abstract**: Pancreatic regenerating (REG) protein belongs to the calcium-dependent lectin superfamily, and is encoded by regenerating gene. As secreted growth factors with multiple functions, REG protein family plays a regulatory role in nutrient metabolism, anti-apoptosis, anti-fibrosis, anti-inflammation and antibacterial. Since 1979, REG protein family has been found to be associated with various diseases, such as diabetes, inflammation and cancer. Several subtypes of REG proteins are involved in different pathogenesis of diabetes. The purpose of this study is to review the origin, structural characteristics, distribution patterns of REG protein family and its pathogenesis and therapeutic regulation in different types of diabetes, and to explore the potential application value of REG protein family in the early warning,

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diagnosis, treatment and prognosis of diabetes, with a view to its wider application in the fields of therapeutic targets and biomarkers in the future.

**Keywords**: Pancreatic regenerating protein; Regeneration of islet beta cell; Diabetes mellitus; Diabetes of exocrine pancreas; Clinical early warning

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胰腺再生(regenerating, REG)蛋白主要在胰腺组织中表达,由胰腺腺泡细胞合成并分泌,在胃肠道、脑组织、泌尿系统中低水平表达。当组织存在炎性损伤时可观察到原位或异位的 REG 蛋白表达增加[1]。REG 蛋白在胰岛 β 细胞和神经细胞中发挥抗凋亡和再生作用,在肝脏、胰腺和胃肠道中发挥增生分化和抗感染作用[2]。本文通过综述探讨 REG 蛋白家族在糖尿病预警及诊疗中的应用价值。

## 1　REG 蛋白家族的起源和分类

1979 年,De Care 等首次从慢性钙化性胰腺炎患者的胰腺结石中分离出一种新型蛋白,称为胰石蛋白(pancreatic stone protein, PSP)。有研究在人体胰腺及胰液中发现一种 pH 依赖性蛋白,称为胰丝蛋白(pancreatic thread protein, PTP);在切除 90%胰腺的大鼠再生胰岛细胞 cDNA 库中筛选出与胰岛 β 细胞的再生、增殖和分化有关的胰腺再生相关基因,命名为再生(*regenerating*, *REG*)基因。*REG* 基因编码的小分子量(16 000)蛋白被称为 REG 蛋白;Watanabe 从人体胰腺中分离出 *REG* 基因,通过测序分析发现 PSP、PTP 和 REG 蛋白可能是同一基因 *REG* 编码的产物,将其名称统一为 REG 蛋白[3]。*REG* Ⅰ、*REG* Ⅱ、*REG* Ⅲ和 *REG* Ⅳ组成了庞大的 *REG* 基因家族,编码不同亚型 REG 蛋白。目前,REG 家族成员名称混杂且尚未统一,本论述基于 NCBI Genebank 对相关术语进行归纳汇总(表 1)[4]。

## 2　REG 蛋白的结构和功能

REG 蛋白家族属于钙依赖性植物凝集素超家族,特征是存在 C 型凝集素结构域(C-type lectin domain, CTLD)选择性结合多种配体和碳水化合物发挥生物学效能。REG 家族各基因间高度同源,蛋白结构保守,但蛋白亚型之间表现出不同特征,发挥不同功能。

*REG* Ⅰ基因位于 2p12 号染色体,全长 2 922 个 bp,编码 166 个氨基酸。REG Ⅰ蛋白 N 端存在 22 个氨基酸构成的信号肽,具有剪切蛋白质链的作用。REG Ⅰ蛋白有 REG Ⅰα 和 REG Ⅰβ 两种亚型,同源性达 87%。人 REG Ⅰ蛋白中含有一个外连的聚糖,产生不同的异构体,可能与蛋白质的定位和稳定性有关。REG Ⅰα 的受体是外生骨疣肿瘤样蛋白 3(exostosin tumor-like 3, EXTL3),能够介导 REG Ⅰα 蛋白调节神经突触的生长。REG Ⅰ蛋白具有促进胰腺细胞(胰岛 β 细胞)、胃上皮细胞和胃祖细胞增殖再生的生物学作用。过表达 REG Ⅰ蛋白显著减弱肿瘤坏死因子-α(tumor necrosis factor-alpha, TNF-α)在胰腺细胞中的凋亡作用[5]。

**表 1**　REG 家族分类一览表
**Tab. 1**　List of REG family classifications

| 名称 | 别名 | 染色体位置 | 蛋白全长(aa)[a] |
|---|---|---|---|
| *Homo sapiens* (human) | | | |
| REG Ⅰα (REG 1A) | PSP, PSPS, PSPS 1, PTP, REG | 2p12 | 166 |
| REG Ⅰβ (REG 1B) | PSPS 2, REGH, REGL | 2p12 | 166 |
| REG Ⅲα (REG 3A) | PAP, PAP 1, REG 3, REGⅢ, INGAP, HIP/PAP | 2p12 | 175 |
| REG Ⅲγ (REG 3G) | PAP 1B, UNQ429, LPPM429, REG Ⅲ | 2p12 | 175 |
| REG Ⅳ (REG 4) | GISP, RELP | 1p12 | 158 |
| *Mus musculus* (house mouse) | | | |
| Reg Ⅰ (Reg 1) | PSP, PTP | 6C3 | 165 |
| Reg Ⅱ (Reg 2) | PSP, PTP, REG-2 | 6C3 | 173 |
| Reg Ⅲα (Reg 3a) | AV063448 | 6C3 | 175 |
| Reg Ⅲβ (Reg 3b) | HIP, Pap, PAP 1, REG-Ⅲ | 6C3 | 175 |
| Reg Ⅲδ (Reg 3d) | INGAP, Ingaprp | 6C3 | 175 |
| Reg Ⅲγ (Reg 3g) | AI449515 | 6C3 | 174 |
| Reg Ⅳ (Reg 4) | GISP, RELP, 2010002L15Rik | 3F2.2 | 157 |
| *Rattus norvegicus* (Norway rat) | | | |
| Reg Ⅰα (Reg 1a) | Reg, RGPI, Reg 1, Rgp 1, LITHOST, RATRGPI, RATLITHOST | 4q33 | 165 |
| Reg Ⅲα (Reg 3a) | Pap 2, Pap Ⅱ | 4q33 | 174 |
| Reg Ⅲβ (Reg 3b) | Pap, Pap 1 | 4q33 | 180 |
| RegⅢγ (Reg3g) | Pap 3, PAP Ⅲ | 4q33 | 174 |
| Reg Ⅳ (Reg 4) | — | 2q34 | 157 |

注:[a] 表示氨基酸(animo acid, aa)。

*REG* Ⅱ基因仅在啮齿动物中表达,*REG* Ⅲ基因在啮齿动物中表达 4 种亚型,在人类中表达 2 种,分别为 REG Ⅲα 和 REG Ⅲγ。人类 REG Ⅲα 蛋白又称为肝癌肠胰腺炎相关蛋白或胰腺炎相关蛋白。REG Ⅲα 蛋白在正常生理状态下无生物学活性,经胰蛋白酶水解后表现出抗菌特性;REG Ⅲγ 蛋白又被称为胰腺炎相关蛋白 B,与 REG Ⅲα 蛋白相似,在早期识别胰腺炎、评估疾病严重程度和预后转归中具

有重要临床意义[6-7]。*REG* Ⅳ基因在人类和啮齿动物中均有表达,但其与 *REG* 基因家族同源性最低,与其它 *REG* 基因具有 6 个外显子不同,*REG* Ⅳ基因有 7 个外显子。*REG* Ⅳ基因独立位于 1p12 号染色体上,参与肿瘤的发生发展[8]。

多项研究提示,胰腺外分泌细胞中的 REG 蛋白家族在损伤或炎症刺激下表达显著增多,通过旁分泌或自分泌的形式与胰腺内分泌细胞表面受体 EXTL3 结合,发挥促进增殖、抵抗凋亡、诱导分化和抗炎抗感染的作用[9]。

## 3　REG 蛋白家族与不同类型糖尿病的关系

糖尿病是一种以高血糖为主要特征的代谢紊乱综合征。2021 年,据国际糖尿病联盟(International Diabetes Federation, IDF)报道,全球成年糖尿病患者为 5.37 亿,预计到 2045 年将达到 7.83 亿[10]。我国糖尿病患者高达 1.4 亿[11],患病人数跃居全球首位。本节对不同类型糖尿病的发病特点和 REG 蛋白家族在糖尿病中的作用价值作概述。

### 3.1　1 型糖尿病(type 1 diabetes mellitus, T1DM)

T1DM 发病率逐年增长,近 2/3 的 T1DM 患者属于成人起病,其发病原因和临床表现具有较大异质性,早期诊断和鉴别诊断更为困难,多被误诊为 2 型糖尿病(type 2 diabetes mellitus, T2DM)。目前 T1DM 有以下四种常见机制。第一种是自身免疫破坏导致的胰岛素缺乏,核心病理生理特征是免疫介导的胰岛 β 细胞损伤和慢性炎症导致的胰岛素分泌绝对不足[12]。第二种机制是胰岛素抵抗学说,部分 T1DM 患者出现“双重糖尿病”特征。同时存在代谢失调和自身免疫异常的 T1DM 患者常出现胰岛素抵抗。“双重糖尿病”患者的遗传学特征与 T1DM 患者有较高相似度[13]。第三种机制是肥胖相关性 T1DM,伴有超重和肥胖的 T1DM 患者比例逐年增加,超重或肥胖女性的后代发生儿童和青少年 T1DM 的风险显著升高,超重和肥胖的 T1DM 患者更容易出现胰岛素抵抗等“双重糖尿病”的特征[14]。第四种机制是程序性死亡受体-1(PD-1)/程序性死亡配体(PD-Ls)途径学说。活化免疫性 T 细胞表达 I 型跨膜糖蛋白 PD-1,PD-1 与其配体 PD-Ls 结合,抑制 T 细胞活化,减轻胰岛 β 细胞损伤,限制 T1DM 的发病。机体缺乏 PD-Ls 可导致自身免疫性 T 细胞活化增多,T1DM 易感性和患病风险增加。

上述四种机制简述了破坏胰岛 β 细胞的不同途径,提示胰岛 β 细胞是 T1DM 发生发展中的关键因素。REG 蛋白家族在胰岛 β 细胞抵抗凋亡和增殖再生过程中发挥一定生物学作用。*REG* Ⅰ基因敲除小鼠的胰岛大小显著减小,数量显著减少;*REG* Ⅰ基因过表达小鼠胰岛 β 细胞再生增加;携带过表达 *REG* Ⅰ基因的 T1DM 子代小鼠糖尿病进展明显延缓。内质网应激是胰岛 β 细胞损伤的重要机制。内质网应激诱导的模型中,REG Ⅰ蛋白水平上调;内质网应激导致的糖尿病患者血清 REG Ⅰ蛋白水平也明显升高[9]。REG Ⅱ蛋白为啮齿动物所独有,其 N 端有自身免疫反应表位,诱发胰岛 β 细胞损伤,参与 T1DM 的发生;但其 C 端又具有钙样凝集素结构域起到胰岛保护作用。小鼠胰岛素瘤细胞过表达内源性 *REG* Ⅱ基因时,胰岛 β 细胞的线粒体损伤和内质网应激被抑制。特异性敲除 *REG* Ⅱ基因导致小鼠胰岛素水平降低和葡萄糖耐量受损。*REG* Ⅱ基因既参与糖尿病发病过程,又调控胰岛 β 细胞的增殖再生。

减重手术逐渐应用于肥胖型 T1DM 患者,调整多种肠道激素的分泌和释放,有助于降低胰岛素抵抗,控制血糖,减轻体重,改善全身代谢[15]。干细胞疗法(stem cell therapy, SCT)的主要优势在于下调免疫排斥反应和促使干细胞分化为功能性胰岛 β 细胞或 β 样细胞治疗 T1DM[16]。诱导胰岛 β 细胞增殖再生是另一种治疗糖尿病的潜在方法。REG 家族在胰岛 β 细胞再生增殖中的生物学作用有望成为 T1DM 治疗的新靶点。

### 3.2　T2DM

2023 年调查显示,全球 T2DM 的患病率每年增长超过 1.5%[17]。T2DM 发病机制复杂,既往 8 种病理生理异常加上 4 种新的发病机制,一起组成了“十二重奏”理论[18]。本节将对 4 种新增机制进行简述。首先是慢性炎症的激活,T2DM 中慢性炎症主要指代谢性炎症,病理特征为免疫细胞的浸润,细胞因子产生异常和炎症信号通路的激活,如 IL-1β、TNF-α 和 IL-6 等均被证明是参与胰岛 β 细胞损伤发生机制的关键细胞因子;c-Jun 氨基末端激酶(JNK)、p38 丝裂原活化蛋白激酶(MAPK)和细胞外调节蛋白激酶 1/2(ERK1/2)等信号通路与胰岛 β 细胞的功能障碍和凋亡有关。针对该靶点治疗药物为胰高血糖素样肽-1(GLP-1)受体激动剂和钠—葡萄糖协同转运蛋白 2(SGLT-2)抑制剂和抗炎药物[19]。其次是免疫功能缺陷,自然杀伤细胞(natural killer cells, NK 细胞)活性降低,使 T 细胞免疫功能异常,多种细胞因子分泌及受体水平异常,造成 T2DM 患者免疫功能障碍。针对该靶点治疗药物为 GLP-1 受体激动剂、SGLT-2 抑制剂和免疫调节剂[20]。再者为肠道菌群

失调,肠道菌群被证实通过多种复杂机制参与 T2DM 的疾病过程。目前公认的是短链脂肪酸理论、胆汁酸理论和内毒素理论。针对该靶点治疗药物:GLP-1 受体激动剂、二肽基肽酶 4(DPP-4)抑制剂、α-葡萄糖苷酶抑制剂、淀粉酶类似物、双胍类药物如二甲双胍[21]。最后是胰腺淀粉样蛋白的过度沉积;健康人体胰腺分泌胰岛淀粉样多肽,帮助调节机体血糖水平和胃内食物容量。病理状态下,胰岛淀粉样多肽变为淀粉样纤维蛋白沉积堆砌在体内破坏胰岛 β 细胞和胰岛结构[22]。淀粉样多肽病变的具体机制尚不明确,针对该靶点的药物研发是未来的重点。

临床研究显示,REGⅠα 蛋白与 T2DM 及其并发症密切相关。除 T1DM 患者外,T2DM 患者血清 REGⅠα 蛋白也有明显升高,提示 REGⅠα 蛋白可作为胰岛 β 细胞损伤和再生的生物标志物。Yang 等[23]报道称,新诊断 T2DM 患者和伴有多种并发症的长期 T2DM 患者均存在血清 REGⅠα 蛋白水平的上调,升高趋势与糖尿病病程相关。糖尿病病程越长,血清 REGⅠα 蛋白水平越高,提示血清 REGⅠα 蛋白有助于预测 T2DM 疾病进展。Zhu 等[24]发现与健康对照、糖尿病患者相比,糖尿病肾脏疾病的患者血清 REGⅠα 蛋白水平更高,且 REGⅠα 蛋白与血清肌酐水平呈正相关,与肾小球滤过率呈负相关,提示 REGⅠα可能是肾功能不全的潜在指标。Wang 等[25]也证实 *REG* Ⅰα 基因可作为预测糖尿病肾脏疾病发生风险的生物标志物。

REGⅠα 蛋白是预警 T2DM 发生发展、T2DM 并发症发生发展的潜在新型生物标志物,具有临床实用价值。

3.3　*妊娠糖尿病和特殊类型糖尿病*　2021 年 IDF 报道全球妊娠期糖尿病(gestational diabetes mellitus, GDM)发病率达 16.7%[10]。胰岛素抵抗是 GDM 最主要的特征,在妊娠中晚期由于母体肥胖和胎盘释放出的多种激素都会引起不同程度的胰岛素抵抗,导致出现 GDM[26]。血清 REGⅠα 可以作为潜在的新型生物标志物早期检测妊娠相关疾病[27]。Zhu 等[28]和 Brun 等[29]发现,血清 REGⅠα 水平与孕妇的肾功能密切相关,是评估 GDM 孕妇肾功能不全的潜在生物学指标。

胰腺外分泌糖尿病(diabetes of exocrine pancreas, DEP)属于特殊类型糖尿病,主要包括胰腺炎后糖尿病、胰腺癌相关糖尿病和囊性纤维化相关糖尿病[30]。胰岛功能障碍及胰岛素分泌不足、胰岛素抵抗、肠促胰岛激素减少、肠道菌群紊乱和遗传因素等是 DEP 的主要发病机制[31]。REGⅠα 是胰腺炎[32]、胰腺癌[33]的生物标志物。虽无直接研究探讨 REG 家族与 DEP 的关系,但鉴于 REG 家族与 DEP 的病因胰腺炎及胰腺癌关系匪浅,提示 REG 可能与 DPE 存在一定关联。REG 家族在胰岛 β 细胞中的保护作用也有望为 DEP 的治疗提供新思路和新靶点。

## 4　结语与展望

综上所述,REG 蛋白家族在糖尿病领域扮演着重要角色,作为细胞再生因子促进胰岛 β 细胞再生、增殖和分化,未来有望为糖尿病靶向治疗提供新思路和新方向。该家族中 REGⅠα 蛋白是糖尿病和糖尿病并发症的新型生物标志物,在糖尿病肾脏疾病发生风险中具有临床预警作用。但目前对 REG 家族蛋白的研究还不够全面和深入,信号通路和表达调控方式仍未统一,作为生物标志物的因果关系尚不明确,需要在分子机制研究和长期多中心前瞻性队列研究中深耕不辍。

**利益冲突**　本文所有作者均声明,不存在任何潜在利益冲突。

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