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(54)发明名称

一种用于治疗肠道疾病的融合蛋白

(57)摘要

本发明提供了一种用于治疗肠道疾病的融合蛋白,具有如下结构:R-L-P其中:R为GLP-2受体激动剂;L为连接肽链;P为长效载体蛋白,本发明提供的融合蛋白具有显著的生物活性及体外稳定性。

1. 一种融合蛋白,由GLP-2受体激动剂、长效载体蛋白和连接肽链组成,其中所述融合蛋白选自SEQ ID NO:16和SEQ ID NO:17。
2. 一种核苷酸序列,编码权利要求1所述的融合蛋白。
3. 一种重组表达载体,携带权利要求2所述的核苷酸序列。
4. 一种宿主细胞,转化权利要求3所述的重组表达载体。
5. 权利要求1所述的融合蛋白的用途,用于制备一种具有预防和/或治疗化疗中导致肠胃损伤、短肠综合症、Corhn' s 肠炎的药物。
6. 一种药物组合物,包含权利要求1所述的融合蛋白和药学上可接受的稀释剂、载体或赋形剂。

一种用于治疗肠道疾病的融合蛋白

技术领域

[0001] 本发明涉及生物医药技术领域,具体涉及一种用于治疗肠道疾病的融合蛋白。

背景技术

[0002] GLP-2是胰高血糖素原 (proglucagon) 基因经转录、翻译后处理加工形成的33个氨基酸的单链多肽,分子量约为3.9KD。GLP-2属于肠道激素,主要由小肠内分泌L细胞在人体摄取食物后分泌,经胰高血糖素原转化酶1/3 (proglucagon prohormone convertase 1/3) 酶切胰高血糖素原 (proglucagon) 获得。另外,部分大脑神经细胞也会分泌GLP-2。在肠道中,GLP-2通过作用于特异性G蛋白偶联受体 (GLP-2受体) 促进正常小肠的生长和发育。研究表明,GLP-2能保护和修复各种肠道疾病中损伤的肠粘膜,增加肠道的血液供应。它在肿瘤放疗化疗、严重创(烧)伤、全肠外营养、炎症性肠病等因素引起的肠粘膜损伤、失血性休克、广泛肠切除、小肠移植等方面均具有很高的临床应用价值。

[0003] GLP-2极易被体内蛋白酶降解而丧失活性,并且由于分子量小容易通过肾小球而被清除。在人体血液循环中,GLP-2_(1~33)的生物半衰期约为7min,原因为GLP-2在血液和组织中可被二肽基肽酶IV (dipeptidyl peptidase IV, DPP-IV) 从氨基端第2位的丙氨酸 (Ala₂) 残基处切割而产生31个氨基酸残基的低活性的GLP-2_(3~33),或被多种内肽酶水解成无活性的小分子短肽。目前,美国NPS制药公司开发的可以抵抗DPP-IV降解作用的GLP-2突变体替度鲁肽 (Teduglutide, 商品名为 **Gattex®**) 已在美国上市。替度鲁肽将天然GLP-2的第2位氨基酸 (Ala) 用甘氨酸 (Gly) 替代,每天皮下注射给药1次 (0.05mg/kg) 用于成人依赖性肠外营养的短肠综合征 (short bowel syndrome, SBS) 的治疗 (Clin Drug Investig. Teduglutide: a guide to its use in short bowel syndrome. 2015; 35 (5): 335-40)。

[0004] 替度鲁肽虽然已成功上市,但其缺点是需要每天给药,而且Ala突变为Gly虽然能降低DPP-IV对GLP-2的降解,但对于内肽酶的降解却无明显作用。小分子量的GLP-2要达到长效的目的,仍需与各种长效方法结合。对于GLP-2类小肽而言,通过单纯的常规延长半衰期的方法,如融合人血清白蛋白 (HSA)、转铁蛋白或人免疫球蛋白Fc片段等,由于融合的长效蛋白并不能显著降低目的蛋白质被内源性蛋白酶降解的作用,因此很难获得理想的结果。目前一般通过定点突变的方法,将对蛋白酶敏感的氨基酸进行替换;或者采用化学修饰的方法,如诺和诺德 (Novo Nordisk A/S) 公司的利拉鲁肽 (Liraglutide, 商品名 **Victoza®**), 其上交联的脂肪酸链 (棕榈酸) 能在一定程度上使GLP-1避免降解,同时脂肪酸链能结合到人血清白蛋白上,延长了半衰期。

[0005] 总而言之,获得一种稳定的、能有效抵抗蛋白酶降解的GLP-2突变体并将其与长效载体蛋白融合或与PEG等高分子交联,是目前的有效解决办法。然而,小肽与长效载体蛋白融合后,最显著的一个缺点就是活性下降。常规的方法可采用柔性的连接肽链 (如G和S组合形成的短肽链) 来减少活性损失,然而,这种连接肽链并不适用于所有的情况,同时单纯的延长连接肽链的长度很可能会增加蛋白酶水解的风险。对于GLP-2而言,筛选获得一种既能

减少GLP-2活性损失,又能防止蛋白酶水解的连接肽链,获得药代和药效良好的长效GLP-2受体激动剂成为当务之急。

发明内容

[0006] 术语解释:

[0007] “胰高血糖素样肽-2 (GLP-2)”指由部分肠道内分泌细胞(L-细胞)分泌的一种激素,由胰高血糖素原(proglucagon)经过体内剪切获得。除了肠道,脑部也会分泌GLP-2,主要作用很可能是控制食物吸收。GLP-2通过结合GLP-2受体起作用,起到治疗或预防肠道疾病、肠道损伤的功能。GLP-2由33个氨基酸组成,天然GLP-2的氨基酸序列如下:

[0008] GLP-2 (1-33)

[0009] HADGSFSDEMNTILDNLAARDFINWLIQTKITD (SEQ ID NO:1)。

[0010] 本发明中的GLP-2受体激动剂,包括天然GLP-2及GLP-2衍生物或突变体。

[0011] 在本发明中,“GLP-2受体激动剂”指可结合GLP-2受体而起到激活GLP-2受体功能的多肽,GLP-2受体激动剂的生理学活性应与天然GLP-2相同或类似。

[0012] “GLP-2衍生物”或“GLP-2突变体”在本文中相互替换,指与天然GLP-2相比具有至少80%氨基酸序列同源性,且具有与天然GLP-2相同或类似生理学活性的多肽。其中部分氨基酸残基甚至可经化学修饰,例如 α -甲基化、 α -羟化、脱氨基等。优选地,本发明的GLP-2衍生物可通过天然GLP-2的N-末端氨基酸取代、C-末端氨基酸添加、缺失或肽链修饰而制备。添加或取代的氨基酸可以是天然的L-氨基酸或者非天然的D-氨基酸等。

[0013] “长效载体蛋白”:本发明的长效载体蛋白指能达到延长活性蛋白在动物体内半衰期功能,且自身的效应功能没有或者可以忽略的蛋白。目前常用的长效载体蛋白包括但不限于:免疫球蛋白(IgG)的Fc恒定区、人血清白蛋白或转铁蛋白等。作为长效载体的另一种形式,聚乙二醇(PEG)也是常用的手段。

[0014] “免疫球蛋白”(IgG)指通过选择性针对抗原作用而参与身体保护免疫性的蛋白质。免疫球蛋白由两条相同的轻链和两条相同的重链构成。轻链和重链包括可变区和恒定区。基于恒定区氨基酸序列的差异,有两种类型的轻链: κ 和 λ 型(Coleman等,Fundamental Immunology,第二版,1989,55-73)。根据重链恒定区的特征,免疫球蛋白分为五种类型:IgG、IgA、IgD、IgE、IgM。其中IgG分为IgG1、IgG2、IgG3和IgG4亚型。目前的单克隆抗体药物中,IgG1和IgG4是使用最多的抗体类型。这是由于IgG1和IgG4的Fc片段能以高亲和力结合FcRn受体而获得循环,因此半衰期很长(平均约为21天)。

[0015] “Fc突变体”:本文所指的Fc突变体为天然人源或其他哺乳动物来源的IgG恒定区Fc片段中,特定氨基酸被取代或插入特定氨基酸而形成的突变体。突变位点并不破坏FcRn结合区域,因此这些突变不影响Fc突变体作为长效蛋白载体的应用。

[0016] 为了克服现有技术中存在的问题,本发明提供了一种融合蛋白,具有如下结构:

[0017] R-L-P 式I

[0018] 其中:

[0019] R为GLP-2受体激动剂;

[0020] P为长效载体蛋白;

[0021] L为连接肽链且具有如下公式:

[0022] (XSSGAPPPS)_u-G/S-(G-W₁-W₂)_m 式II

[0023] 其中X选自P、GP、GGP或NGGP中的任一种；

[0024] G/S为G和S任意组成的肽链，长度为5-25个氨基酸；

[0025] W₁,W₂分别为除Cys之外的19种任意天然氨基酸残基；

[0026] u为0或1；m为1-20的整数。

[0027] 式I中，R为GLP-2受体激动剂，包括天然GLP-2及GLP-2衍生物。GLP-2衍生物包括在天然GLP-2序列基础上进行氨基酸突变、缺失、插入或氨基酸修饰、非天然氨基酸替换等方式获得的GLP-2突变体。优选的，所述GLP-2受体激动剂为天然GLP-2序列(SEQ ID NO:1)的第2位丙氨酸被甘氨酸替代形成的突变体(SEQ ID NO:2)。在本发明中，所述GLP-2受体激动剂还可以选自天然GLP-2序列的第2位丙氨酸被甘氨酸替代且C末端缺失1-6个氨基酸残基的GLP-2突变体，如SEQ ID NO:3和SEQ ID NO:4。在本发明的一个实施例中，所述的GLP-2受体激动剂为第2位丙氨酸被甘氨酸替代的突变体(SEQ ID NO:2)；在另一个实施例中，所述的GLP-2受体激动剂为第2位丙氨酸被甘氨酸替代且C末端缺失6个氨基酸残基的GLP-2突变体(SEQ ID NO:4)。本发明中的蛋白质可以有各种衍生物，这些衍生物可以是但不局限于其不同形式的盐、修饰产物等，如多肽的氨基、羧基、羟基、巯基上再进行修饰。

[0028] 式I中，所述长效载体蛋白包括但不限于哺乳动物来源的免疫球蛋白IgG1或IgG4的恒定区Fc部分或人血清白蛋白或转铁蛋白等。优选的，所述长效载体蛋白选自人免疫球蛋白IgG1(SEQ ID NO:5)或IgG4的恒定区Fc部分(SEQ ID NO:6)及其突变体，更优选的，所述长效载体蛋白选自N297位无糖基化的人免疫球蛋白IgG1或IgG4的恒定区Fc突变体。在本发明的一个实施例中，所述长效载体蛋白选自人免疫球蛋白IgG1的恒定区Fc突变体且具有SEQ ID NO:7所述序列；在本发明的另一个实施例中，所述长效载体蛋白选自人免疫球蛋白IgG4的恒定区Fc突变体且具有SEQ ID NO:8所述序列。对于IgG4抗体，进一步的S228P突变是为了减弱IgG4抗体特有的链交换现象。这些Fc片段都能明显地延长GLP-2突变体在体内的半衰期。

[0029] 式I中，L为连接GLP-2突变体与长效载体蛋白的连接肽链。L为连接肽链且具有如下结构：

[0030] (XSSGAPPPS)_u-G/S-(G-W₁-W₂)_m 式II

[0031] 其中X选自P、GP、GGP或NGGP中的任一种；W₁,W₂分别为除Cys之外的19种任意天然氨基酸残基；u为0或1；m为1-20的整数。所述G/S为G和S任意组成的肽链，长度为5-25个氨基酸；优选的，G/S为GGGGG(SEQ ID NO:98)、GGGGG(SEQ ID NO:99)或GGGGSGGGG(SEQ ID NO:100)中的任一种。优选地，所述W₁,W₂各自独立地选自以下氨基酸A、N、D、Q、E、K、P、S、R。更优选的，W₁,W₂各自独立地选自A、P、S、E、Q、D。

[0032] 优选的，所述L选自SEQ ID NO:30((GGGGG)₂GPPGPA)，SEQ ID NO:31((GGGGG)₂GPNGAPGPS)，SEQ ID NO:32((GGGGG)₂GPSGAPGPPGPEGPA)中的任一种。

[0033] 一般而言，活性蛋白与其他蛋白融合后，极有可能会显著降低其生物学活性，尤其是GLP-2受体激动剂类的小肽。这是由于小肽分子量相对较小，受空间位阻的影响较大而导致活性大幅下降。

[0034] 另外有文献报道，Exendin-4(HGDGSFSDEMNTILDNLAARDFINWLIQTKITD，SEQ ID NO:101)在酵母中表达仍会出现N端二肽的降解，而敲除了酵母STE13基因后则明显改善

(Prabha L等,Protein Expr Purif.2009:155-61.Identification of the dipeptidyl aminopeptidase responsible for N-terminal clipping of recombinant Exendin-4 precursor expressed in Pichia pastoris.),这说明对于GLP-2突变体而言,第二位A突变为G也许仍不足以抵抗二肽酶的降解。然而本发明人发现,在酵母中表达GLP-2突变体时,远离N端的序列内部降解问题更为突出。因此,即便GLP-2突变体在酵母STE13基因失活后N端仍保持完整,然而序列内部的降解仍会降低活性。

[0035] 在本发明中,G/S-(G-W₁-W₂)_n的融合可显著缓解GLP-2突变体融合蛋白的活性损失。G/S序列是本技术领域人员熟知的柔性连接肽链,常用于连接两个不同的蛋白。然而,本发明人发现,单独加入G/S肽(最常用的为GGGGGS单元)并不能显著地降低GLP-2受体激动剂的生物学活性损失,但是在加入(G-W₁-W₂)单元后,GLP-2突变体的活性损失则随着GGGGGS单元的长度的增加而呈梯度地减少。同样地,单独加入(G-W₁-W₂)单元不仅不能降低GLP-2受体激动剂的生物学活性损失,反而有进一步降低活性的趋势。本发明人发现,只有G/S-(G-W₁-W₂)_m的组合形式才能显著减少GLP-2突变体的生物学活性损失。

[0036] 进一步地,本发明提供的连接肽链还可以加入XSSGAPPPS单元。在本发明中,XSSGAPPPS序列融合在GLP-2突变体的C末端后,可增加部分GLP-2突变体的稳定性且并未影响GLP-2突变体的生物学活性,从而延长了GLP-2在体内的活性半衰期。在甲醇酵母GS115中分泌表达时,PSSGAPPPS与C末端缺失的GLP-2突变体融合后,减少了GLP-2突变体的酶解条带,提高表达量。

[0037] 本发明人发现,与不含连接肽链的GLP-2突变体融合蛋白R-P相比,(XSSGAPPPS)_u-G/S-(G-W₁-W₂)_n形式的连接肽链能有效减少GLP-2突变体的酶解及生物学活性损失。u可以为0或1,这取决于GLP-2突变体的形式。

[0038] 本发明的另一个突出优点,是克服了GLP-2与Fc片段融合后形成的多聚体形成现象,如GLP-2 MIMETIBODY™)很容易形成非共价的二聚体(Baker AE等,The dimerization of glucagon-like peptide-2 MIMETIBODY™ is linked to leucine-17 in the glucagon-like peptide-2 region.J Mol Recognit.2012 25(3):155-64.)。由于GLP-2 MIMETIBODY™技术中,IgG4-Fc片段与GLP-2之间同样也含有柔性G/S连接肽链,然而本发明的实施例中,加入了(XSSGAPPPS)_u-G/S-(G-W₁-W₂)_n的GLP2突变体融合蛋白的SEC-HPLC结果显示却并未出现明显的聚体峰。这可能是由于本发明提供的连接肽链特定构象与GLP-2突变体的疏水区域作用,避免了二聚体的形成。

[0039] 在由两个不同蛋白组成的融合蛋白中,连接肽链作为两个不同结构域之间的桥梁,起到极其关键的作用;而且对于不同蛋白,一般需要采用不同的连接肽链。这是因为不同活性蛋白具有不同的高级结构,分子量也不相同,因此在形成融合蛋白时,连接肽链的优化是必须的。尽管G与S组成的柔性肽链成功地应用于多种蛋白,但并不足以达到理想的效果。在本发明中,发明人经过大量的实验筛选,获得了一系列针对GLP-2突变体与长效载体蛋白之间融合的连接肽链。这些肽链能有效地减少GLP-2受体激动剂的活性损失,而且能缓解蛋白酶水解。本发明的实施例中,采用了以下GLP-2突变体与连接肽链的组合形成融合蛋白序列(表1)。

[0040] 表1各种GLP-2融合蛋白序列

[0041]

融合蛋白 SEQ ID NO:	DNA序列 SEQ ID NO:	GLP-2 突变体	连接肽链	长效载体蛋白
9	33	A2G	无	hIgG4/S228P、 N297A
10	34	A2G	GGGGS	hIgG4/S228P、 N297A
11	35	A2G	(GGGGS) ₃	hIgG4/S228P、 N297A
12	36	A2G	GGGGS GPA	hIgG4/S228P、 N297A
13	37	A2G	(GGGGS) ₂ GPQ	hIgG1/N297A
14	38	A2G	(GGGGS) ₃ GPA	hIgG4/S228P、 N297A
15	39	A2G	(GGGGS) ₅ GPD	hIgG4/S228P、 N297A
16	40	A2G	(GGGGS) ₂ GPPGPA	hIgG4/S228P、 N297A
17	41	A2G	(GGGGS) ₂ GPPGPA	hIgG1/N297A
18	42	A2G	(GGGGS) ₂ GPEGAPGPS	hIgG4/S228P、 N297A
19	43	A2G	(GGGGS) ₂ GPSGAPGPPGPEG PA	hIgG4/S228P、 N297A
20	44	A2G	(GGGGS) ₂ (GPSGAPGPP) ₃	hIgG4/S228P、 N297A
21	45	A2G	(GGGGS) ₂ (GPAGEPGPS) ₅	hIgG4/S228P、 N297A
22	46	A2G	(GGGGS) ₂ (GPPGPA) ₁₀	hIgG4/S228P、 N297A
23	47	A2G	PSSGAPPPS	hIgG4/S228P、

[0042]

				N297A
24	48	A2G、 Δ C6	GGGGS	hIgG4/S228P、 N297A
25	49	A2G、 Δ C3	(GGGGS) ₂	hIgG4/S228P、 N297A
26	50	A2G、 Δ C6	PSSGAPPPSGGGGS	hIgG4/S228P、 N297A
27	51	A2G、 Δ C3	NGGPSSGAPPPS (GGGGS) ₂	hIgG4/S228P、 N297A
28	52	A2G、 Δ C6	NGGPSSGAPPPSGGGGSGP AGPN	hIgG4/S228P、 N297A
29	53	A2G、 Δ C3	PSSGAPPPSGGGGSGPA	hIgG4/S228P、 N297A

[0043] 注：表中GLP-2突变体序列仅标注突变的氨基酸位点，如A2G表示天然GLP-2序列 (SEQ ID NO:1) 中第二位的A替换为G， Δ C表示C末端缺失， Δ C后的数字表示缺失的氨基酸数目，如 Δ C6代表C末端缺失6个氨基酸的GLP-2突变体。同样地，hIgG4及hIgG1 Fc片段突变体也仅标注突变的氨基酸位点，h代表人源。

[0044] 本发明的另一方面提供了编码所述融合蛋白的核苷酸序列。

[0045] 本发明的另一方面是提供携带编码本发明所述融合蛋白编码基因序列的重组表达载体。目前常用的重组表达载体包括但不限于真核表达载体，如pPIC9质粒、pPIC9K质粒、pPICZalpha A质粒、pcDNA3.1等，原核表达载体如pET41a质粒、pET32a质粒或其他自行构建的具有必须表达外源重组蛋白所需元件的质粒等，皆可用于构建表达本发明的制备。

[0046] 本发明的再一方面是一种表达所述融合蛋白的方法。所提供的表达所述融合蛋白的方法是将含有上述融合蛋白编码基因序列的重组表达载体导入宿主细胞，诱导或组成型地表达得到所述融合蛋白。所述的表达宿主可为酵母菌、大肠杆菌或哺乳动物细胞等，优选为酵母菌，尤其优选的为毕赤酵母 (*Pichia pastoris*)。

[0047] 本发明的融合蛋白的纯化处理，其中包括盐析、沉淀、超滤、层析等技术及这些技术的组合。其中层析可以用亲和、离子交换、疏水、反相等层析技术。

[0048] 本发明中的蛋白质及其衍生物可单独使用，也可以加入一种或多种药学上可以接受的辅料一起组成药物制剂的形式使用。所述的辅料包括药学领域常规的辅料为水、糖类如乳糖、右旋糖等，醇类如山梨醇、甘露醇、木糖醇，氨基酸等。另外，本发明的药学组合可进一步包括赋型剂和抑菌剂。

[0049] 本发明的融合蛋白可以制成注射剂。该剂型的药物可以按照药学领域的常规方法制备。药物制剂可以存在于单一剂量或多剂量的容器中，如密封的安瓶或西林瓶中。冻干制剂是将液体制剂冷冻干燥制备的，使用前加入无菌、无热原的液态溶剂，如注射用水。

[0050] 本发明中的融合蛋白及其衍生物或其药物组合物,作为肠道保护激素可用于各种原因引起的肠道损伤修复及代偿疾病,如肿瘤放化疗、肿瘤靶向药物治疗、严重创(烧)伤、全肠外营养、炎症性肠病等因素引起的肠粘膜损伤,以及广泛肠切除和小肠移植等病人的治疗。

[0051] 本发明中的融合蛋白及其衍生物可以通过静脉注射,皮下注射等方法给药。治疗包括在一段时间内使用单一剂量或复合剂量。

附图说明

[0052] 图1是GLP-2突变体诱导筛选的SDS-PAGE电泳图;其中,A中泳道1-8分别为SEQ ID NO:9-11、23-27;B中泳道1-11为SEQ ID NO:12-22;C皆为空白pPIC9质粒转化GS115获得的表达株诱导样品;M为低分子量蛋白MARKER:97、66、44、29、21、14KD。

[0053] 图2是GLP-2突变体纯化样品SDS-PAGE电泳图;其中,泳道1-9为SEQ ID NO:12-20纯化后的结果。M为低分子量蛋白MARKER:97、66、44、29、21、14KD。

[0054] 图3是GLP-2突变体融合蛋白对大鼠小肠重量/体重改变影响。

[0055] 为了更好的理解本发明的内容下面结合具体实例对本发明作进一步的说明。

具体实施方式

[0056] 下述具体的实施方式,如无特别说明,均为本领域技术人员熟知的常规方法。如重组表达质粒的构建过程,可以根据常见的分子生物学文献,如《分子克隆实验指南》第三版(Sambrook J,Russell DW,Molecular cloning:A laboratory manual.3rd edition,New York:Cold Spring Harkbor Laboratory Press,2001)或商业公司提供的操作说明书中的技术方案。

[0057] 实施例1.目的基因的克隆及表达载体的构建

[0058] 各种GLP-2突变体基因、连接肽链基因及人IgG1和IgG4的Fc基因根据表1中氨基酸序列及酵母偏爱密码子设计,通过基因合成。利用SOE-PCR(splicing by overlap extension,简称SOE)的方法扩增获得完整的融合基因。本领域技术人员根据表1氨基酸序列可以轻易推导其基因序列,并设计相应引物扩增,在GLP-2突变体基因的上游引物和Fc片段的下游引物末端分别添加酶切位点XhoI和EcoRI,用于将PCR(Polymerase Chain Reaction,聚合酶链式反应)产物克隆至pPIC9载体,表达SEQ ID NO:9-29的融合蛋白。用于做对照的SEQ ID NO:2通过化学合成获得。表2列举了扩增表1中各个GLP-2突变体融合蛋白时使用的引物序列。

[0059] 表2 GLP-2突变体融合蛋白时使用的引物序列。

[0060]

SEQ ID NO:	序列 (5'-3')
54	gtactcgagaaaagacatggtgatggtctttctct
55	gggaccatattggactcgtcagtgatcttggctg
56	gagtccaaatatggtccc
57	accggaattcctattaacctaagacagggaaagact
58	agaaccaccaccaccgtcagtgatcttggctg
59	ggtggtggtggttctgagtccaaatatggtccc
60	agatcctcctcctccagaaccaccaccaccgtcagtgatcttggctg
61	ggaggaggaggatctggcggcggcggcagtgagtccaaatatggtccc
62	ggtggtggtggttctggacctgctgagtccaaatatggtccc
63	ggaggaggatctggacctcaagacaaaactcacacatgc
64	ctagaattcctattaacccggagacagggagagaga
65	ggaggaggatctggcggcggcggcagtgacctgctgagtccaaatatggtccc
66	tctggaggaggaggatctggcggcggcggcagtggtggaggcgggtctggcggagggt
67	gggtctggcggagggtgtagtgacctgatgagtccaaatatggtccc
68	ggaggaggaggatctggcccaccaggacctgctgagtccaaatatggtccc
69	tctggaggaggaggatctggcccaccaggacctgctgacaaaactcacacatgccc
70	tctggaggaggaggatctggtccagaagggtgctccaggtccatctgagtccaaatatggtccc
71	tctggaggaggaggatctggtccatctggtgctccaggtccaccagggtccagaa
72	ggtccaccagggtccagaagggtccagctgagtccaaatatggtccc
73	tctggaggaggaggatctggtccatctggtgctccaggtccaccaggaccttcc
74	gccgggggctccggaaggaccaggaggaccaggggctccggaaggctctggtggacc
75	cctccggagccccggcccgcctgagtccaaatatggtccc
76	tctggaggaggaggatctggtccagctggtgaaccagggtccatctggtcctgctgga
77	aggacctggctctccagctggtccagaaggaccagggttccagcaggaccagatgg
78	gctggagagccaggtccttcaggccctgctggtgaacctggccttctgggaccagct
79	gggaccatattggactactagggccgggtcaccagctggcccagaagggcc
80	gagtccaaatatggtccc

[0061]

81	aggaggaccagatcctcctcctccagaaccaccaccaccgtcagtgatcttggctcg
82	ggatctggctcctcctggctcctgctggctcctcctggctcctgctggctcctcctggctcctggaccacca
83	gcaggacctgggggcccggctggctcctggctggctccggctggctcctggctggctccagcagg
84	gccccaggctcctgctggctcctcctggctcctgctggctcctcctggctcctgctggaccac
85	accatattggactcggctggctcctggctggctccggctggctcctggctggctccagcaggac
86	gaccatattggactcagatggctggctggagcaccagaagaagggtcagtgatcttggct
87	gggaccatattggactcagaaccaccaccaccaatcaaccagttgataaa
88	agatcctcctcctccagaaccaccaccacccttggctcctgaatcaacca
89	tctggaggaggaggatctgagtcctcaaatatggctcc
90	cagaaccaccaccaccagatggctggctggagcaccagaagaaggaatcaaccagttgata
91	tctggctggctggcttctgagtcctcaaatatggctcc
92	ccaccagatggctggctggagcaccagaagaaggctcctccttcttggctcctgaatcaacca
93	ccaccaccatctggctggctggcttctggaggaggaggatctgagtcctcaaatatggctcc
94	caccaccagatggctggctggagcaccagaagaaggctcctcctgtaatcaaccagttgata
95	ccaccatctggctggctggcttctggaccagctggaccctcaaatgagtcctcaaatatggctcc
96	agaaccaccaccaccagatggctggctggagcaccagaagaaggcttggctcctgaatcaac
97	tctggctggctggcttctggaccagctgagtcctcaaatatggctcc

[0062] PCR反应体系(50 μ L):5 μ L 10 \times Pfu buffer,dNTP mix(200 μ mol/L),上游引物(0.5 μ mol/L),下游引物(0.5 μ mol/L),0.1 μ g模板,0.5 μ L Pfu DNA聚合酶(5U/ μ L),无菌水补足至50 μ L,所有PCR反应程序均为:94 $^{\circ}$ C预变性2分钟,94 $^{\circ}$ C变性30秒,58 $^{\circ}$ C退火30秒,72 $^{\circ}$ C延伸3分钟,27个循环,72 $^{\circ}$ C延伸5分钟后4 $^{\circ}$ C保存。PCR产物经琼脂糖凝胶电泳检测,实验结果与理论一致。

[0063] 融合基因通过两端的XhoI和EcoRI内切酶克隆至同样酶切的酵母表达载体pPIC9(Life technologies,USA)中,获得重组表达质粒。以甲醇酵母Pichia pastoris GS115(His⁻)为表达宿主菌,通过电转化将线性化的重组质粒转化到GS115中。在组氨酸缺陷的筛选平板培养基上30 $^{\circ}$ C培养3天,至单菌落出现。

[0064] 实施例2.重组蛋白的获得

[0065] 将上述转化的重组酵母单菌落接种至10ml BMGY液体培养基中,30 $^{\circ}$ C,250rpm培养24小时后,静置过夜,弃上清,加入10ml含1%甲醇的BMMY液体培养基,30 $^{\circ}$ C,250rpm诱导表达。选取相对表达较高的菌株作为表达株。具体步骤参见操作说明书(Pichia Expression Kit.For Expression of Recombinant Proteins in Pichia pastoris.Catalog no.K1710-01)。

[0066] 将筛选获得的高表达菌株接种至YPD液体培养基(酵母浸出粉胨葡萄糖培养基)中,30 $^{\circ}$ C,220rpm培养20-24h至OD₆₀₀达10~20,作为上罐种子液。将培养好的种子液接入Biostat B Twin MO 5L发酵罐,培养基按Life technologies公司Pichia Fermentation Process Guidelines配置。接种量为10%,设定发酵温度30 $^{\circ}$ C,pH5.0,待甘油耗尽,开始加

甲醇进行诱导表达。表达阶段控制发酵温度25℃,诱导72小时放罐。诱导表达图如图1所示。

[0067] 如图1A所示,与不含任何连接肽链的SEQ ID NO:9相似,仅含G/S柔性肽或XSSGAPPS单元或两者组合的GLP-2突变体融合蛋白,如SEQ ID NO:10-11和23-27对于发酵过程中的降解并无明显的效果,而加上了(G-W₁-W₂)_n单元后(图1B),如SEQ ID NO:12-22,在发酵过程中检测不到明显的降解条带。

[0068] 实施例3:融合蛋白的分离纯化

[0069] 将实施例2中获得的发酵液经8000rpm,室温离心30分钟收集上清,上样至经缓冲液A(0.5M NaCl,20mM PB,pH 7.0)平衡后的Diamond Protein A BestChrome层析柱(博格隆(上海)生物技术有限公司),再次经缓冲液A平衡后用洗脱缓冲液B(0.1M Gly-HCl,pH 3.0)洗脱,洗脱峰加1/10峰体积的中和液(1M Tris-HCl,pH8.0)调节pH。加去离子水稀释至电导小于4ms/cm后,上样至经缓冲液A(20mM PB,pH 7.0)平衡后的TOSOH Super Q 650-M层析柱,再次经缓冲液A平衡后用洗脱缓冲液B(0.5M NaCl,20mM PB,pH 7.0)洗脱。SuperQ洗脱样品用PBS透析置换。由于各种GLP-2突变体融合蛋白具有相似的性质,且Protein A对Fc序列的高特异性简化了纯化步骤(然而降解带也很难彻底去除),而Super Q则能去除酵母细胞分泌的本底杂蛋白,因此纯化步骤也相近。部分GLP-2突变体融合蛋白纯化样品如图2所示。重组蛋白浓度采用BCA法测定。

[0070] 实施例4融合蛋白的理化性质分析

[0071] 纯化得到的蛋白通过SDS-PAGE、SEC-HPLC、RP-HPLC、质谱等理化性质检测鉴定。如图1所示,GS115中表达的重组蛋白与理论分子量一致。加入了(XSSGAPPS)_n-G/S-(G-W₁-W₂)_m连接肽链的GLP-2突变体融合蛋白在SDS-PAGE上呈单一条带(图1B),分子量介于44和29KD分子量MARKER带之间,且并未见明显的降解带或共价聚体,而无连接肽链的GLP-2突变体融合蛋白或其他形式连接肽链的突变体则出现多条低于理论分子量的条带(图1A),应为降解带。

[0072] 采用Sepax SRT SEC-300(7.8*300mm,5μm,300Å)对纯化的样品进行SEC-HPLC分析,流动相为100mM PBS,pH6.4。结果表明,相对于仅以G/S作为连接肽的GLP-2突变体融合蛋白(SEQ ID NO:10-11及SEQ ID NO:23-27)以及无连接肽的SEQ ID NO:9,加入了G/S-(G-W₁-W₂)_m连接肽链的GLP-2突变体融合蛋白(SEQ ID NO:12-22)在SEC柱上呈单峰,且并未见明显的聚体或分子量偏小的降解峰,而无连接肽链的GLP-2突变体融合蛋白(SEQ ID NO:9)则出现多个降解峰及其聚体峰;另外进一步含有XSSGAPPS单元的SEQ ID NO:28-29同样具有显著的聚体减少趋势(表3)。

[0073] 表3 GLP-2突变体融合蛋白在SEC-HPLC上的聚体含量分析

[0074]

SEQ ID NO:	单体 [*] (%)	SEQ ID NO:	单体 [*] (%)
9	26	21	94
10	30	22	96
11	21	23	27
12	95	24	17
16	99	25	23
17	99	26	29

18	98	27	21
19	96	28	89
20	94	29	91

[0075] 单体^{*}:此处指两条Fc链通过共价形成的活性分子。

[0076] 表中仅显示单体含量,数据为3批次发酵液纯化的重组蛋白平均值。

[0077] 采用Phenomenex Jupiter C4 (4.6*150mm, 5 μ m, 300 \AA) 对纯化的样品进行RP-HPLC分析,流动相为0.1%TFA+水(A), 0.1%TFA+乙腈(B), 梯度为5%B-100%B (0-30min)。结果表明,加入了(XSSGAPPPS)_n-G/S-(G-W₁-W₂)_m连接肽链的GLP-2突变体融合蛋白在RP柱上呈单峰,而其他连接肽链或无连接肽链的GLP-2突变体融合蛋白则出现多个降解峰,与电泳结果几乎一致。

[0078] 纯化后的样品进行质谱分析,结果显示加入了(XSSGAPPPS)_n-G/S-(G-W₁-W₂)_m连接肽链的GLP-2突变体融合蛋白检测到与理论分子量一致的主峰($\geq 90\%$),其他峰包含了电泳及RP-HPLC无法检测到的N端降解峰($\leq 10\%$);而其他的GLP-2突变体融合蛋白与理论分子量一致的峰含量小($\leq 20\%$),大部分为小于理论分子量的质量峰。

[0079] 实施例5:体外细胞学活性检测

[0080] GLP-2融合蛋白体外细胞学活性检测采用荧光素酶报告基因检测法。将GLP-2R基因克隆至哺乳动物细胞表达质粒pCDNA3.1中,构建成重组表达质粒pCDNA3.1-GLP-2R,同时荧光素酶(luciferase)全长基因克隆至pCRE-EGFP质粒上,替换EGFP基因,得到pCRE-Luc重组质粒。pCDNA3.1-GLP-2R和pCRE-Luc质粒按摩尔比1:10的比例转染CHO细胞,筛选稳转表达株,获得重组GLP-2R/Luc-CHO稳转细胞株。

[0081] 在10-cm细胞培养皿中用含10%FBS和300 μ g/ml G418的DMEM/F12培养基培养细胞,等汇合度至90%左右时,弃去培养上清,加入2ml胰酶消化2min后,加入2ml含10%FBS和300 μ g/ml G418的DMEM/F12培养基中和,转移至15ml离心管中,800rpm离心5min后,弃去上清,加入2ml含10%FBS和300 μ g/ml G418的DMEM/F12培养基重悬,计数。用含10%FBS的DMEM/F12培养基稀释细胞至 3×10^5 ,96孔板中每孔铺100 μ l,即每孔3万细胞,贴壁后换成含0.1%FBS的DMEM/F12培养基培养。

[0082] 铺在96孔板的细胞弃去上清后,将实施例3中纯化的重组蛋白用含0.1%FBS的DMEM/F12培养基稀释至一系列指定浓度,加入到细胞培养孔中,100 μ l/孔,刺激6h后检测。根据lucifersae reporter kit (Ray Biotech, Cat:68-LuciR-S200)说明书进行检测。结果如表3所示。不同连接肽链对于空间位阻和GLP-2突变体降解的作用差异导致了细胞活性的不同。对于SEQ ID NO:9-11或23-27而言,聚体的产生(实施例4)可能进一步减弱了细胞学活性。

[0083] 表3各种GLP-2突变体融合蛋白体外细胞活性检测结果

[0084]

SEQ ID NO:	EC50 (nM)	SEQ ID NO:	EC50 (nM)
9	85.8	20	13.1
10	80.2	21	14.4
11	92.6	22	12.5
12	25.8	23	82.4

13	19.6	24	95.8
14	21.9	25	83.4
15	24.1	26	81.7
16	7.8	27	92.1
17	6.4	28	23.2
18	10.7	29	27.3
19	11.0	2 (A2G)	1.8

[0085] 实施例6:体内动物模型药效检测

[0086] 癌症化疗药物通过诱导细胞凋亡和细胞周期停滞而对细胞产生毒性,尤其容易导致小肠上皮细胞的损伤,而导致胃肠道粘膜炎、腹泻及菌血症,目前并无可靠的预防措施。GLP-2已被证明对于肠道隐窝细胞具有显著的抗凋亡效果,并改善化疗药物引起的肠道黏膜炎。本实施例通过大鼠模型比较各种GLP-2突变体融合蛋白的体内生理活性。

[0087] SD大鼠雌雄各半,分为8组,每组6只:1) 氟尿嘧啶(5-FU)+GLP-2突变体1 (SEQ ID NO:16);2) 氟尿嘧啶(5-FU)+GLP-2突变体2 (SEQ ID NO:17);3) 氟尿嘧啶(5-FU)+GLP-2突变体3 (SEQ ID NO:18);4) 氟尿嘧啶(5-FU)+GLP-2突变体4 (SEQ ID NO:9)5) 氟尿嘧啶(5-FU)+GLP-2突变体5 (SEQ ID NO:10);6) 氟尿嘧啶(5-FU)+GLP-2突变体6 (SEQ ID NO:25);7) 氟尿嘧啶(5-FU)+生理盐水;8) 生理盐水。记录每只大鼠的体重,并在注射5-FU前3天开始连续7天,组1)至组6)以25nmol/kg的剂量皮下注射GLP-2突变体,每天一次;组7)和8)注射相同体积的生理盐水。第4天至第7天,组1)至组7)连续每天以50mg/kg的剂量腹腔注射5-FU,最后一次注射5-FU后24小时,所有大鼠处死。剪开大鼠腹腔,在冰浴中,截取大鼠的小肠、大肠,用生理盐水冲洗后,测量其长度并进行测湿重。计算小肠重量与体重比例,不同GLP-2突变体融合蛋白对肠道的保护作用结果如图3所示。

[0088] 如图3所示,与5-FU+生理盐水对照组相比,GLP-2突变体1至6都能明显地缓解5-FU对小肠的损伤,其中突变体1-3的疗效相对于突变体4-6具有更好的效果,说明蛋白在体内的药效与体外细胞学活性相对应。每组内6只大鼠间药效学数据之间差异计算标准差(SD):对照组,5-FU+生理盐水组,5-FU+突变体1,5-FU+突变体2,5-FU+突变体3,5-FU+突变体4,5-FU+突变体5,5-FU+突变体6的SD分别为 4.21 ± 0.79 , 1.88 ± 0.24 , 3.85 ± 0.53 , 3.77 ± 0.22 , 3.58 ± 0.73 , 2.48 ± 0.44 , 2.76 ± 0.27 和 3.41 ± 0.14 。

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[0437]	Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
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[0439]	Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
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[0441]	Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
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[0456]	Asp Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[0457]	35 40 45
[0458]	Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Pro Asp Glu Ser Lys
[0459]	50 55 60
[0460]	Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
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[0464]	Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
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[0466]	Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
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[0471]	145 150 155 160
[0472]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
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[0474]	Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
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[0479]	210 215 220
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[0482]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
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[0484]	Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
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[0502]	Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
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[0504]	Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
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[0561]	Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val		
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[0563]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		
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[0569]	Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val		
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[0585]	20	25	30
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[0588]	Pro Gly Pro Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro		
[0589]	50	55	60
[0590]	Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys		
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[0592]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		
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[0594]	Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr		
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[0596]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
[0597]	115	120	125
[0598]	Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
[0599]	130	135	140
[0600]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
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[0602]	Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
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[0604]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met		
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[0606]	Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[0607]	195	200	205
[0608]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn		
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[0610]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
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[0612]	Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val		
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[0614]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
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[0635]	Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr	
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[0637]	Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu	
[0638]	100	110
[0639]	Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys	
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[0641]	Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser	
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[0643]	Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys	
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[0645]	Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile	
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[0647]	Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro	
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[0649]	Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu	
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[0651]	Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn	
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[0653]	Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser	
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[0655]	Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg	
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[0657]	Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu	
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[0676]	Gly Ala Pro Gly Pro Pro Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro	
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[0678]	Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro	
[0679]		85 90 95
[0680]	Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr	
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[0682]	Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn	
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[0684]	Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg	
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[0692]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu	
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[0696]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu	
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[0698]	Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe	
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[0700]	Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly	
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[0702]	Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
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[0715]	Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile Thr
[0716]	20 25 30
[0717]	Asp Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Pro Ala Gly Glu
[0718]	35 40 45
[0719]	Pro Gly Pro Ser Gly Pro Ala Gly Glu Pro Gly Pro Ser Gly Pro Ala
[0720]	50 55 60
[0721]	Gly Glu Pro Gly Pro Ser Gly Pro Ala Gly Glu Pro Gly Pro Ser Gly
[0722]	65 70 75 80
[0723]	Pro Ala Gly Glu Pro Gly Pro Ser Glu Ser Lys Tyr Gly Pro Pro Cys
[0724]	85 90 95
[0725]	Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
[0726]	100 105 110
[0727]	Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
[0728]	115 120 125
[0729]	Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
[0730]	130 135 140
[0731]	Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
[0732]	145 150 155 160
[0733]	Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu
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[0735]	Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
[0736]	180 185 190
[0737]	Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
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[0739]	Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
[0740]	210 215 220

[0741]	Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
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[0743]	Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
[0744]	245 250 255
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[0746]	260 265 270
[0747]	Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
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[0749]	Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
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[0762]	Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile Thr
[0763]	20 25 30
[0764]	Asp Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Pro Pro Gly Pro
[0765]	35 40 45
[0766]	Ala Gly Pro Pro Gly Pro Ala Gly Pro Pro Gly Pro Ala Gly Pro Pro
[0767]	50 55 60
[0768]	Gly Pro Ala Gly Pro Pro Gly Pro Ala Gly Pro Pro Gly Pro Ala Gly
[0769]	65 70 75 80
[0770]	Pro Pro Gly Pro Ala Gly Pro Pro Gly Pro Ala Gly Pro Pro Gly Pro
[0771]	85 90 95
[0772]	Ala Gly Pro Pro Gly Pro Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro
[0773]	100 105 110
[0774]	Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
[0775]	115 120 125
[0776]	Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[0777]	130 135 140
[0778]	Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
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[0780]	Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
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[0782]	Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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[0784]	Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[0785]	195 200 205
[0786]	Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
[0787]	210 215 220
[0788]	Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
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[0790]	Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[0791]	245 250 255
[0792]	Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
[0793]	260 265 270
[0794]	Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
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[0801]	325 330
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[0812]	20 25 30
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[0814]	35 40 45
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[0817]	Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
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[0827]	Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
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[0831]	Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
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[0854]	Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
[0855]	35 40 45
[0856]	Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
[0857]	50 55 60

[0858]	Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
[0859]	65 70 75 80
[0860]	Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
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[0864]	Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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[0867]	130 135 140
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[0870]	Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
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[0876]	Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
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[0878]	Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
[0879]	225 230 235 240
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[0894]	20 25 30
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[0897]	Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
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[0899]	Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
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[0903]	Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
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[0905]	Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu
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[0913]	Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
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[0916]	195 200 205
[0917]	Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
[0918]	210 215 220
[0919]	Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
[0920]	225 230 235 240
[0921]	Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
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- [1134] aaatatggtc ccccatgccc accttgceca gcacctgagt tectgggagg accatcagtc 180
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- [1136] tgtgtttggg ttgatgtctc tcaagaggac ccagaagttc aatttaactg gtacgttgat 300
- [1137] ggtgttgaag ttcataacgc taagactaag ccaagagaag aacaatttgc ttctacttac 360
- [1138] agagttgttt ctgttttgac tgttttgcat caagattggt tgaacggtaa ggaatacaag 420
- [1139] tgtaaggctc ccaacaaagg ccttccgtcc tccatcgaga aaaccatctc caaggctaag 480
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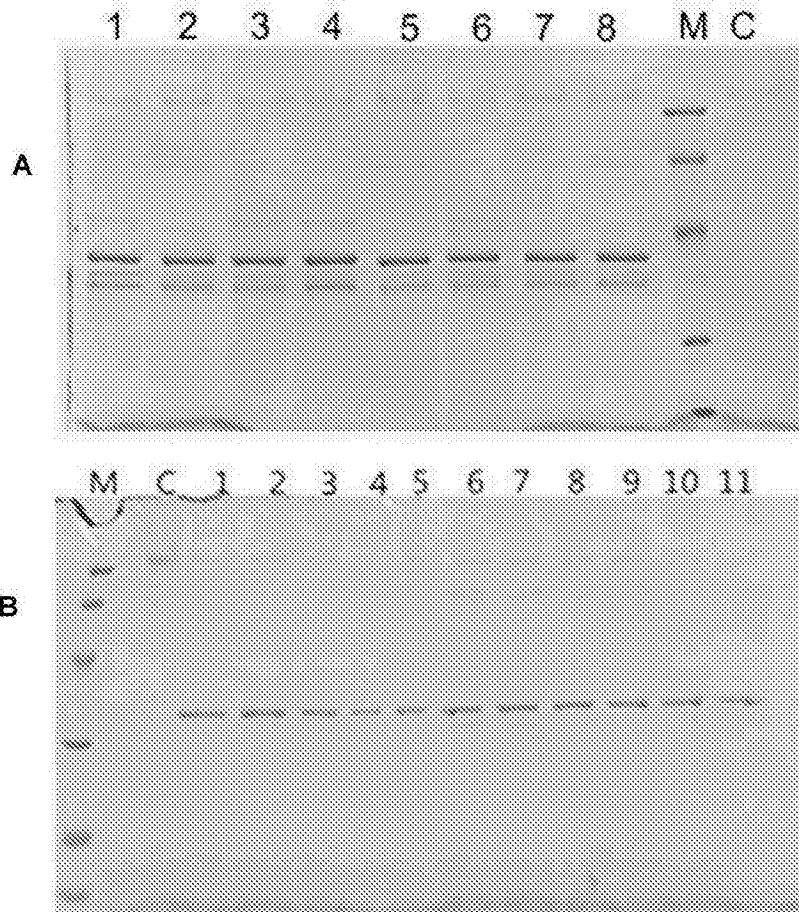


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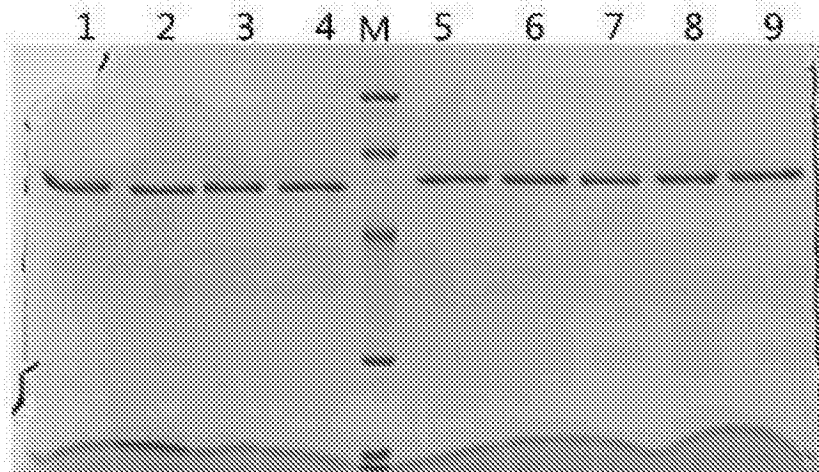


图2

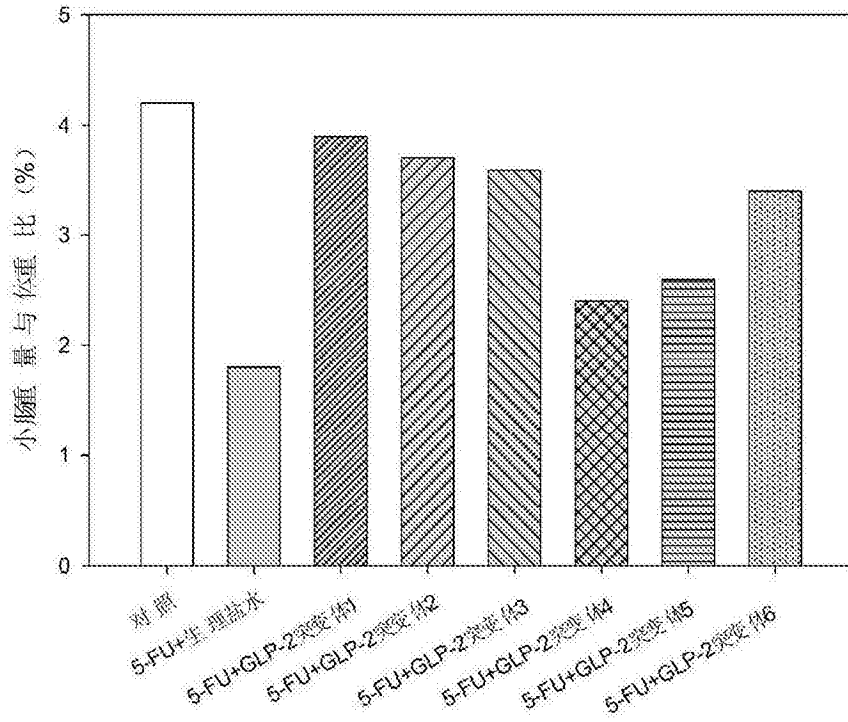


图3