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# 肠道黏蛋白 2 的分泌、结构、合成调控及其在肠道疾病发生发展中的作用

聂　烁　闻正顺*

(浙江海洋大学食品与医药学院,舟山 316022)

**摘　要:** 哺乳动物肠道分泌大量黏液形成黏液层,其主要成分是黏蛋白 2(MUC2)。黏液层对肠道的润滑、保护及强大的屏障功能依赖于 MUC2 自身的特殊网状结构、性质与功能。肠道 MUC2 的存在对维系肠腔微环境稳定和肠上皮细胞功能正常具有重要作用。本文综述了肠道 MUC2 的分泌、结构、合成调控及其在肠道疾病发生发展中的作用,为经调控 MUC2 防治肠道疾病提供理论依据。

**关键词:** 肠道;黏液层;黏蛋白 2;肠道疾病

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肠上皮细胞表面覆盖着杯状细胞合成分泌的大量黏液,可避免肠黏膜组织受潜在的病原体、诱变剂、物理和化学损害,从而抑制感染和炎症,避免疾病的发生。小肠黏液层较薄且不连续[1],而结肠黏液有 2 层,1 层疏松,1 层牢固[2]。黏液的主要成分是黏蛋白(MUC),迄今发现 21 种 *MUC* 基因,这些基因编码 2 类 *MUC*:分泌型(*MUC*2、*MUC*5*AC*、*MUC*5*B*、*MUC*6、*MUC*7、*MUC*9)和膜结合型(*MUC*1、*MUC*3*A*、*MUC*3*B*、*MUC*4、*MUC*12、*MUC*13、*MUC*15、*MUC*16、*MUC*17、*MUC*20)。正常结肠与直肠中的主要 MUC 为 MUC1、MUC2、MUC3A、MUC3B、MUC4、MUC13 和 MUC17[3],其中 MUC2 是肠道黏液的主要分泌物和凝胶形成的组分,MUC1、MUC3A、MUC3B、MUC4、MUC13 和 MUC17 同膜结合形成结合型 MUC,并参与细胞信号传导、黏附、生长和免疫调节[4]。MUC2 利用自身密集的网状结构及富含碳源糖基侧链来捕获和黏附细菌,并通过不断地更新与补充将细菌和肠上皮细胞隔离开来,防御病菌对肠上皮细胞的侵袭以发挥屏障功能[5]。MUC2 通过与肠内树突细胞(DC)直接相互作用,参与传递免疫调节信号来限制肠道抗原的免疫原性,保护肠上皮细胞免受腔内细菌和食物抗原的侵害,增强肠道稳态和耐受,从而预防炎症[6]。MUC2 形成的肠道黏液层与肠上皮细胞、微生物群和宿主免疫防御之间呈动态相互作用,维持肠黏膜稳态。而 MUC2 的缺陷使黏液屏障功能减弱和肠黏膜渗透性增加,引起肠黏膜细胞的炎症和损伤。因此,MUC2 在动物肠道疾病发生发展中具有重要作用。本文简要总结了 MUC2 的分泌、结构、合成分泌调控以及其在动物肠道疾病发生发展中的作用。

## 1　杯状细胞分泌 MUC2

肠上皮细胞按其功能作用可分为肠细胞、杯状细胞、潘氏细胞、肠内分细胞、微体细胞和杯型细胞[7]。MUC 由杯状细胞合成分泌,MUC2 属于最早被鉴定和表征的分泌型凝胶状 MUC,染色体 11P15 位点有编码 *MUC*2 基因序列。杯状细胞质核糖体翻译的 *MUC*2 单体转移至内质网上通过分子间二硫键结合成二聚体,接着被移送到高尔基

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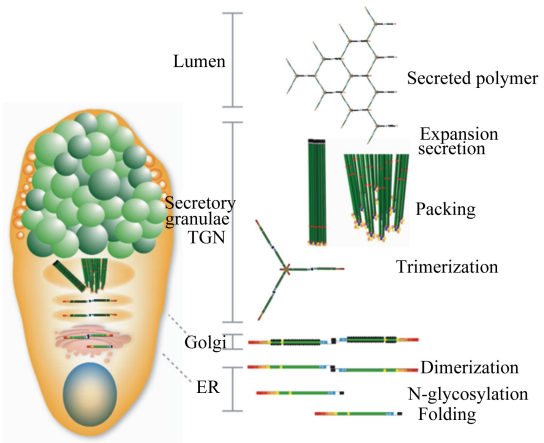
**作者简介:**聂　烁(1996—),男,山东淄博人,硕士研究生,从事海洋天然产物与肠道健康研究。E-mail: nieshuo1314@yeah.net

* **通信作者:**闻正顺,副教授,硕士生导师,E-mail: zswenmr@163.com

体在一系列糖基转移酶催化下进行 O 型糖基化，蛋白质核心区域连接着大量寡糖侧链，完全糖基化和加工完的 MUC2 被密集包装并储存在分泌颗粒或囊泡中，被运送到细胞表面，释放后进入肠腔，与大量的水和其他一些物质形成黏液凝胶。释放途径主要有 2 种：一种是依赖于细胞骨架运动分泌颗粒的基础型，呈现连续低剂量的分泌；另一种是涉及到外界活性因子刺激的胞吐作用的调节型[8]，如胆碱能激动剂、激素、微生物、微生物产物、毒素、炎性细胞因子、活性氧（ROS）和氮物质等。释放后的 MUC2 形成 COOH-末端二聚体和 $NH_2$-末端三聚体，构成复杂分层的大型聚合物网状结构作为黏液层的骨架。MUC2 进入肠内后体积很快扩大千倍以上，以六边形网络状瓦片般铺叠在一起，附在肠上皮细胞表面（图 1）[9]。




ER：内质网 endoplasmic reticulum；Golgi：高尔基体 Golgi apparatus；TGN：反面高尔基体网状结构 trans Golgi network；Secretory granules：分泌颗粒；Lumen：肠腔；Folding：折叠；N-glycosylation：N-糖基化；Dimerization：二聚体；Trimerization：三聚化；Packing：填充；Expansion secretion：分泌扩张；Secreted polymer：分泌聚合物。

**图 1 在杯状细胞中装配 MUC2**

Fig.1 Assembly of MUC2 in goblet cells[9]

## 2 MUC2 的结构与组成

### 2.1 蛋白骨架

MUC2 是一种高分子质量（约为 2.5 Mu）、高糖基化的糖蛋白，其单体结构约含有 5 179 个氨基酸，形成了多个结构域的多肽链，最重要的是富含脯氨酸（Pro）、苏氨酸（Thr）、丝氨酸（Ser）的中心串联重复的结构域，称之为 PTS 区域，PTS 区域被 2 个小的 CysD 区域隔开，并且串联 4 个 vWD（von Willebrand D domain）区域，3 个在 N-末端，1 个在 C-末端[2]，还有 C-末端半胱氨酸（CK）结构域（图 2）[10]。PTS 结构域的这 3 种氨基酸含量约占整个肽链氨基酸含量的 50%，通过 O-糖苷键连接到许多不同长度和组成的寡糖侧链。

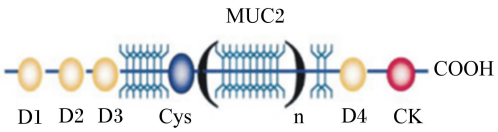



**图 2 MUC2 蛋白骨架**

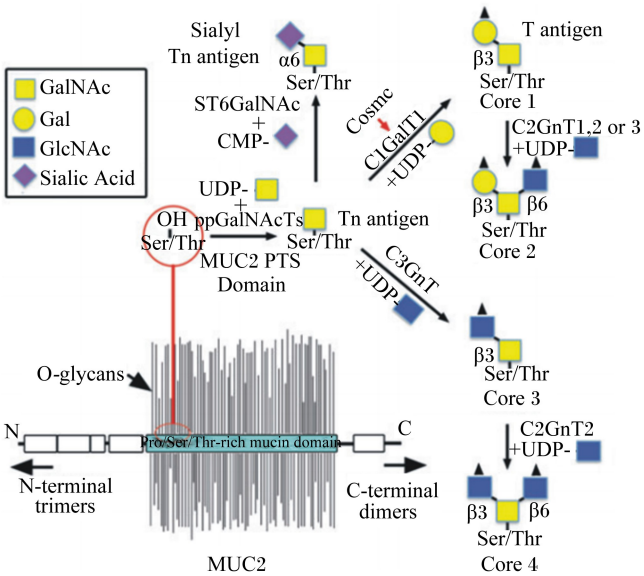
Fig.2 Skeleton of MUC2 protein[10]

### 2.2 糖基化

糖基化是 *MUC2* 转录翻译后的加工修饰，也是 MUC2 发挥功能作用的决定性因素。MUC2 有 30 个潜在 N-糖基化区域，N-糖基化的存在控制 MUC2 的正确折叠和二聚化的正常进行，O-糖基化更丰富[11]。MUC2 糖链占 MUC2 总量的 50%～80%，能使 MUC2 质量增加 5 倍，完全糖基化的 MUC2 分子质量高达 2.5 Mu。

MUC2 进行 O-糖基化的第 1 步是将尿苷二磷酸-N-乙酰半乳糖胺（UDP-GalNAc）中的 N-乙酰半乳糖胺（GalNAc）添加到 PTS 结构域的 Ser 或 Thr 残基上，形成 GalNAcα-Ser/Thr 结构，称为 Tn 抗原[12]。该过程由一类特殊的同源多肽 N-乙酰半乳糖胺基转移酶（GalNAc-T，亦称 ppGalNAcTs）催化，Tn 抗原也是核心 1β1，3-半乳糖基转移酶（C1GalT1 或 T-合酶）和核心 3β1，3N-乙酰氨基葡萄糖氨基转移酶（C3GnT）的底物，形成 Core 1 结构和 Core 3 结构，并在此基础上衍生出更多寡糖链。Core 1 和 Core 3 在核心 2β1，6 N-乙酰氨基葡萄糖氨基转移酶（C2GnTs）催化下衍生出 Core 2 和 Core 4 结构。Core 1、2、3、4 结构聚糖在肠 MUC 中最常见（图 3）[13]。Core 3 结构是在人体肠道 MUC2 中最主要的聚糖结构，已经证明人体乙状结肠中 MUC2 聚糖主要是 Core 3 结构[14-16]。小鼠十二指肠、空肠、回肠 MUC 中 Core 2结构占主导地位，也有 Core 1 结构[17]。这些核心结构可用 GalNAc、半乳糖（Gal）、N-乙酰氨基葡萄糖（GlcNAc）、岩藻糖（Fuc）和唾液酸（NeuAc）糖残基进一步延伸，后 2 个残基经常占据末端位置[18]。小鼠小肠 MUC 中大多数是唾液

酸化和硫酸化聚糖[17],人类的乙状结肠 MUC 同样具有很高的唾液酸和硫酸盐残基[19]。因此,MUC 的聚糖链在肠道中有不同分布和不同性质,MUC 的聚糖链可利用性影响着肠道微生物的组成[20]。研究发现在多种炎症和恶性肠道疾病中 *MUC* 表达和糖基化发生了改变[21]。




-OH:羟基;Ser:丝氨酸 serine;Thr:苏氨酸 threonine;ppGalNAcTs:多肽 N-乙酰半乳糖胺基转移酶 polypeptidyl GalNAc transferases;MUC2 PTS Domain:黏蛋白 2PTS 结构域;UDP:尿苷二磷酸 uridine diphosphate;Tn antigen:Tn 抗原;CMP:一磷酸胞苷 cytidine monophosphate;ST6GalNAc:α2,6 唾液酸转移酶 α2,6 sialytransferase;C1GalT1:核心 1β1,3-半乳糖基转移酶 1 core 1 β1,3 N-galactosyltransferase;C3GnT:核心 3β1,3N-乙酰氨基葡萄糖氨基转移酶 core 3 β1,3 N-acetylglucosaminyltransferase;C2GnT1,2 or 3:核心 2β1,6 N-乙酰氨基葡萄糖氨基转移酶 1,2,3 core 2 β1,6 N-acetylglucosaminyltransferases 1,2,3;T antigen:T 抗原;GalNAc:N-乙酰半乳糖胺 N-acetylgalactosamine;Gal:半乳糖 galactose;GlcNAc:N-乙酰氨基葡萄糖 N-acetyleneglucosamine;Sialic Acid:唾液酸;Sialyl Tn antigen:唾液酸化 Tn 抗原;O-glycans:氧型聚糖;N-terminal trimers:氮末端三聚体;C-terminal dimers:碳末端二聚体;MUC2:黏蛋白 2 mucin 2。

**图 3　MUC2 核心聚糖链的合成路径**

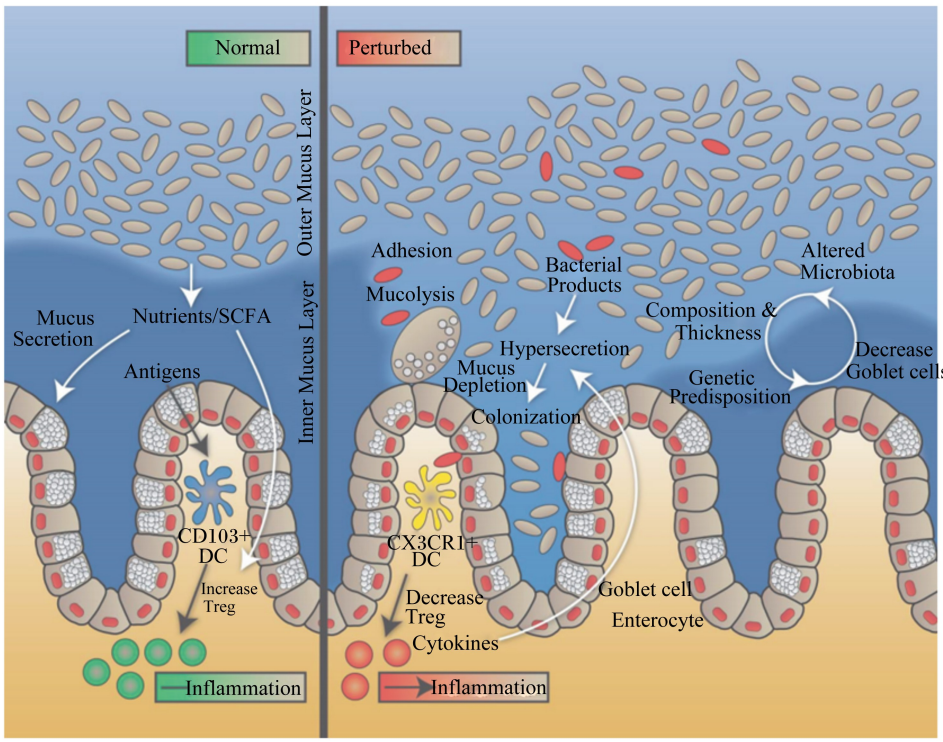
Fig.3　Synthesis of MUC2 core glycans[13]

## 3　MUC2 合成分泌的调控

### 3.1　微生物与 MUC2

微生物及其代谢产物可以影响 MUC2 的合成与分泌,调节 MUC2 的生成。铜绿假单胞菌的脂多糖(LPS)激活非受体酪氨酸激酶(c-Src)-鸟苷酸结合调节蛋白(Ras)-Ser/Thr 蛋白激酶(Raf)-丝裂原活化蛋白激酶激酶(MEK)-细胞外信号调节激酶(ERK)-90 Ku 核糖体 S6 激酶(pp90rsk)信号通路,使核转录因子-κB(NF-κB)活化,被激活的 NF-κB 与 *MUC*2 基因 5' 端侧翼的 κB 位点结合诱导 *MUC*2 转录[22]。金黄色葡萄球菌中的脂磷壁酸刺激人 HM3 和 NCI-H292 细胞分泌 MUC2,可能是通过激活 Ras/Raf/MEK/ERK/pp90rsk/NF-κB 通路[23]。溶组织性变形杆菌通过激活黏液颗粒上存在的囊泡网膜囊泡相关膜蛋白 8(VAMP8)调节杯状细胞的胞吐作用,增加 MUC2 的分泌[24]。创伤弧菌分泌一种弹性蛋白酶(VveP)介导肠上皮细胞脂筏诱导 ROS 的产生及 *MUC*2 启动子诱导区域的高甲基化,从而抑制 *MUC*2 的表达[25]。微生物代谢物次级胆汁酸通过激活表皮生长因子受体(EGFR)/蛋白激酶 C(PKC)/Ras/Raf/MEK/ERK/环磷腺苷效应元件结合蛋白(CREB)、磷脂酰肌醇 3-激酶(PI3K)/蛋白激酶 B(Akt)/NF-κB 抑制蛋白(IκB)/NF-κB 和 p38 丝裂原激活蛋白激酶(p38)/丝裂原和应激活化蛋白激酶 1(MSK1)/CREB 通路,从而上调 *MUC*2 的转录[26]。霉菌毒素脱氧雪腐镰刀菌烯醇

(DON)极易引起猪的呕吐,抑制抵抗素样分子β的双链RNA依赖性蛋白激酶(PKR)和丝裂原活化蛋白激酶(MAPK)阻抑杯状细胞表达*MUC2*[27]。志贺菌、具核梭杆菌、黄曲霉毒素M1和赭曲霉毒素都能上调*MUC2*的表达[28-30],艾美球虫(EM)和产气荚膜梭菌(CP)抑制MUC2的分泌[31]。病毒也会影响MUC2生成,禽流感病毒亚型H9N2和轮状病毒等都对MUC2的分泌有抑制作用[32-33]。微生物还直接影响MUC2的结构组成,改变MUC2的分子结构。微生物产生的某些碳水化合物活性酶(CAZymes)通过切割MUC2中的特定键来降解O-连接的聚糖,像糖苷水解酶(GH)家族、M60样蛋白酶和硫酸酯酶等对聚糖有靶向识别作用[7]。GH2含有β-半乳糖苷酶活性,GH98可将末端三糖从A或B型血型结构释放出来,GH101可以裂解与肽连接的GalNAc。产气荚膜梭菌的锌金属蛋白酶(ZmpB)可以断裂糖基化的Ser和Thr残基相连肽键。粪便拟杆菌(*Bacteroides caccae*)型菌株参与低膳食纤维诱导的结肠黏液层破坏[34]。肠道微生物及其代谢产物调控MUC2的合成分泌过程是通过激活各种信号通道和肠上皮细胞产生的细胞因子来实现的(图4)[35]。脆弱芽孢杆菌在体外降解猪结肠MUC中O-聚糖的能力有限,但是当纯化的结肠MUC作为唯一碳源时,足以支撑其在培养基中的生长[36]。MUC2的O-聚糖可作为产正丁酸菌的内源性发酵产物[37]。MUC2自身的O-聚糖成为特异性细菌黏附位点,为肠道细菌提供寄居场所及能量来源。因此,MUC2与微生物共生互作存在双向调节。




Normal:正常;Outer Mucus Layer:外部黏液层;Mucus Secretion:黏液分泌;Nutrients/SCFA:营养物/短链脂肪酸;Inner Mucus Layer:内部黏液层;Antigens:抗原;CD103+DC: CD103+树突细胞;Increase Treg:调节性T细胞增加;Inflammation:炎症;Perturbed:扰动;Adhesion:黏附;Mucolysis:黏液溶素;Bacterial Products:细菌产物;Altered Microbiota:菌群改变;Hypersecretion:分泌过多;Mucus Depletion:黏液损耗;Colonization:定植;Composition & Thickness:组成&厚度;Decrease Goblet cells:杯状细胞减少;Genetic Predisposition:遗传易感性;CX3CR1+DC: CX3CR1+树突细胞;Decrease Treg:调节性T细胞减少;Cytokines:细胞因子;Goblet cell:杯状细胞;Enterocyte:肠上皮细胞。

**图4 肠黏液层与宿主-微生物群相互作用**

Fig.4 Intestinal mucus layer and host-microbiota interactions[35]

### 3.2　细胞因子与 MUC2

细胞因子是免疫细胞、上皮细胞、内皮细胞和成纤维细胞等多种细胞被激活并与病原体相关的分子模式(PAMP)接触时分泌的生物活性因子[35]。细胞因子可为 Th1 类细胞因子和 Th2 类细胞因子。细胞因子可调节多种细胞类型中 *MUC*2 的转录表达[35]。几种 Th1 类细胞因子调节 MUC2 的合成和分泌,如白细胞介素(IL)-1β 和肿瘤坏死因子-α(TNF-α)。IL-1β 通过 PKC/MEK/ERK/磷脂酰肌醇 3 激酶(PI3K)信号途径上调 *MUC*2 的表达[38]。TNF-α 通过 NF-κB 诱导激酶(NIK)和 PI3K/Akt 2 条通路介导的 NF-κB 活化正调节 *MUC*2 转录,也通过激活 c-jun 氨基末端激酶(JNK)途径负调节 *MUC*2 转录,但 *NF-κB* 转录激活能够抵消 JNK 途径的抑制作用[38]。Th2 类细胞因子(IL-4、IL-6、IL-9、IL-10、IL-13)在体外和体内均可诱导 *MUC*2 基因表达。IL-4 和 IL-13 通过激活 MAPK 的磷酸化来增加 *MUC*2 基因的表达[39]。IL-6 增加了 LS180 细胞中 *MUC*2 的表达并刺激其分泌[40]。IL-9 诱导了气道上皮细胞 *MUC*2 表达的增加[41]。IL-10 可增强杯状细胞中 MUC2 的正确折叠防止内质网应激来促进 MUC2 的分泌[42]。

### 3.3　营养素与 MUC2

MUC2 在动物断奶应激引起腹泻、感染病原微生物引起肠炎、肠黏膜功能障碍等疾病中发挥着屏障、免疫功能,保护着动物肠道健康。维持健康不可或缺的重要营养素调控 MUC2 的合成和分泌,起到了对肠道的保护作用。食物难以消化的碳水化合物(可溶性膳食纤维、低聚糖、抗性淀粉等)可被肠道微生物发酵成短链脂肪酸[38]。短链脂肪酸可以作为结肠上皮的营养物质[43],增加 MUC2 的产生[44]。膳食纤维联合非淀粉多糖降解酶增加猪回肠杯状细胞数量和 *MUC*2 的表达[45]。膳食豌豆纤维改变肠道短链脂肪酸谱增加 *MUC*2 的表达[46]。断奶猪仔胃中注入短链脂肪酸增加小肠 *MUC*2 表达,改善肠黏膜屏障功能[47]。断奶仔猪饲粮中添加羧甲基纤维素提高消化液黏度、回肠杯状细胞数量和成熟度[48],增加 MUC2 的生成。罗望子木葡聚糖降低了 Toll 样受体 4(Toll-like receptor 4,*TLR*4)、髓样分化因子(myeloid differentiation factor 88,*MyD*88)、*IκB* 和 *NF-κB* 的表达同时降低了 *MUC*2 的表达[49]。β-葡聚糖增加断奶仔猪空肠 *MUC*2 的表达,改善肠道屏障功能[50]。甘露寡糖可显著增加鸡胚 *MUC*2 mRNA 的水平[51]。高可发酵蛋白质饲粮增加断奶仔猪 *MUC*2 等多种 MUC 的表达[52]。膳食奶酪乳清蛋白增加大鼠粪便排泄物中 MUC2 的含量,可保护其肠道抵抗轻度右旋糖酐硫酸钠引起的结肠炎[53]。Thr 对维持肠道健康非常重要,增加断奶仔猪小肠 *MUC*2 表达[54],接种在鸡卵中增加肠道 *MUC*2 的表达,有利于改善肠黏膜的形态和功能[55]。非氧化鱼油在增加仔猪肠道 MUC2 保护肠道健康方面效果比氧化鱼油要好[56]。维生素 A 缺乏症会损害 *MUC*2 表达并抑制雏鸡呼吸道的黏膜免疫功能[57]。微量元素锌也能影响 *MUC*2 的表达,有机锌增加雏鸡 *MUC*2 的表达,缓解肠道损伤[58]。

## 4　MUC2 在肠道疾病发生发展中的作用

### 4.1　肠道应激性疾病

肠道应激性疾病是动物在应激状态下肠黏膜结构和生化异常导致的肠屏障障碍和肠功能紊乱性疾病,多致腹泻。人容易因精神受到刺激出现心理应激,家畜经常受饲粮、温度、断奶等刺激产生生理应激。应激在神经系统、内分泌系统、免疫系统等多方面影响肠黏膜致其损伤,通过刺激神经[59]、促进炎症因子的分泌[60]、抑制免疫细胞使肠黏膜对细菌与病原体通透性增加[61]。因此,应激状态下杯状细胞大量分泌 MUC2 来抵御通透性的增加,提高屏障功能,但长时间作用后,杯状细胞的消耗将加剧肠道黏膜屏障的损害。鼠模型常用于研究 MUC2 在应激状态下的作用及变化,应激期释放的促肾上腺皮质激素释放因子激活神经元和肥大细胞促进结肠杯状细胞 MUC2 分泌,在后期杯状细胞出现损耗[62]。*MUC*2$^{-/-}$小鼠易患结肠炎,将其断奶后结肠炎症状加重[63]。慢性应激大鼠结肠 MUC2 分泌减少[64],O-聚糖出现改变[65]。断奶是仔猪必须经历的过程,仔猪断奶后因缺乏母乳中的营养成分且肠道生理机能发育不成熟出现应激反应,损害猪肠黏膜屏障功能的发挥[66],影响肠道的形态、结构、生理和肠道免疫反应[67],干扰 MUC2 的合成分泌,肠道结构功能改变影响肠屏障功能紊乱从而引起腹泻。仔猪断奶 1 d 后肠道 *MUC*2 基因表达增加,7 d 后肠道 *MUC*2 基因表达降低;断奶后 *MUC*2 表达先增加

可能是肠道应对应激的保护机制,后期杯状细胞损耗导致 *MUC*2 表达减少[68]。热应激改变猪肠道通透性,发生肠道炎症反应[69],使猪肠上皮杯状细胞凋亡,减少 MUC2 的分泌。热应激引起肉鸡肠道 *MUC*2 表达减少[70],破坏肠黏膜完整性。应激引起动物肠道黏液 MUC2 生成异常,MUC2 构成的肠道黏液屏障破坏,肠道微生物发生易位并接触黏膜上皮细胞引起炎症,这可能是肠道应激性疾病所致腹泻的重要原因。

### 4.2 肠道感染性疾病

当动物患肠道感染性疾病时,杯状细胞的数量和 MUC2 的分泌均有上升,因其润滑和隔离作用可以加快病原体的排出,保护肠黏膜。而肠道慢性炎症使杯状细胞的数量耗损,导致 MUC2 的合成和分泌下降。肠道感染寄生虫后,黏液层被破坏降解。溶组织内阿米巴原虫产生的半胱氨酸蛋白酶分解 MUC2,破坏 MUC 网络结构[71]。鞭虫产生的丝氨酸蛋白酶特异性识别 MUC2 的 N-末端聚合域,降解 MUC2 来破坏黏液网络[72]。肝片吸虫产生蛋白酶也能破坏黏液层。巴西钩虫和旋毛型线虫通过 Th2 免疫应答 IL-13 和 IL-4 介导杯状细胞增殖,促进 MUC2 分泌[73]。缺乏 MUC2 的小鼠感染蠕虫,驱除蠕虫会延迟,黏液增加可以捕捉寄生虫,避免其黏附在肠上皮表面,限制其移位及存活能力,且有助于保护肠黏膜清除蠕虫排除线虫[74]。定植于脊椎动物肠道的空肠弯曲杆菌黏附在 MUC2 上,损伤黏液层[75]。感染鼠伤寒沙门氏菌的猪结肠出现微观变化产生炎症,*MUC* 表达减少[76]。健康猪感染胞内劳森菌减少 MUC2 的产生,破坏黏液屏障,加剧其对细胞的侵袭[77]。猪结肠感染猪痢疾短螺旋体导致黏液样出血性腹泻和黏液层变化,刺激 MUC2 分泌增加[78]。细菌代谢的硫化物能破坏 MUC2 的二硫键,从而裂解 MUC2 的网状结构,破坏黏液屏障[79]。鸡感染肠炎沙门氏菌引起 *MUC*2 基因表达显著降低[80],造成肠道损伤。人感染艰难梭状芽孢杆菌,造成其肠道 MUC2 合成减少及寡糖链组成改变,引起菌群定植[81]。肠道感染病毒后,MUC2 合成分泌受到影响。鸡感染禽流感亚型 H9N2 病毒,回肠 MUC2 合成分泌减少,肠道发炎出现损伤[32]。小鼠感染轮状病毒造成 *MUC*2 的表达减少和肠道结构改变[82]。感染仔猪猪流行性腹泻病毒(PEDV)后肠道结构破坏、杯状细胞分泌 MUC2 的功能明显下降[83],黏液中 MUC2 含量的下降可能是感染 PEDV 所致腹泻的重要原因。动物患肠道感染性疾病,肠道黏液中 MUC2 分子受到破坏,其黏性下降,肠黏膜通透性增加,肠上皮细胞与肠道中的毒素和病原微生物接触增加,诱导肠道损伤和炎症。

### 4.3 坏死性肠炎

新生儿坏死性小肠结肠炎(NEC)是一种由多因素导致新生儿肠黏膜的损害从而出现小肠结肠弥漫性或局部坏死的重症肠道疾病。家畜坏死性结肠炎的发病率呈逐年上升的趋势,成为兽医临床上主要多发病。Martin 等[84]研究表明,NEC 病人回肠杯状细胞数目明显减少,而胆汁酸含量显著上升,胆汁酸的主动运输减少 MUC2 的分泌,在 NEC 发展中起重要作用。Jing 等[85]通过对新生大鼠供氮气和灌胃脂多糖建立 NEC 模型,发现 NEC 大鼠 *MUC*2 表达降低。Tian 等[86]发现 *MUC*2 表达上调可保护肠黏膜的物理和免疫屏障功能,改善 NEC 大鼠的症状和降低发病率。Rasmussen 等[87]和 Puiman 等[88]发现早产仔猪肠黏膜屏障功能减弱,易患坏死性结肠炎,MUC2 合成减少。禽类感染产气荚膜梭菌(CP)易患坏死性结肠炎,原因是 CP 分泌的 NetB 外毒素会降解 MUC2,破坏肠道黏液屏障影响禽类肠道健康[89-90]。Forder 等[91]通过用 CP 和艾美球虫(EM)感染肉雏鸡建立坏死性肠炎模型,发现肠道 MUC2 合成分泌减少。肠黏膜受损和 MUC2 合成分泌减少是坏死性结肠炎的主要特征,但 MUC2 在坏死性肠炎的发生发展中的作用及其机制仍不清楚。

### 4.4 炎症性肠病

炎症性肠病(IBD)是一种原因尚不明确的慢性肠炎,包含溃疡性结肠炎(UC)和克罗恩病(CD)2 种类型。在 IBD 中,MUC2 分泌和 MUC 糖链结构的变化,影响黏液完整性和通透性,减弱黏液屏障功能[4]。在 CD 和 UC 患者的末端回肠和结肠中 *MUC*2 的基因表达都已发生改变[92]。UC 患者杯状细胞 *MUC*2 mRNA 水平显著降低,发炎的 CD 患者末端回肠 *MUC*2 的 mRNA 水平较低,而在非发炎的 IBD 患者中 *MUC*2 表达水平明显升高。MUC2 糖基化的改变也与 IBD 有关[93]。C1GalT1 缺乏症主要导致远端结肠炎的发作,而同时缺乏 C1GalT1 和 C3GnT 的小鼠在结肠远端和近端区域都出现结肠炎症现象,这表明 C3GnT 在近端结肠中起保护作用[94]。UC 患者杯状细胞

数量减少,黏液层变薄,糖基化程度下降。Larsson 等[95]表示活动性 UC 患者中 MUC2 的糖基化异常,其中唾液酸转移酶的上调导致 MUC2 的唾液酸-GalNAc-S/T 增加,并产生了较短的糖链。CD 患者的黏液层与 UC 相反,黏液层变厚,可能因为活化碱性螺旋-环-螺旋转录因子 *Hath*1 基因和 Kruppel 样因子 4(*KLF*4),加快杯状细胞增生,促进 MUC2 的分泌;但其糖链长度减少了 50%,唾液酸化却增加,黏液层的黏性、弹性下降,屏障功能削弱[96-97]。内层黏液 MUC2 分泌不足或结构改变可能促进了结肠炎的发生[98]。Faure 等[99]在葡聚糖硫酸钠(DSS)大鼠模型中发现整个肠道的 MUC 中 Thr 和 Ser 含量明显降低,这可能导致潜在的 O-糖基化位点减少。Lu 等[93]发现 MUC2 缺陷导致 2 和 4 周龄 *MUC*2$^{-/-}$小鼠自发炎症反应,4 周龄的 *MUC*2$^{-/-}$小鼠还表现出肠上皮屏障功能的降低和肠上皮细胞增殖的减少。MUC2 的异常导致黏液稳态失衡,进而诱导肠道黏膜炎症,恢复黏液 MUC2 功能有望成为防治炎症性肠病的途径之一。

## 5　小　结

MUC2 具有物理屏障和免疫调节双重功能,在抵抗感染和防止消化道疾病的发生和发展中扮演着重要角色。MUC2 的合成、分泌缺陷以及糖基化结构的改变会导致肠道疾病的发生,成为相关肠道疾病发生发展的研究热点。MUC2 的糖链作为内源多糖影响着肠道微生物的组成和分布,MUC2 的变化影响肠道通透性及肠黏膜免疫功能,进而影响肠黏膜屏障。黏液层、肠上皮细胞、微生物群和宿主免疫防御之间的平衡和动态互作,共同调控肠道稳态,影响动物肠道健康,但它们之间的关系以及调控方式仍不清楚,需要进一步揭示黏液 MUC2 与肠道菌群、营养调控之间的关系,为动物肠道健康提供理论依据。

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# Secretion, Structure, Synthesis Regulation of Intestinal Mucin 2 and Its Role in Development of Intestinal Diseases

NIE Shuo WEN Zhengshun*

(*School of Food Science and Pharmaceutics, Zhejiang Ocean University, Zhoushan* 316022, *China*)

**Abstract**: Mucin 2 (MUC2) is the main component of mucus, which is secreted by intestinal tract and forms a mucus layer. Mucus layer has protects, lubricates intestinal tract and barrier functions because of the special network structure, properties and functions of MUC2. The presence of intestinal MUC2 is of great value in maintaining the stability of the intestinal microenvironment and normal function of intestinal epithelial cells. This article reviews the secretion, structure, synthesis and regulation of intestinal MUC2 and role in the development of intestinal diseases, and provides a theoretical basis for the regulation of MUC2 in the prevention and treatment of intestinal diseases. [***Chinese Journal of Animal Nutrition*, 2020, 32(6): 2521-2532**]

**Key words**: intestinal tract; mucus layer; MUC2; intestinal diseases

* Corresponding author, associate professor, E-mail: zswenmr@163.com

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