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文献综述 REVIEW

三叶因子3研究进展

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Advances in research of trefoil factor 3

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Abstract

As one of important defensive factors, trefoil factor 3 (TFF3) has considerable relation to the lesion, recovery, proliferation and malignancy of gastrointestinal mucosa. Furthermore, the correlation between TFF3 and tumor, including its pathogenesis, progress and prognosis, has been reported remarkably. However, the binding proteins of TFF3 remains to be confirmed and the research of TFF3 on the mechanism of action and signal transduction pathway is just initial. This article reviewed the progress in TFF3 research.

Key Words: Trefoil factor 3; Tumor; Signal transduction

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摘要

TFF3作为胃肠黏膜中一个重要的黏膜保护因子, 与胃肠黏膜的损伤、修复、增殖、恶变都有着重要的关系. TFF3与肿瘤的发生、发展、预后有一定的关系, 但TFF3的结合蛋白尚未明确, 其细胞内作用机制、具体信号转导途径的相关研究尚处于起始阶段. 本文对TFF3的研究进展作一综述.

关键词: 三叶因子3; 肿瘤; 信号转导

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■背景资料
TFF3作为胃肠黏膜中一个重要的保护因子, 与胃肠黏膜的损伤、修复、增殖、恶变都有着重要的关系, 但TFF3的结合蛋白尚未明确, 其细胞内作用机制、具体信号转导途径的相关研究尚处于起始阶段.

0 引言

三叶因子家族是近年来研究较多的一群小分子多肽, 又称三叶肽(trefoil peptide). 在哺乳动物体内他们具有黏膜保护、修复、肿瘤抑制或促肿瘤发生、信号转导、调节细胞凋亡等功能. 目前在哺乳动物体内发现的三叶肽有3种, 即乳癌相关肽(the breast cancer-associated pS2 peptide, pS2/TFF1)、解痉多肽(spasmolytic polypeptide, SP/TFF2)和肠三叶因子(intestinal trefoil factor, ITF/TFF3). 其中TFF3于1991年由Suemori *et al*首次在大鼠空肠发现[1]. 三叶因子家族都至少含有一个特殊的P结构域, 后者由38-39个氨基酸组成, 通过6个高度保守的半胱氨酸残基经由3个分子内的二硫键相互联接使整个肽链扭曲折叠形成三叶状结构[2], 三叶肽由此而命名.

1 分子结构及表达定位

TFF3分子由59个氨基酸组成, 含有1个P结构域, 质谱分析表明TFF3存在单聚体及二聚体两种形式. 单聚体分子质量为6692 kDa, 二聚体分子质量为13 146.8 kDa, 其同源二聚体是由2个Cys58形成的分子间二硫键连接而成[3]. TFF3主要在小

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■创新盘点
本文从TFF3的生理功能、TFF3在病变组织中的表达、TFF3表达的调节、TFF3与细胞信号转导及TFF3与肿瘤等多个方面对TFF3的研究进展作一综述.

肠及结肠杯状细胞、胃窦黏膜[4]中表达; 人食管黏膜下腺(主要在Z线和胃贲门之间)可见TFF3较高量表达; 胃体黏膜下腺可见TFF3少量表达[4]. 此外, 研究表明TFF3在人胰腺[5]、唾液腺[6]、泪腺[7]、前列腺[8]、鼻黏膜[9]、十二指肠乳头[10]、子宫[11]、乳腺[12]、下丘脑[13]、垂体[14]、肺[15]等组织中也有低水平表达, 而在病理条件下, TFF3的表达发生了明显改变.

2 生理功能

2.1 黏膜保护及修复 与黏液中的糖蛋白结合形成稳定的凝胶复合物加强黏液凝胶层, 减少胃肠道表面有害物质及机械应力等因素对黏膜的损伤. 研究表明在应用TFF3后, 可明显增加胃肠道黏膜可溶性黏液的分泌量并增加其黏度[16]. 给小鼠*po*重组人类解痉多肽、小鼠肠三叶因子, 均能明显减轻非甾体类抗炎药物、酒精导致的胃黏膜损伤[17]. Kjellev *et al*人检测DSS(丁二酸二辛酯磺酸钠)引发的小鼠结肠炎中TFF3的含量, 发现当结肠炎发生时, TFF3表达明显增高; 此外, 通过外源性TFF3全身用药(静脉、腹腔、皮下), 发现结肠炎部位TFF3结合明显增多, 并能减轻炎症的程度, 说明TFF3对于结肠黏膜的完整性具有非常重要的作用[18]. 但TFF3表达增加出现于黏膜修复期, 在黏膜损伤早期, TFF3含量是下降的.

三叶肽参与损伤组织的修复过程. 三叶因子是一种运动因子能与表皮生长因子(epidermal growth factor, EGF)和转化生长因子(transforming growth factor, TGF)协同作用参与损伤组织的上皮重建过程, 即促进受损黏膜周围完好的上皮细胞向损伤黏膜表面迁移, 覆盖并促进损伤黏膜的修复, 但并不促使细胞分裂. TFF3促进细胞迁徙的作用机制可能和EGF不同, 通过IEC-18细胞刮伤及迁徙实验, 发现加入TFF3后细胞呈片状迁徙, 细胞间隙很小, 而EGF引起的细胞迁徙则呈网络状, 细胞彼此之间间隙很大, 只通过一些接触进行联系.相比之下, TFF3较EGF更能精密修复黏膜损伤部位, 且减少间隙的产生[19]. TFF3对于黏膜的修复作用, 推测是通过下调E-钙黏蛋白、加强细胞间连接、促进细胞迁徙来实现的; 此外, TFF3亦可上调上皮细胞中tightening claudin-1的含量、下调tightening claudin-2的含量, 增强表层细胞的抵抗力、降低上皮的渗透性来达到黏膜修复的目的[20]. 另有研究表明, TFF3可能通过增加Vangl1基因的表达, 进而减少E-钙黏蛋白来达到促进黏膜修复的作用, 此外, 当IEC-18细胞被敲除了Vangl1基因后, 细胞对TFF3的促迁徙反应也明显下降, 这说明Vangl1蛋白可能是TFF3的效应蛋白之一[21].

2.2 细胞保护、分化和凋亡 往IEC-18细胞培养基中添加TFF3, 能促进IEC-18细胞中环氧化酶-2的产生, 进而减少氧自由基对细胞的损伤, 且环氧化酶-2特异性阻断剂NS-398能够阻断这种作用, 由此推论, TFF3可能通过促进环氧化酶-2合成, 继而促进前列腺素-2生成, 来发挥细胞保护作用[22].

TFF3可促进黏膜干细胞如胃窦黏膜干细胞、支气管纤毛细胞的分化, 这种作用, 部分是通过EGF-R受体途径来实现的[23].

HT29细胞系中存在结肠腺瘤性息肉病(APC)相关的基因突变, 但能表达正常的上皮细胞钙粘蛋白-链蛋白复合物. Efstathiou *et al*发现rTFF3可引起HT29细胞钙黏蛋白下调, 减弱细胞与细胞、细胞与基底层之间的黏附作用, 下调APC及钙黏蛋白-链蛋白的表达, 使APC从细胞质移位到细胞核中并诱导细胞凋亡[24].

2.3 神经递质 大鼠及人类的视上核及室旁核的大细胞性催产素神经元细胞能合成TFF3. Derbyshire *et al*研究发现, TFF3的释放并不能促进催产素神经元释放催产素, 但却能促进Fos蛋白质的合成, 而Fos蛋白质是催产素神经元中主要发挥作用的蛋白质, 这说明TFF3有可能作为一种神经递质在催产素神经元发挥功能的过程中起到重要作用[13]. 此外, 有研究报道将TFF3注入小鼠脑扁桃体中, 可具有一定的抗焦虑作用, 进一步提示TFF3在神经系统内可能是一种调节情绪的神经递质[25].

3 TFF3在病变组织中的表达

3.1 TFF3在炎症病变中的表达 胃黏膜、结肠黏膜炎症可导致TFF3表达水平增高. Taupin *et al*通过制造大鼠胃黏膜炎症模型, 继而采用放射免疫测定、免疫印迹及免疫组化方法检测大鼠胃黏膜中TFF3的含量, 发现4 d时胃黏膜中TFF3表达水平即明显增高, 而40 d时, TFF3的表达水平已成百倍增高, 同时, 在非病变组织中也可见TFF3表达水平增高; 几个月后, 当出现胃黏膜萎缩、肠化生和重度异常增生等病理变化时, 仍可见TFF3表达水平增高[26]. 在反流性食管炎患者中, 食管胃移行部、小肠炎症病灶中也可检测到TFF3表达水平增高[27-28]. 此外, 药物性肠炎

时, 疾病初始期TFF3表达水平降低, 修复期表达水平增高, 说明TFF3对大肠黏膜的修复有一定的作用[29].

研究发现, 硬化性胆管炎患者的小胆管中, 均存在TFF3表达缺失, 这说明TFF3表达缺失在胆管损伤发生机制中可能占有重要地位[30].

3.2 TFF3在溃疡病变中的表达 慢性溃疡附近区域存在一个特有的解剖结构, 即溃疡相关细胞体系(ulcer-associated cell lineage, UACL). 消化性溃疡、溃疡性结肠炎及Crohn病时均可出现UACL. UACL是一种腺样结构, 起源于肠腺隐窝基部的干细胞群. UACL腺体可以不断地产生新的细胞, 后者迁移到溃疡表面, 以促进溃疡修复. UACL表达表皮生长因子、转化生长因子α[31]、三种已知的三叶因子(PS2、hSP和TFF3)以及一些相关的黏蛋白(MUC5AC、MUC6), 其中, TFF3和MUC2共同表达[32]. TFF3在消化道慢性溃疡病变中多见表达升高, 但当溃疡处于活动期时, TFF3表达下降. Longman *et al*人通过检测活动期溃疡性结肠炎患者中TFF3, 发现其表达下降, 提示TFF3的表达下降可能与结肠黏膜的损伤有关[33].

4 TFF3表达的调节

4.1 TFF3表达的生理调节 TFF3的表达受发育控制, 其基因调控在胎儿期和出生后不同. Mashimo *et al*发现TFF3在成年小鼠的胃肠道存在表达, 而幼年或胚胎期小鼠的胃肠道无表达[34]. Otto *et al*对胎儿胃TFF3的表达进行了动态观察, 发现TFF3于胚胎第13天开始在胃表达, 15、16 d时表达部位不明确, 17 d起TFF3仅局限表达于小肠及末端胃[35]. 此外, 研究表明大鼠妊娠第20天后TFF3蛋白表达明显增高, 而在胚胎早期表达相对较低[36].

4.2 TFF3表达的病理调节 (1)幽门螺杆菌: Matsuda *et al*检测了感染幽门螺杆菌ATCC 43504的AGS、MKN45和KATOⅢ细胞中三叶因子家族含量的变化, 结果发现, 三种三叶因子家族成员分泌表达均增高, 这提示幽门螺杆菌有可能为调节TFF3表达的因素之一[37]. (2)肠道细菌感染、寄生虫感染均可引起肠黏膜中TFF3表达水平增高[23,38]. (3)雌激素: Walker *et al*采用荧光定量PCR检测发现, 增加17-β雌二醇可刺激TFF3表达增高, 而三苯氧胺(雌二醇抑制剂)能够阻断这种调节作用, 提示雌激素可能是TFF3的调节因子之一[39]. (4)酒精、胃肠道高渗压、丁酸钠和5-氨基水杨酸等化学药物造成的肠道炎症均能引起TFF3的合成增加[40-41]. (5)同源结构域蛋白CDX2: Shimada *et al*发现, 在CDX2高表达的COS-7和AGS细胞系中, TFF3的转录水平明显增高; 进一步通过电泳迁移率变动分析发现, 在人TFF3基因启动子中, 至少存在2个以上的CDX2结合位点; 通过向AGS细胞转染CDX2表达载体, 可导致TFF3高表达[42]. (6)DNA结合蛋白A: 检测DNA结合蛋白A转基因小鼠发现, 其TFF3的表达明显增高, 说明DNA结合蛋白A可能与调节TFF3表达密切相关[43]. (7)白介素: IL-4、IL-13可能通过STAT6途径促进杯状细胞中TFF3的合成[44], 而IL-1β通过NF-kappaB途径、IL-6通过C/EBPβ途径降低TFF3的合成[45]. (8)三叶因子各成员之间也可相互调节: 研究发现, 在TFF3基因敲除的小鼠体内, 其结肠损伤修复功能受到了致命性的损害, 此外, 三叶因子家族其他成员如TFF1、TFF2的转录也明显降低[46], 而在TFF2敲除小鼠胃黏膜中, TFF3的表达量明显升高[47], 这说明三叶因子家族中的各成员有可能作为独立的因素影响其他三叶因子的转录. (9)氨甲酰甲胆碱、蛙皮素、P物质、16, 16-二甲基PGE2和IL-1β可促进TFF3的表达, 其中氨甲酰甲胆碱、蛙皮素的促表达作用呈剂量依赖性[48].

5 TFF3与细胞信号转导

5.1 STAT途径 TFF3在结肠癌中的作用机制, 有可能通过启动促癌信号途径STAT3来进行, 研究发现, TFF3和VEGF均能促进STAT3-α和STAT3-β的磷酸化, 相反的, 当通过RNA干扰的方法阻断STAT3的表达, 均能减少TFF3及VEGF介导的细胞迁徙, 降低接种在裸鼠身上HCT8/S11肿瘤的生长速度[49]. Tebbutt *et al*发现敲除STAT1/3和IL-6介导的gp130信号转导途径的小鼠, 其结肠黏膜损害程度与敲除TFF3基因的小鼠极其相似, 提示TFF3与STAT1/3、gp130信号转导途径有着密切联系[50].

5.2 EGF受体途径 在人类呼吸道细胞未分化前, 加入重组人类TFF3, 能促进FOXJ1阳性细胞和β-微管蛋白纤毛细胞的增殖, 且这种增殖作用能被EGF特异性受体阻滞剂所阻断, 说明TFF3能促进纤毛发生, 且能促进呼吸道上皮纤毛细胞的分化, 而这种作用可能部分通过EGF受体信号转导途径实现[51]. Rodrigues *et al*研究发现, TFF3虽然和TFF1、TFF2同属于三叶因子家族, 但他

■应用要点

目前对于TFF3的研究主要局限于结肠, TFF3在其他部位的研究报道较少. TFF3与肿瘤的发生、发展、预后有一定的关系, 其能否作为肿瘤检测及预后判定的一个重要指标, 能否作为胃肠道疾病治疗的一个新的作用靶点, 都需要深入探讨.

■同行评价
本文内容全面, 层次分明, 对研究TFF3的生物学活性提出了重要的理论依据, 具有指导意义.

们促进细胞迁徙的细胞内信号转导途径不同, 当缺失EGF受体或加入EGF酪氨酸激酶受体阻断剂-ZD1839均可阻断TFF2诱导的细胞侵袭效应, 但却对TFF3诱导的细胞侵袭效应无作用[52].

5.3 PI3-K途径 研究发现, 在HT-29、CL.16E和MTX细胞中, 细胞的早期增殖和晚期汇合阶段, TFF3 mRNA表达增加了30倍, 细胞内TFF3含量增加了10倍, 采用LY294002(一种特异性PI3-K细胞阻断剂)进行阻断, 发现TFF3和MUC2的表达明显下降; 进一步通过基因敲除HT-29和CL.16E细胞中STAT6序列, 对TFF3的表达量并无影响, 因此推论, TFF3的表达有可能通过PI3-K途径, 而非STAT6途径[53].

5.4 Ras/MEK/ERK途径 前已述及, 缺乏TFF3的小鼠结肠的修复严重受损, TFF1、TFF2的表达严重下降, 这提示三叶因子家族中的成员能独立影响整个家族其他因子的合成, 而这些因子可能是通过既能自分泌也能交叉诱导的早期快反应基因的顺式作用调节区来发挥作用的. 进一步研究发现, 三叶因子家族诱导的转录调节作用需要Ras/MEK/MAPK信号转导途径的激活[54].

5.5 NF-kappaB途径 TFF3能促进IEC-18细胞中NF-kappaB p50/p65异源二聚体的活性, 且能增强IEC-18细胞的抗凋亡能力, 此外, NF-kappaB阻断剂能显著降低TFF3诱导的IEC-18细胞的抗凋亡能力, 由此推测TFF3能够增强IEC-18的抗凋亡能力, 而这种能力可能是通过NF-kappaB途径来实现的[55].

5.6 PLC/PKC、RhoA、COX-2、TXA2-R途径 有研究发现, TFF3促进癌细胞侵袭和转移的作用可能通过src、Rho-A信号转导途径介导, 此外, 也有可能通过PI3磷酸激酶、磷脂酶C、蛋白激酶C和雷怕霉素靶蛋白TOR等相关途径来执行他的促癌细胞侵袭和转移功能[56]. Rodriques *et al*在研究中发现, Rho小鸟苷三磷酸酶抑制剂(C3胞外酶), 磷脂酶C抑制剂(U-73122), 环氧合酶抑制剂(SC-560、NS-398)和血栓素A2受体对抗物SQ-295能够完全阻断TFF3, pS2和src诱导的MDCKts.src和PCmsrc细胞的侵袭作用, 且细胞的侵袭作用能被血栓素A2受体类似物U-46619诱导, 也能被血栓素A2受体信号转导下游分子-异源三聚体的G蛋白部分引发, 此外, 当细胞转染src后, 细胞培养基中COX-2蛋白和PGH2/TXA2代谢物TXB2稳定增加, 故而提示, TFF3可能通过COX-2、TXA2-R、PLC/PKC途径促进细胞侵袭[57].

6 TFF3与肿瘤

Kirikoshi *et al*发现, 在胃癌细胞及胃癌组织中, 三叶因子表达量发生明显改变, TFF1在OKA-JIMA、TMK1、MKN45、KATO-Ⅲ细胞中表达, TFF2在KATO-Ⅲ细胞中表达, 而TFF3在MKN45、KATO-Ⅲ细胞中表达; 在早期胃癌组织标本中, 58.3%的标本TFF1表达下降, 83.3%的标本TFF2表达下降, 16.7%的标本TFF3表达下降, 而41.7%的标本中TFF3表达增高[58]. Leung *et al*发现, TFF3在25%的非癌组织和24%的癌旁组织中能被检测得到, 在胃癌组织中TFF3的表达率较正常组织明显升高, 达到了62%[59], 这说明三叶因子的表达量变化可能与胃癌的发生有着密切关系. 在结肠肿瘤中, TFF3的含量也发生了变化, 通过免疫组织化学的方法发现在结直肠增生型息肉、无蒂锯齿状腺瘤、传统的锯齿状腺瘤中, TFF3表达下降[60]. John *et al*研究结肠癌演变过程时发现, 在结肠腺瘤性息肉中, TFF3表达明显降低, 在腺瘤中表达量和正常黏膜基本相同, 而在黏液癌和腺癌中, TFF3呈高表达状态[61]. Uchino *et al*发现, 当向不表达TFF3的LoVo和SW837结肠癌细胞中转染表达人类TFF3载体后, 细胞的增长率明显下降, 提示TFF3有可能抑制结肠癌的生长[62]. 此外, 在滤泡性甲状腺癌[63]、肝细胞性肝癌、小细胞性肺癌均发现TFF3高度表达.

TFF3可以诱导HT29细胞的β-连结素(β-catenin)和EGF受体的酪氨酸磷酸化, 导致细胞间粘连的破坏, 细胞间失去粘连将使上皮细胞互相分离, 从而增加HT29结肠癌细胞的迁移力, 表明TFF3与细胞迁移有关[64]. Chan *et al*研究发现, 在胃癌组织中TFF3呈现过表达, 并上调Rat-2细胞β-连接素、MMP-9的mRNA表达, 下调E-钙粘连蛋白和TIMP-1的表达, 可能通过上述因素最终影响到细胞的转移和侵袭过程[65]. 有研究报道TFF3能使胃癌细胞系对无血清培养及神经酰胺所致凋亡的抵抗性增加, 这意味着TFF3可能拮抗化疗药物的作用[66]. 通过绒毛膜尿囊膜实验及研究涂抹有人类脐静脉细胞的基质胶的管状重构现象发现, 三叶因子家族可能是一种促血管生成因子, 而且他们的这种促血管生成作用有可能与血管内皮生长因子、转化生长因子α相当[67].

TFF3表达与结肠肿瘤的分期有关, Dukes A期结肠癌中TFF3的表达明显高于DukesB、C、D期. 已经证实TFF3过度表达可抑制结肠癌细

胞株LoVo和SW837在体外的生长[62]. Yamachika通过对209例原发性胃腺癌患者进行统计学分析, 发现TFF3在女性胃癌患者中的表达率较高, 占到了一半以上(55%); 但在男性胃癌患者中, TFF3的表达多见于晚期、浸润型、淋巴结转移阳性胃癌患者, 提示在男性胃癌患者中TFF3可作为评价预后的一个指标[68]. 通过比较胆管癌患者中染色体21q22-qter区域及TFF3基因的扩增情况, 发现D21S1893、D21S1890和TFF3有扩增的胆管癌患者, 预后均比较差, 相反的, 该部位缺失的患者预后相对较为理想[69]. Khoury *et al* 通过运用免疫组织化学的方法检测1998-2003年30例肝细胞癌中TFF3的表达, 发现在93.3%标本中出现TFF3表达, 且TFF3的表达与肿瘤分期、肿瘤细胞分化程度有关, 但未能显示TFF3与患者预后有一定的相关性[70]. 在进展期前列腺癌的患者中, TFF3的含量较原位癌患者明显增高, 这种显著增高尤其见于骨转移情况下, 如果以200 pmol/L为界限, TFF3在区别原发性和转移性前列腺癌的敏感性为74%, 特异性为81%[71].

7 结论

TFF3作为胃肠黏膜中一个重要的细胞因子, 与胃肠黏膜的损伤、修复、增殖、恶变都有着重要的关系. 目前对于TFF3的研究主要局限于结肠, TFF3在其他部位的研究报道较少. TFF3与肿瘤(如胃癌、结肠癌、胆管癌等)的发生、发展、预后有一定的关系, 但TFF3的结合蛋白尚未明确, 其细胞内作用机制、具体信号转导途径的相关研究尚处于起始阶段. TFF3能否作为肿瘤检测及预后判定的一个重要指标, 能否作为胃肠道疾病治疗的一个新的作用靶点, 都需要深入研究来证实.

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