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三叶因子家族在胃癌中的研究进展

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摘　要

三叶因子家族(TFF)是一类具有三叶因子结构域的小的分泌蛋白，因为它们具有较高的氨基酸序列同一性和二硫化物桥的数量和定位。二硫化物键的特定模式形成了典型的三叶形状，称为三叶结构域。三叶因子家族具有耐酶、耐热和耐酸等特性，研究表明，TFFs与多种肿瘤之间存在密切关联，近年来的一些研究正在逐步揭示这一点。TFFs的表达在多种恶性肿瘤中均有上调，包括胃癌、结肠癌、肝细胞癌、乳腺癌、前列腺癌等。此外，这些肿瘤组织或患者血清中的TFFs水平与恶性程度和预后密切相关。TFFs通过增强细胞增殖、侵袭、转移和血管生成以及抑制细胞凋亡来促进肿瘤的发生和转移。但主要在胃肠道中的研究较多，以下就三叶因子的蛋白质结构、组织表达和分布等方面进行综述。为今后更好地了解该肽家族及其在胃癌中的诊断及治疗效果提供指导。

关键词

三叶因子家族，胃癌，结构

Research Progress in the Trefoil Factor Family in Gastric Cancer

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Abstract

The Trefoil Factor Family (TFF) is a class of small secreted proteins with trefoil factor domains because of their high amino acid sequence identity and number and localization of disulfide bridges. The specific pattern of disulphide bonds forms the typical trefoil shape, called the trefoil domain. The trefoil

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factor family is characterized by enzyme, heat and acid resistance, which has shown a close association between TFFs and multiple tumors, and some recent studies are revealing this step by step. The expression levels of TFFs are significantly increased in several types of malignant tumors, such as gastric cancer, colon cancer, hepatocellular carcinoma, breast cancer, and prostate cancer, among others. Additionally, the concentration of TFFs found in tumor tissues or patient serum correlates closely with the severity of malignancy and overall prognosis. TFFs facilitate tumor development and spread by promoting cell proliferation, invasion, metastasis, and angiogenesis, as well as inhibiting apoptosis. However, there are many studies mainly in the gastrointestinal tract. The protein structure, tissue expression and distribution of trefoil factor are reviewed below. It provides guidance for a better understanding of this peptide family and its diagnosis and treatment effect in gastric cancer in the future.

Keywords

Trilateral Factor Family, Gastric Cancer, Structure

1. 引言

胃癌(Gastric Cancer)是全球最常见的消化道恶性肿瘤之一，其发病率、死亡率均处于世界前列。2022年全球癌症及其新发病例数顺位排序前 10 位的癌症分别是肺癌、乳腺癌、结直肠癌、前列腺癌、胃癌、肝癌、甲状腺癌、宫颈癌、膀胱癌、非霍奇金淋巴瘤。胃癌新发病例和死亡病例顺位均排第 5 位，粗发病率和标化发病率顺位均排第 6 位，而粗死亡率和标化死亡率顺位均排第 7 位[1]。内镜检查是目前诊断和临床病理评估胃癌的标准方法，然而，我国由于人口基数比较大，用内镜检查作为首选的人群筛查胃癌的方式对于我国是一个挑战，因此，我国早期胃癌的诊断率仍然较低。此外，内窥镜是高度侵入性的，严重依赖于内窥镜仪器和专业技能的可用性。早期研究有效的预防、诊断和治疗的解决方案是非常必要的。

1.1. TFF 的结构

三叶因子家族(Trefoil Factor Family, TFF)是一类含有一个或几个三叶因子结构域的一群小分子多肽，主要由胃肠道的黏液细胞分泌。三叶因子(Trefoil Factor, TFF)属神经肽家族，由 38 至 39 个氨基酸残基组成，含有 6 个半胱氨酸的小分子肽。其结构域主要包含 3 个二硫键，形成稳定且又特异的结构[2]。由于其分子构象具有一个或者多个“三叶草形结构”，因此被称为三叶肽(Trefoil Peptide)。TFF 主要由乳腺癌相关肽、解痉多肽和肠三叶因子三个家族成员组成。TFF1 和 TFF3 是特殊的，因为它们含有奇数的半胱氨酸残基，与半胱氨酸 VII 位于保守的 TFF 结构域之外。一般来说，分泌性蛋白极不可能存在未配对的半胱氨酸残基，因为二硫键的形成是在内质网(ER)中进行的[3]。

1.2. TFF 的调控机制

近几十年来，一些研究发现三叶因子家族在很多肿瘤中的表达异常，参与了肿瘤的发生、发展，并且与肿瘤的恶性程度和预后紧密相关。TFFs 参与控制胃肠道细胞增殖、凋亡和分化的协调。血管生成增多、细胞迁移增多和胃癌侵袭与 TFF 过表达有关。这些都是伤口愈合和肿瘤发生的关键过程。这些影响可能是由于 TFF 基因突变，染色质重塑，杂合子丢失或启动子甲基化，先前的研究已充分证明 TFFs 作

为胃肠道细胞分化的调节因子的作用，TFFs 的存在可能有助于在早期肿瘤发生过程中维持胃肠道细胞增殖与凋亡之间的平衡[4]。因此，TFFs 在胃癌的发生与发展中扮演着重要的角色。TFF 水平可能作为胃癌从癌前病变进展到癌变的危险指标，TFF 的表达状态也似乎是胃癌患者一个很有前途的预后指标。

2. TFF 与胃癌的关系

2.1. TFF1

自从 1980s 发现了三叶因子家族，首先证实了 TFF 对胃肠道黏膜保护和损伤表达后修复具有重要作用[5]。TFF1 于 1892 年首次在乳腺癌细胞系 MCF-7 中被发现。在正常组织中，TFF1 主要在胃体和胃窦的黏膜上皮中表达，显现出一定的部位特异性。然而，在溃疡等病理条件下，TFF1 的位点特异性表达缺失，从正常胃黏膜到发育不良和胃癌，TFF1 表达呈下降趋势。TFF1 可在任何受损的黏膜中被识别出来，其表达上调，参与胃肠道上皮的重建和修复过程[6]。研究发现[7]，TFF1 主要在胃黏膜细胞的胞浆中表达。核周积累最明显，阳性的细胞呈棕色。它越靠近细胞膜，颜色就越深。从正常胃黏膜、黏膜异常增生到胃癌，TFF1 的表达呈逐渐下降的趋势。另一研究[8]表明，TFF1 对胃肠道细胞具有双重作用：一方面，TFF1 能阻断 G1 期向 S 期的过渡，从而中断胃肠道的细胞分化，减少细胞增殖；另一方面，TFF1 能阻止化学因子诱导的细胞凋亡，这些都揭示 TFF1 是胃肠道中细胞分化的调节因子，减少细胞的增殖和诱导分化是肿瘤抑制剂的功能特点，细胞凋亡是指细胞在生长、发育和分化过程中以及在病理环境中发生的程序性细胞死亡，是不同于坏死的细胞死亡类型，近年来研究发现，细胞凋亡在胃肠道黏膜的更新和某些消化系统疾病的病理过程中发挥着独特的作用，TFF1 通过调节细胞增殖和细胞凋亡之间的平衡发挥其抗肿瘤作用。单体 TFF1 的反应性半胱氨酸 VII 不仅作为胃肿瘤抑制因子具有细胞内和细胞外的保护功能。TFF1 也被认为在炎症过程中发挥保护作用，因为它与氧化应激(“氧化爆发”) [9]有基本联系。

2.2. TFF2

TFF2 是 TFF 分子中第一个被分现的，在胰岛素[10]纯化过程中在猪胰腺中被发现。实验表明，它对胃运动和胃酸分泌有抑制作用，因此被称为胰腺痉挛多肽(PSP) [11]。包含 106 个氨基酸，含有从鸟类到人类的分泌肽，含有两个 TFF 结构域。TFF2 是一种凝集素，可以特异性地识别粘蛋白 MUC6 的 o-连接的 GlcNAcα1→4Galβ1→R 部分。TFF2 通常与粘蛋白 MUC6 共同分泌，分别来自胃底腺和胃窦腺(分别为粘液颈和胃窦腺细胞)以及十二指肠 Brunner 腺，是胃十二指肠粘液的特征性成分。特别值得注意的是，在胃底腺中，TFF2 mRNA 和蛋白不能共同定位[12]。TFF2 转录本仅在黏液颈细胞祖细胞中可检测到。这已经在人类[13]、小鼠[14]和大鼠[15]中得到证实。TFF2 被证明在消化道中发挥保护作用[16]；例如，TFF2 通过增加人结肠上皮细胞的迁移和抑制急性胃损伤的发生来促进胃黏膜损伤的修复[17]。TFF2 的表达已被证明在胃肠道溃疡性疾病中迅速增加，特别是在再生上皮细胞中[18]或非甾体抗炎药物治疗后[19]。另一项研究表明，胃癌患者的血清和肿瘤组织中 TFF2 的水平明显低于正常组织，这可能是由于 TFF2 启动子的甲基化所致[20] [21]。

2.3. TFF3

三叶因子 3 是一种水溶性多肽，主要由肠道杯状细胞分泌，又叫肠三叶因子。在胃肠道发挥黏膜修复作用。TFF3 基因定位于染色体 21q22.3 上，cDNA 全长为 222 bp。TFF3 包含 59 个氨基酸和第 57 位的第 7 个游离半胱氨酸残基，这对二聚体的形成至关重要[22]。新的证据表明，TFF3 在胃癌、结直肠癌、肺癌、甲状腺癌和乳腺癌等癌症中显著上调，并在肿瘤进展[23]中起关键作用。肿瘤的形成与发展主要与肿瘤细胞的增殖、转移、血管生成和抗凋亡机制密切相关。血管生成是肿瘤生长、侵袭和转移过程中不

可或缺的环节。

TFF3 无论是在体内还是体外，均有促进血管生成的作用。其可以促进绒毛膜尿囊膜的血管生成，并可诱导微血管结构的形成。TFF3 通过有丝分裂活化蛋白激酶(MAPK)/ERK、PI3K/AKT、STAT3 和缺氧诱导因子(HIF)-1α 信号通路参与了这四个重要的致癌过程[24]。一些研究人员先前的研究报道，TFF3 的致癌潜能归因于细胞增殖[25]、抑制细胞粘附[26]、阻断凋亡[27] [28]、侵袭[29]和血管生成[30] [31]。Im [32]等研究了胃癌组织中 TFF3 表达水平，结果有 44.2%的胃癌组织 TFF3 高表达，TFF3 的高表达与血管生成、侵袭显著相关，并且 TFF3 的高表达较低表达的患者生存期较短。TFF3 高表达可能是早期胃癌患者预后不良的标志[33]-[36]。

3. 总结与展望

研究显示，在我国，胃癌主要影响 50 岁以上的群体。该疾病在早期阶段的治愈率较为理想，但在晚期阶段的五年生存率仅为五分之一。因此，早期研究有效的预防、诊断和治疗的解决方案，在一些高危地方开展内镜筛查工作，以及开发新型的或者侵入性小的早期胃癌的检测工具，来提高胃癌筛查的敏感性，来降低胃癌的发病率，可以提高患者的生存率。

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