综述

组织因子在肺癌中的研究进展

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摘　要:组织因子(TF),又称凝血因子Ⅲ、凝血酶原或CD142,是外源性凝血系统的启动因子。TF参与许多细胞内信号传导,如细胞存活、基因和蛋白表达、增殖、血管生成等。近年来,随着对TF研究的深入,人们发现其不仅可以激活机体的凝血系统,还参与肺癌、乳腺癌等肿瘤的恶性生物学行为。全文重点对肺癌中组织因子的表达以及在肺癌中的作用机制作一综述。

主题词:组织因子;肺癌;作用机制
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Research Progress on Tissue Factor in Lung Cancer

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Abstract: Tissue factor(TF), also known as coagulation factor Ⅲ, prothrombin or CD142, is the priming factor of exogenous coagulation system. In addition, TF is also involved in several intracellular signal transduction, such as cell survival, gene and protein expression, proliferation, angiogenesis and so on. In recent years, with the further study of TF, it has been found that it can not only activate the coagulation system of the body, but also participate in the malignant biological behavior of lung cancer, breast cancer and other tumors. This article reviews the expression of tissue factor and mechanism in lung cancer.

Subject words: Tissue factor; lung cancer; treatment

1865年,Armand Trousseau首次认识到凝血和恶性肿瘤之间的联系[1]。后来,研究发现在某些恶性肿瘤系统中血清和肿瘤组织中均可检测到组织因子(tissue factor,TF)的高表达[2-3]。此外,肿瘤源性TF阳性微粒 (tissue factor-positive microparticles,TF+-MPS)在晚期疾病患者血浆中含量丰富[4],与静脉血栓栓塞症(vein thromboembolism,VTE)密切相关[5]。靶向TF对肿瘤的诊断和治疗具有潜在的意义。本文就TF在肺癌中的表达以及目前在肺癌中的作用机制和治疗进展作一阐述。

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1　组织因子概述

组织因子是由F3基因编码的一种由263个氨基酸组成的47KDa糖蛋白。F3基因位于染色体1p22~p21上,含有6个外显子,编码294个氨基酸的前体蛋白。前体的功能结构由胞外区(219AA)、跨膜残基(23AA)和细胞质部分(21AA)组成[6]。胞外区是与Ⅶ/Ⅶa结合并激发凝血的关键部位,具有促凝活性和蛋白水解的功能;胞内区末端的三个丝氨酸残基磷酸化具有细胞内信号传导功能,能促进血管内皮生长因子 (vascular endothelial growth factor,VEGF)的转录和合成[7]。由于选择性剪接,TF有3种表达形式:全长型TF(full length TF,flTF)、选择剪切型TF(alternatively spliced TF,asTF)和第三个变体(tf-A)。flTF是一种膜结合的高促凝蛋白,除此之

外，flTF 在细胞膜上参与多种生物学过程，如蛋白酶激活受体(protease-activated receptor，PAR-)2 介导的细胞信号转导和肿瘤的进展[8]。asTF 缺乏跨膜结构域，因此是可溶性的[9]。与 flTF 相比，asTF 具有较低的促血栓形成潜能[9-10]，但具有较强的促血管生成、促进细胞增殖[11-12]。Tf-A mRNA 剪接变异体不能被翻译成蛋白质，由于外显子 1A 内的终止序列，导致翻译提前终止[13]。TF-A mRNA 在多种肿瘤细胞系和人血管内皮细胞中均有表达，然而，TF-A 生物学功能尚不清楚[14]。

2 TF 在肺癌中的表达

在生理条件下，TF 只能由内皮细胞在应激状态下产生。然而，在原发性肿瘤中，TF 可由肿瘤细胞或肿瘤微环境中的细胞(如间质细胞、单核细胞、组织巨噬细胞和血管内皮细胞)诱导产生[15]。研究发现肺癌患者的肿瘤组织和血清中存在 TF 异常表达，而且与肿瘤类型、分期、预后相关。目前研究认为小细胞肺癌(small cell lung cancer，SCLC)表达的 TF 较非小细胞肺癌(non-small cell lung cancer，NSCLC)高[16]，腺癌较鳞癌高[17]，晚期肺癌较早期高[18]，出现远处转移或侵犯者高[19-20]。TF 可作为判断肺癌患者预后的一个指标[21-23]。Regina 等[24]研究发现肺癌中的高 TF 表达可能是由 K-ras 突变引起的，并可能通过血管生成以外的其他机制促进 NSCLC 进展。此外，体外实验发现 TF 在肺转移细胞系中表达更多。Salge 等[25]人体外培养 SCLC 细胞系 NCI-H69 发现细胞中 TF 的表达升高与基质金属蛋白酶-2 (matrix metalloproteinase-2，MMP2)、基质金属蛋白酶-9(matrix metalloproteinase-9，MMP9)分泌有关。

3 TF 在肺癌中作用机制

3.1 TF 调节肺癌细胞增殖

目前研究证实 TF 可以促进肿瘤细胞增殖[26-27]和抑制肿瘤细胞的凋亡[28]。在肺腺癌的体内外研究中发现通过小 RNA 干扰 TF 表达后可以抑制肺腺癌的生长、增殖[29]。Lavergne 等[10]研究发现组织因子途径抑制剂-2 (tissue factor pathway inhibitor-2，TFPI-2)在 65%小细胞肺癌(SCLC)患者低表达，在 NCI-H209 SCLC 细胞中过表达 TFPI-2 后，将细胞原位植入裸鼠中，肺肿瘤生长抑制，这种抑制可以通过体外肿瘤细胞活力的降低，G1/S 期细胞周期转变的阻断和表达 TFPI-2 的 NCI-H209 细胞中显示的细胞凋亡的增加来解释。Cao Y 等[31]研究发现赖氨酸特异性脱甲基酶 2 通过调节 TFPI-2 的表达而促进小细胞肺癌增殖。此外，Hamamoto 等[32]研究发现异常 DNA 甲基化沉默 TFPI-2 来上调跨膜丝氨酸蛋白酶 4 (transmembrane protease，serine 4，TMPRSS4)，并促进 NSCLC 中的肿瘤发生[32]。总之，TF 可以通过调节甲基化水平、改变细胞周期、影响细胞凋亡等促进肺癌细胞的增殖。

3.2 TF 促进肺癌血管生成和转移

肿瘤组织中的血管是肿瘤发生发展的关键，而新生血管是肿瘤血行转移的前提条件。Koomagi 等[33]发现在非小细胞肺癌细胞中 TF 表达与 VEGF 表达和微血管密度有关。此外，他们还发现 TF 免疫阴性的患者的生存时间比 TF 阳性的患者更长。同样，Goldin-Lang 等在一组 NSCLC 组织和血浆样本上对 flTF 和 asTF 在 mRNA 和蛋白质水平(使用免疫组织化学，免疫印迹和 ELISA)上进行定量分析，结果发现 flTF 上调，尤其是腺癌中的 asTF，血栓和肿瘤进展形成风险增加，从而这些患者的预后不良[21]。在体外，Nishi 等 [34] 发现在低氧条件下 asTF 通过增加 Cyr61、CC 趋化因子配体(CCl2)和血管内皮生长因子而促进 A549 细胞管腔的形成。Hsieh 等[35]发现在人肺癌 A549 细胞中，缺氧可以上调 TF 表达，缺氧诱导因子-1α 抑制剂 YC-1 可以通过抑制 p38/NF-κB 途径来预防癌细胞中的缺氧诱导的 TF 的表达，从而抑制 A549 细胞的促凝活性和抑制肿瘤相关血栓的形成。TF 除了在肺癌中具有促血管生成作用外，还可以促进肿瘤转移。Tseng 等[36]在临床研究中发现血浆中组织因子阳性微泡的水平升高与肺癌的远处转移相关。同样，Sawada 等[37]也在有转移的非小细胞肺癌患者的细胞中观察到较强的 TF 染色[37]。此外，Yeh 等[38]发现激活 STAT3 上调组织因子的表达，从而增强肺腺癌中的肿瘤转移和血管通透性，进而促进恶性胸腔积液的产生。总之，无论在体内还是在体外，TF 都能促进肺癌细胞的血管生成和转移，进而影响肿瘤患者的预后和生存情况。

3.3 TF 调节肿瘤微环境中的免疫应答

众所周知，抗肿瘤免疫受到抑制的主要原因是肿瘤微环境中细胞毒性 T 淋巴细胞和 NK 细胞的功能障碍以及髓系来源的抑制细胞 (myeloid derived suppressor cells,MDSCs)的积聚[39]。TF 可激活凝血酶原为凝血酶,从而激活补体系统产生 C5a[40]。C5a 可以通过将 MDSCs 招募到肿瘤微环境中产生促肿瘤效应,从而产生免疫抑制环境[41]。同时,TF 介导的肿瘤微环境内血栓形成可能导致局部缺血缺氧，而低氧又可上调 flTF,从而产生 asTF,这一潜在的正反馈环可能有助于肿瘤细胞的增殖和血管生成，并增加 MDSC 在肿瘤微环境中的浸润[42]。目前研究发现在有 TF 阳性癌细胞存在的情况下,CAR 修饰的 T 细胞 (chimeric antigen receptor T-cell,TF-CAR T)在体外被高度激活，并对 TF 阳性非小细胞肺癌细胞表现出特异性的细胞毒作用[43]。TF 可以促进肿瘤微环境中 MDSCs 积聚,抑制宿主免疫系统,进而协助肿瘤细胞转移。

4 针对 TF 肿瘤靶向治疗

由于 TF 在大多数的癌细胞中有着高表达以及快速的转化效率，因此 TF 可以作为人体抗体—药物偶联物(antibody-drug conjugate,ADC)的理想靶标。最近,伦敦癌症研究所发明了一种新型的抗癌药物—Tisotumabvedotin (TV),是针对组织因子的首个人体抗体—药物偶联物(ADC)。目前,正处于Ⅰ~Ⅱ期临床试验阶段，用于治疗 9 种实体瘤，包括宫颈癌、卵巢癌、子宫颈癌、子宫内膜癌、膀胱癌、前列腺癌、头颈部癌、食管癌和肺癌[44]。针对 TF 的靶向抗血管治疗,Li S 等[45]将 tTF 与具有低 pH 诱导的跨膜结构(pHLIP)的肽融合,产生融合蛋白(tTF-pHLIP),该蛋白质靶向酸性肿瘤血管内皮并有效诱导局部血液凝固。体内实验中,tTF-pHLIP 中可选择性地诱导患瘤小鼠肿瘤血管的血栓形成闭塞，减少肿瘤血液灌注从而抑制肿瘤生长而无明显的副作用。针对 TF 靶向免疫治疗,Hu 等构建了活性位点突变的 FVⅡ与人 IgG1Fc(FVⅡ-IgG1Fc)的免疫结合物,命名为 I-CON[46-48]。当与 TF 表达的癌细胞结合时,ICON 可以介导自然杀伤细胞(NK 细胞)依赖抗体依赖性细胞介导的细胞毒性 (antibody-dependent cellular cytotoxicity,ADCC) 和补体依赖性细胞毒性(complement dependent cytotoxicity,CDC)作为其作用机制[49]。

目前，对于肺癌临床治疗中缺乏有效的抗血管生成的靶向治疗。而针对 TF 潜在的肿瘤靶向治疗具有特异性高,对正常组织损伤小等特点,在癌症的靶向治疗中潜力巨大。现阶段,针对组织因子 TF 的靶向免疫治疗和光动力疗法等用于相关肿瘤的临床治疗。我们相信,随着对 TF 研究的不断深入,针对肺癌 TF 的靶向药物或技术也将用于临床，造福肺癌患者。

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