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## 胰腺癌中的静脉血栓形成机制

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**[摘要]** 胰腺癌(pancreatic cancer, PC)是一种高转移性的恶性肿瘤,其发生静脉血栓栓塞(venous thromboembolism, VTE)的风险明显高于其他肿瘤。目前,PC患者发生VTE的机制仍不清楚,可能涉及凝血系统激活,肿瘤细胞相关炎症因子产生增多等,因此,仍需对PC患者VTE的发生机制做更进一步的研究。

**[关键词]** 胰腺癌; 静脉血栓栓塞; 炎症因子; 凝血功能异常

## Mechanisms of venous thrombosis in pancreatic cancer

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**Abstract** Pancreatic cancer (PC) is a highly metastatic malignant tumor, and its risk of venous thromboembolism (VTE) is significantly higher than other tumors. Currently, the mechanisms VTE occurrence in PC remain unclear, which may involve the activation of blood coagulation system and increased production of tumor cell-associated inflammatory cytokines. Therefore, further studies to investigate the pathogenesis of VTE in PC are warranted.

**Keywords** pancreatic cancer; venous thromboembolism; inflammatory cytokines; coagulant dysfunction

癌症患者静脉血栓栓塞(venous thromboembolism, VTE)的发生率为非癌症患者的4~6.5倍,其中胰腺癌患者静脉血栓发生的风险尤其高(增加58倍)<sup>[1-2]</sup>。研究<sup>[3-4]</sup>发现,高达40%的胰腺癌患者深受血栓栓塞并发症的影响。胰腺癌患者的高病死率与静脉血栓事件的发生密不可分<sup>[5]</sup>。因此,预防VTE事件是治疗胰腺癌过程中最重要的事情之一。

肿瘤相关血栓形成已成为研究热点,特别是胰腺癌中静脉血栓的形成机制更是引起大家的多种猜测。本文就胰腺癌血液中相关因子与胰腺癌血栓栓塞的相关性作一综述。

### 1 炎症细胞因子

炎症在癌变中起着关键作用,炎症细胞和其分泌物如细胞因子和趋化因子塑造了导致癌症的炎症微环境<sup>[6]</sup>。胰腺癌细胞分泌多种炎症细胞因子,包括白细胞介素(interleukin, IL)-6、IL-8和肿瘤坏死因子 $\alpha$ (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ )。研究<sup>[7-9]</sup>证实:在早期胰腺癌患者体内,炎症细胞因子IL-6、IL-8和TNF- $\alpha$ 水平明显升高,IL-6、IL-8对中性粒细胞有趋化作用和激活作用,TNF- $\alpha$ 对内皮细胞(endothelial cells, ECs)有刺激作用,且TNF- $\alpha$ 可损伤ECs。中性粒细胞激活、ECs损伤后

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可产生一系列凝血级联反应,造成胰腺癌患者体内血液的高度凝集状态。

炎症细胞因子可诱导血管内皮功能障碍,下调ECs血栓调节蛋白(其正常功能是控制凝血酶的生成)的表达,促进纤溶酶原激活物抑制剂(plasminogen activator inhibitor, PAI)的合成,增加ECs异质细胞黏附分子的表达,促进血液的高凝状态<sup>[10]</sup>。细胞黏附分子,如细胞间黏附分子(intercellular adhesion molecule-1, ICAM-1)或血管细胞黏附分子(vascular cell adhesion molecule-1, VCAM-1),在白细胞黏附在ECs上和炎症细胞迁移到组织或黏附依赖性免疫反应中发挥重要作用<sup>[7]</sup>。同时,在胰腺癌患者中,细胞黏附分子的上调促进白细胞黏附于ECs,为炎症细胞通往血管提供通道。越来越多的证据<sup>[8]</sup>表明:IL类的表达变化与晚期胰腺癌的不良预后有关。

## 2 促凝机制

### 2.1 组织因子与微粒

组织因子(tissue factor, TF)的过表达被认为在肿瘤相关VTE的发生和肿瘤进展中起关键作用。研究<sup>[11]</sup>证实:循环TF水平升高与胰腺癌VTE的发生有关。TF是内皮下细胞的跨膜受体,可诱导凝血酶生成<sup>[12]</sup>,是外源性凝血级联反应的关键启动因子,也是胰腺癌高凝状态的促进因素。TF-VIIa复合物激活因子X,产生生理止血所需的凝血酶。研究<sup>[11]</sup>发现:TF通路可能在胰腺癌静脉血栓形成的急性期发挥关键作用。

癌细胞,特别是胰腺癌细胞过量表达TF,并以微粒的形式释放出来,从而启动血液凝固反应。微粒是癌细胞释放到血液循环中的小泡,血浆中微粒-TF活性和促凝活性呈相关性<sup>[11-13]</sup>。研究<sup>[14]</sup>发现:发生VTE的胰腺癌患者的微粒-TF活性高于胰腺癌患者体内未发生VTE的其他部位的TF活性,表明胰腺癌患者中以微粒形式释放的TF具有更高的促凝活性,提示微粒-TF的释放可能是导致胰腺癌患者VTE发生的原因之一。

### 2.2 磷脂酰丝氨酸

磷脂酰丝氨酸(phosphatidylserine, PS)是一种与凝血因子结合的带负电荷的促凝磷脂,与血栓形成有关。氧化应激使PS暴露在胰腺癌细胞的血管内皮表面,而不暴露在正常细胞上<sup>[15]</sup>。在补体激活或对细胞损伤作出反应时,PS会在细胞膜外表面重新排列<sup>[16]</sup>。胰腺癌血液环境存在的炎性物

质可损伤血管ECs,导致ECs功能障碍,促使ECs上的PS外翻、释放促凝因子,如微粒、血管性血友病因子、细胞黏附因子等,加速血液微环境呈现高凝状态。同时,ECs受损时释放的炎症因子会与肿瘤本身炎性环境形成级联叠加作用。研究<sup>[17]</sup>发现:在PS外翻的ECs上有PS依赖性纤维蛋白的生成,纤维网络的形成便于凝血酶原、血小板等促凝物质的沉积,加速血栓栓子的形成。

### 2.3 中性粒细胞诱捕网

中性粒细胞作为抗炎因子,参与炎症反应。此外,中性粒细胞也参与血栓的形成,而这一过程依赖于中性粒细胞胞外诱捕网(neutrophil extracellular traps, NETs)的形成<sup>[18-19]</sup>。当被肿瘤环境中炎症因子激活的中性粒细胞释放出含有DNA、组蛋白、TF、高迁移率族蛋白B1(high mobility group box-1, HMGB1)和其他成分的细胞内容物到周围组织或循环中时,NETs就形成了。

研究<sup>[20]</sup>证实NETs与胰腺癌静脉血栓形成有关。在胰腺癌血液环境中,NETs可快速释放,为环境中的促凝物质提供可黏附及扩散的靶点。在静脉切应力作用下,NETs具有诱捕和激活血小板的能力,从而促进血栓的形成。与此同时,血小板也可能在癌症的NETs释放中起着的重要作用<sup>[21-23]</sup>。此外,研究<sup>[22]</sup>证实:NETs中的蛋白质成分也能促进血小板黏附、活化和形态改变,且NETs释放的DNA和晚期糖基化终末产物受体(receptor for advanced glycation end products, RAGE)对诱导血小板聚集是必要的<sup>[24]</sup>。NETs刺激血小板的活化和聚集,且NETs释放的物质与血小板相互影响,协同作用,营造血液高凝状态,进一步激活凝血瀑布级联反应,导致血栓生成。

### 2.4 HMGB1

HMGB1是一种普遍存在的核蛋白,在多种类型的癌症,特别是胰腺癌中表达升高,且与肿瘤进展有关。癌细胞中过表达的HMGB1释放到细胞外微环境中,可能通过促进细胞迁移和新生血管生成促进恶性进展。此外, HMGB1不断释放到细胞外微环境中,会形成类似于慢性炎症的微环境,这是癌症发生的诱发条件<sup>[25]</sup>。炎症微环境与HMGB1的相互作用,诱导胰腺癌血液环境异常改变。此外, HMGB1在DNA修复中发挥关键作用,与多种癌症发展相关转录因子有关,并刺激其活性<sup>[26]</sup>。HMGB1也是一种负信号分子,参与对感染、损伤和炎症的反应,造成细胞或者

组织损伤, 被认为是组织损伤介导的无菌炎症和病原体介导的感染的治疗靶点<sup>[27-28]</sup>。

HMGB1已被证实与胰腺癌血栓形成有关。HMGB1介导炎症和组织损伤, 并且在胰腺癌炎症环境的基础上激活中性粒细胞, 在中性粒细胞强烈激活的条件下, NETs生成增加, 进一步激活ECs, 增加细胞间黏附分子的表达和促炎介质的释放<sup>[29]</sup>, 促炎因子的生成增强了ECs活化与中性粒细胞激活之间的相互作用, 细胞进一步被激活、损伤并加剧炎症和损伤, 最终导致高凝状态下栓子的形成。

### 3 抗凝机制

蛋白C生理功能参与止血、炎症和信号转导, 且对内皮屏障有保护作用。活化的蛋白C裂解从而抑制Va和VIIIa因子发挥止血功能<sup>[30-31]</sup>。研究<sup>[32]</sup>证实: 凝血活化产物水平升高, 抗凝物质随之增加, 同时又不断被消耗, 这可能是导致胰腺癌患者体内蛋白C水平降低的原因。然而, 这就意味着高凝状态水平的进一步提升。

### 4 纤溶机制

纤维蛋白溶解是血液凝块被分解的过程。癌症促进纤维蛋白凝块的形成, 抑制纤维蛋白溶解。研究<sup>[10]</sup>表明: 纤溶酶原激活系统在胰腺癌生物学中起重要作用, 此外, 纤溶酶原激活也使其配体PAI-1在胰腺癌患者中增加。人胰腺肿瘤和细胞系已被证实表达PAI-1。血浆中PAI-1抗原及其相关活性升高可能导致患者发生VTE的原因<sup>[33]</sup>。

### 5 总结

循环中的炎症因子、TF对机体以及血液内环境有着较为重要的影响, 但是目前在胰腺癌中的研究较为单一。关于NETs、HMGB1等物质在胰腺癌中的研究也越来越多, 但其在胰腺癌发生发展中的作用及具体机制尚未明确, 需要进一步研究。

PC患者VTE的发生率较高, 严重影响后期治疗, 导致预后不良。但是, 肿瘤源性物质导致VTE发生的机制仍不明确。胰腺癌VTE形成的机制主要有肿瘤环境下炎症性物质损伤增加、促凝与抗凝功能失调、纤溶功能紊乱等, 并且这些机制间存在相互影响。因此, 血液状态异常在PC患者VTE的发生中起重要作用, 成为重点研究方向。对

NETs、HMGB1等小分子物质研究的不断深入可能为PC患者VTE的预防及治疗提供新思路, 应引起广泛关注并进行深入研究。

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