综述

多能蛋白聚糖在恶性肿瘤中的表达及生物学作用的研究进展

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［摘要］恶性肿瘤严重威胁着人类健康，是全球人类死亡的主要原因之一。为了进一步提高对于恶性肿瘤的治疗效果，延长患者生存时间，明确恶性肿瘤的发病机制以及寻找新的诊断和治疗靶点变得尤为重要。研究发现，恶性肿瘤的发生发展是肿瘤细胞与肿瘤微环境（tumor microenvironment，TME）相互作用的结果。多能蛋白聚糖（versican）是一种硫酸软骨素蛋白聚糖，属于外源凝集素蛋白聚糖家族，由*VCAN*基因编码，是细胞外基质的主要成分，在胚胎发育和炎症反应过程中均发挥重要作用。作为TME的重要组成部分，versican在肾细胞癌、肝细胞癌、胃癌等多种肿瘤组织中异常表达，且与患者的临床病理特征及预后密切相关，是肿瘤早期诊断和预后评估的潜在生物标志物。进一步的研究显示，versican可通过促进肿瘤细胞增殖、侵袭和转移，抑制肿瘤细胞凋亡，促进肿瘤血管生成和抑制抗肿瘤免疫反应等多种方式促进肿瘤的发展。该文就versican在恶性肿瘤中的表达及生物学作用的研究现状进行综述，旨在为肿瘤的后续研究及临床诊治提供参考依据。
［关键词］多能蛋白聚糖；恶性肿瘤；肿瘤微环境；细胞外基质
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Research progress in the expression of versican in malignant tumors and its biological roles

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[Abstract] Malignant tumors pose a serious threat to human health and are one of the main causes of human death worldwide. In order to further improve the therapeutic outcomes of malignant tumors and prolong patients′ survival time, clarifying the pathogenesis of malignant tumors and searching for new diagnostic and therapeutic targets become particularly important. It has been found that the occurrence and development of malignant tumors are the results of the interaction between tumor cells and the tumor microenvironment (TME). Versican, encoded by the *VCAN* gene, is a type of chondroitin sulfate proteoglycan belonging to the exogenous lectin proteoglycan family. It is a major component of the extracellular matrix and plays an important role in embryonic development and inflammatory responses. As an important component of TME, versican is abnormally expressed in various tumor tissues such as renal cell carcinoma, hepatocellular carcinoma, and gastric cancer, and is closely related to the clinical pathological characteristics and prognosis of the patients. It is a potential biomarker for early diagnosis and prognostic evaluation of tumors. Further researches have shown that versican can promote tumor development in a number of ways, such as promoting tumor cell proliferation, invasion and metastasis, inhibiting tumor cell apoptosis, promoting tumor angiogenesis, and inhibiting anti-tumor immune responses. This article reviews the current research status of the expression and biological effects of versican in malignant tumors, aiming to provide reference for subsequent research, clinical diagnosis and treatment of tumors.
[Key words] versican; malignant tumor; tumor microenvironment; extracellular matrix

近年来，随着肿瘤的预防、诊断和治疗方法的不断进步，很多肿瘤患者的预后得到改善，但恶性肿瘤仍是全球人类死亡的主要原因之一[1]。因此，明确恶性肿瘤的发生发展机制，探索新的治疗靶点，对提

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高肿瘤治疗效果，改善患者预后尤为重要。肿瘤的发生发展不仅取决于肿瘤细胞自身，而且与肿瘤微环境（tumor microenvironment，TME）也密切相关[2-3]。细胞外基质（extracellular matrix，ECM）是TME的重要组成部分，在肿瘤的发生发展中起着关键作用[4]。多能蛋白聚糖（versican）是一种大分子的硫酸软骨素蛋白聚糖，属于外源凝集素蛋白聚糖家族，由染色体5q12~5q14位点上的*VCAN*基因编码，是ECM的主要成分[5]。体内外研究显示，泌尿系统肿瘤[6-7]、肝细胞癌[8-10]、结直肠癌[11-12]、胃癌[13-16]等多种肿瘤组织中均存在versican的高表达，且与患者的不良预后密切相关，这为肿瘤的早期诊断和预后评估提供了新的生物标志物。然而，versican在恶性肿瘤中的作用机制尚未完全明确，现就目前versican在恶性肿瘤中的表达及生物学作用的相关研究进行综述。

1 Versican概述

1.1 Versican的基本结构

Versican由3个不同的区域组成，分别为N端的G1结构域、C端的G3结构域及连接G1和G3的糖胺聚糖（glycosaminoglycan，GAG）[17]。其中G1结构域由1个免疫球蛋白（immunoglobulin，Ig）样模块和2个透明质酸结合区（即链接模块）构成[17]；而G3结构域则由2个类表皮生长因子（epidermal growth factor，EGF）重复序列、1个碳水化合物识别区域（carbohydrate recognition domain，CRD；又称类凝集素序列）和1个补体结合蛋白（complement binding protein，CBP）调控序列组成[18]。GAG位于versican的中心，是硫酸软骨素（chondroitinsulfate，CS）链的附着区[19]。由于mRNA的选择性剪切，versican至少存在5种亚型，即V0~V4，每一种亚型具有不同长度的GAG，相对地可以结合不同数量的CS链[19]。其中V0亚型包含α-GAG和β-GAG，V1和V4亚型仅包含β-GAG，V2亚型仅包含α-GAG，而V3亚型则没有GAG[17]。

1.2 Versican的功能

Versican在胚胎发育和炎症反应过程中均发挥重要作用。首先，在胚胎发育过程中，versican对于心血管形态的发生、神经及骨骼的发育至关重要[20-22]。研究[20]发现，在心脏的发育过程中，水解versican可以使心脏共同出口远端区域的心肌退化，逐渐被平滑肌取代并发育成动脉组织，促进心脏流出道（outflow tract，OFT）的形成。最近研究[23]发现，versican在心肌细胞增殖和心肌修复过程中发挥重要作用。同时，versican还可以影响神经轴突的生长，从而调节神经组织的发育过程[21]。间充质细胞的凝聚是软骨发育的重要步骤，versican的CS链可以促进间充质基质的形成和软骨细胞的分化[22]。其次，在由感染和组织损伤引起的炎症反应过程中，versican也发挥着关键作用[24]。Versican作为ECM的重要组分之一，可以与透明质酸、肿瘤坏死因子刺激基因-6（tumor necrosis factor-stimulated gene-6，TSG-6）蛋白、间α胰蛋白酶抑制剂（inter-α-trypsin inhibitor，ITI）等多种分子相互作用，形成稳定的支架，为侵入组织的炎症细胞充当“着陆带”[25-27]。Versican可以直接通过CD44、P-选择素糖蛋白配体-1（P-selectin glycoprotein ligand-1，PSGL-1）、Toll样受体（toll-like receptor，TLR）等细胞表面分子，或间接通过透明质酸与炎症细胞相互作用，从而促进肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、白细胞介素-6（interleukin-6，IL-6）和核因子κB（nuclear factor κB，NF-κB）等炎症细胞因子的合成和分泌[27]。Versican还可以通过与多种调节炎症的细胞因子相互作用，影响它们的生物利用度和生物活性[28]。在小鼠肺炎模型中，敲除*Vcan*基因，可降低蛋白versican表达，显著减少白细胞对肺的侵袭，并减少炎症细胞因子的表达[29]。不同的versican亚型的功能各不相同。如在神经系统发育过程中，versican V0和V1亚型可以抑制神经嵴细胞的迁移[30]。V1亚型可以促进神经轴突的生长[31]，而V2亚型则表现为抑制[21]。此外V1亚型可以通过增强表皮生长因子受体（epithelial growth factor receptor，EGFR）和整合素的表达来诱导神经元的分化，而V2亚型则无此功能[31]。V3亚型的表达可以减少脂质的沉积和单核巨噬细胞的积累，从而降低动脉粥样硬化的发生[32-33]。近年来，研究人员在乳腺癌组织中发现了V4亚型的存在，但其功能仍待进一步明确[34]。

2 Versican在肿瘤中的表达及其与临床病理特征的关系

Versican在多种肿瘤组织中异常表达，且与患者

的临床病理特征及预后密切相关。一项研究[6]表明，versican在肾细胞癌组织中高表达，并且其高表达与根治性肾切除术后的肿瘤复发转移率升高及患者5年生存率下降密切相关。Versican的V1亚型在肝细胞癌组织中高表达，并与不良预后相关[8,35]；与正常肝脏组织相比，肝细胞癌组织中versican表达上调，并且恶性程度越高的亚型中versican的表达水平越高[8]。与腺瘤相比，结直肠癌组织中versican的表达显著增高，并且versican的表达促进了腺瘤向结直肠癌发展[11]。胃癌组织中versican的表达水平明显高于正常胃黏膜组织，并且versican的高表达与较高的TNM分期及患者的不良预后密切相关[15]，是胃癌患者预后不良的独立预测因子[36]。在食管鳞状细胞癌组织中，versican较癌旁组织显著增高，且versican高表达患者的无病生存期明显缩短[37]。进一步的研究[38]表明，食管癌组织中versican高表达与肿瘤血管和淋巴管浸润增加、淋巴结转移及患者预后不佳显著相关。在卵巢癌组织中，同样存在versican的高表达，且versican的高表达与卵巢癌腹膜转移率增加密切相关[39]。

3　Versican促肿瘤发展的机制

3.1　Versican促进肿瘤细胞的增殖

目前研究认为versican主要通过2种机制促进肿瘤细胞的增殖（图1）：一是通过G3结构域中的2个类EGF重复序列促进肿瘤细胞增殖[40]；二是通过G1结构域破坏细胞间黏附，从而促进细胞增殖[41]。Versican的V1亚型通过G3结构域中的类EGF重复序列激活表皮生长因子受体/磷脂酰肌醇3-激酶/蛋白激酶B（epithelial growth factor receptor/phosphatidylinositol 3-kinase/protein kinase B，EGFR/PI3K/AKT）信号通路，促进肝癌细胞的增殖[35]。此外，versican还可以通过G1结构域与透明质酸、CD44、透明质酸和蛋白多糖连接蛋白1（hyaluronan and proteoglycan link protein 1，HAPLN1）等分子相互作用来促进细胞的增殖[42]。

3.2　Versican抑制肿瘤细胞的凋亡

研究[43]显示，versican G1结构域高表达的肉瘤细胞可以抵抗细胞毒性药物所诱导的以及Fas介导的细胞凋亡。Versican V1亚型的表达与BCL-2相关细胞死亡激动剂（BCL-2 associated agonist of cell death，BAD）的表达呈负相关，当应用小干扰RNA减少versican V1亚型的表达时，促凋亡蛋白BAD的表达增加，versican V1亚型抑制肿瘤细胞凋亡的能力减弱[44]。一项关于多发性骨髓瘤（multiple myeloma）的研究[45]显示，肿瘤组织中高表达的miR-135b可以通过激活Wnt/β连环蛋白（Wnt/β-catenin）信号通路来抑制肿瘤细胞的凋亡；versican在多发性骨髓瘤组织中高表达，是Wnt/β-catenin信号通路的关键分子，沉默*VCAN*基因逆转了miR-135b抑制肿瘤细胞凋亡的作用；这表明miR-135b及其介导的Wnt/β-catenin信号通路可以通过调控versican来抑制肿瘤细胞的凋亡。（图1）

3.3　Versican促进肿瘤细胞局部侵袭和远处转移

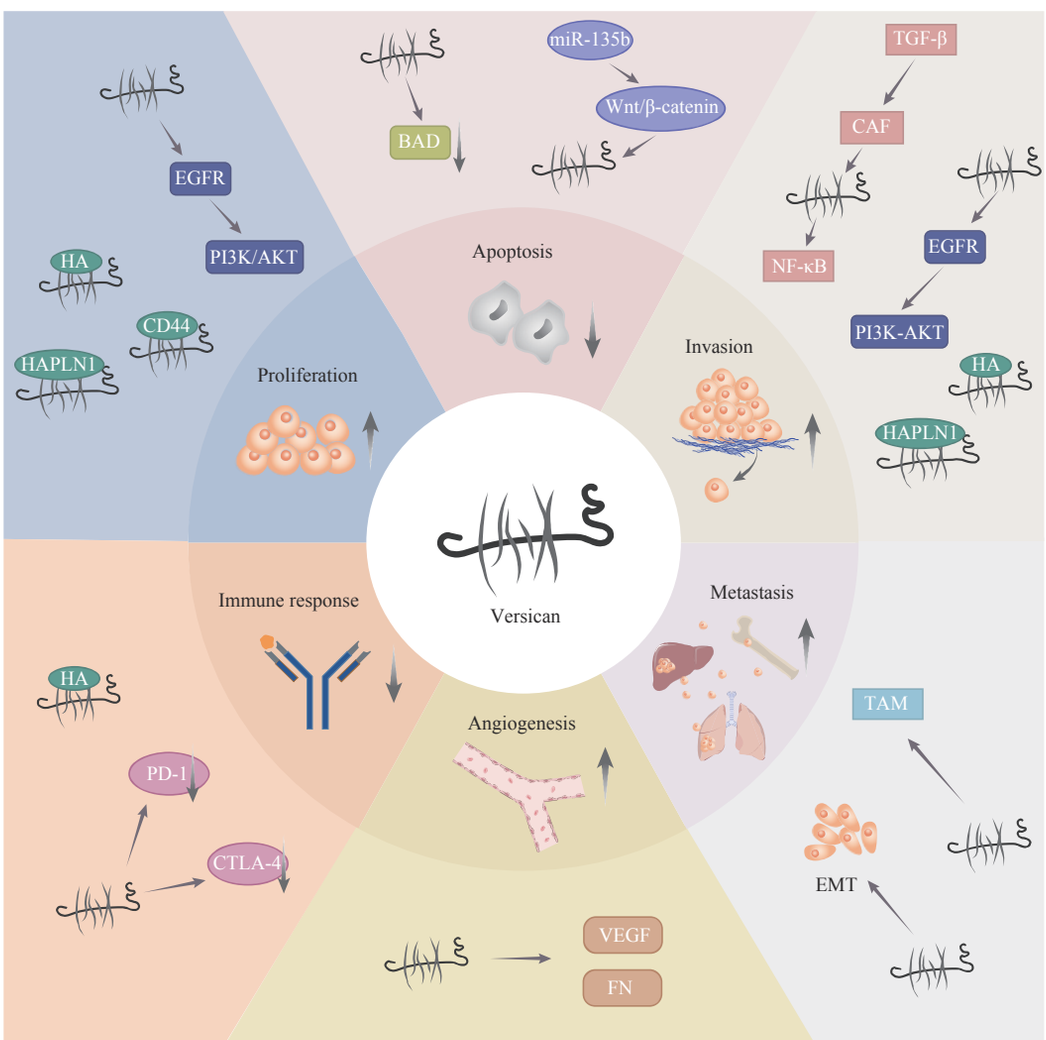
关于恶性星形细胞瘤的研究[41,46]显示，versican的G1结构域通过与透明质酸、HAPLN1结合来减少肿瘤细胞的黏附，增强肿瘤细胞的迁移能力。而G3结构域的类EGF重复序列通过激活EGFR/PI3K/AKT信号通路，促进肝癌细胞的迁移和侵袭[35]。抑制素βA亚基可以通过上调versican的表达来促进结肠癌细胞的迁移和侵袭[12]。在卵巢癌中，转化生长因子-β（transforming growth factor-β，TGF-β）可以上调癌症相关成纤维细胞（cancer-associated fibroblast，CAF）来源的versican的表达，高表达的versican通过激活NF-κB信号通路促进肿瘤细胞的迁移和侵袭[47]。一项关于肝细胞癌的研究[9]也显示，CAF来源的versican可显著促进肿瘤细胞的迁移和侵袭。胃癌组织中versican的表达与上皮-间质转化（epithelial-mesenchymal transition，EMT）相关蛋白的表达密切相关，且高表达versican的患者更容易发生淋巴结转移，提示versican可以通过调节EMT促进胃癌细胞的远处转移[48]。一项关于乳腺癌的研究[49]发现，versican不仅可以增强肿瘤细胞在骨组织中的迁移、侵袭及生存能力，而且还能够抑制前成骨细胞的生长和分化，进而促进乳腺癌的骨转移。另一项乳腺癌的研究[50]显示，ECM中versican的高表达与肿瘤相关巨噬细胞（tumor-associated macrophage，TAM）的大量浸润相关，而后者又与小鼠乳腺癌的肺转移结节数量的增加有关。Versican或将成为治疗恶性肿瘤转移的新靶点。（图1）

3.4 Versican促进肿瘤血管生成

血管生成是恶性肿瘤进展的先决条件之一。Versican的G3结构域可以促进血管内皮生长因子（vascular endothelial growth factor，VEGF）和纤维连接蛋白（fibronectin，FN）的表达，三者互相协同可促进肿瘤血管的生成[51]；同时新生血管内皮的形成又反过来促进versican的表达[52]。一项关于睾丸生殖细胞瘤的研究[52]发现，versican高表达的肿瘤间质中微血管数量增加，这与其促进内皮细胞的迁移密切相关。（图1）

3.5 Versican抑制肿瘤的免疫应答

Versican与透明质酸相互作用可以吸引免疫细胞的黏附，从而减缓免疫细胞在组织中的迁移速度[53-54]。此外，versican与其他ECM蛋白相互结合形成纤维结构来增加组织硬度，以形成天然的“物理屏障”，阻碍T细胞浸润，抑制肿瘤的免疫应答[55]。肝细胞癌组织中versican的表达与程序性死亡受体-1（programmed death-1，PD-1）、细胞毒性T淋巴细胞相关抗原-4（cytotoxic T lymphocyte-associated antigen-4，CTLA-4）的表达均呈明显的正相关，而与肿瘤突变负荷（tumor mutational burden，TMB）呈明显的负相关，这表明versican可能是恶性肿瘤免疫治疗耐药的潜在生物标志物之一[10]。（图1）



Note：EGFR—epithelial growth factor receptor; PI3K/AKT—phosphatidylinositol 3-kinase/protein kinase B; HA—hyaluronic acid; HAPLN1—hyaluronan and proteoglycan link protein 1; BAD—BCL-2-associated agonist of cell death; TGF-β—transforming growth factor-β; CAF—cancer-associated fibroblast; NF-κB—nuclear factor κB; TAM—tumor-associated macrophage; EMT—epithelial-mesenchymal transition; VEGF—vascular endothelial growth factor; FN—fibronectin; PD-1—programmed death-1; CTLA-4—cytotoxic T lymphocyte-associated antigen-4.

图1 Versican促肿瘤发展的机制

Fig 1 Mechanism of versican promoting tumor development

4　结语与展望

Versican在多种肿瘤组织中高表达，且与患者的临床病理特征及不良预后密切相关，这为肿瘤的早期诊断和预后评估提供了新的生物标志物。Versican作为TME的重要组成部分，在肿瘤发展的多个方面发挥关键作用，包括促进肿瘤细胞增殖、侵袭和转移，抑制细胞凋亡，促进新血管生成和抑制肿瘤的免疫应答。越来越多的证据表明，versican同ECM的其他成分一样，在肿瘤免疫中发挥着重要作用，因此靶向versican具有提高肿瘤免疫治疗效果的潜力。然而，versican作用机制的复杂性及显著的肿瘤异质性则可能成为其靶向治疗的限制性因素。在未来，以versican为靶点的药物或许能为肿瘤患者提供新的治疗选择并改善患者预后。

利益冲突声明/Conflict of Interests

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