KNG1结构及其在疾病中的研究进展

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摘要 激肽原-1(kininogen-1, KNG1)蛋白, 又称高分子量激肽原(high molecular weight kininogen, HK)(P01042), 由*KNG1*基因编码。在参与凝血过程的同时, 它还在心血管、呼吸、消化等系统疾病中起着重要的作用。因此, 该文对KNG1的结构、功能及其在人体生理和病理条件下的调控机制进行了综述, 意在提供对KNG1更全面的认识, 以实现KNG1参与疾病诊断和治疗的可能。

关键词 激肽原-1; 结构; 肿瘤

The Structure of Kininogen-1 and Its Research Progress in Diseases

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Abstract KNG1 (kininogen-1) protein, also known as high molecular HK (weight kininogen) (P01042), is encoded by the *KNG1* gene. While participating in the coagulation process, it also plays an important role in cardiovascular, respiratory, digestive, and other systemic diseases. Therefore, this paper provides a review of the structure of KNG1 and its mechanism of action in diseases, aiming to provide a more comprehensive knowledge of KNG1 and to realize the possibilities of KNG1 in clinical diagnosis and treatment.

Keywords kininogen-1; structure; tumor

1 KNG1简介

激肽原-1(kininogen-1, KNG1)蛋白, 又称高分子量激肽原(HK)(P01042), 由*Kng1*基因编码。*Kng1*基因位于人类第三号染色体, 全长序列为27 Kb, 由11个外显子和10个内含子组成[1-2]。人KNG1是一种由626个氨基酸组成的糖蛋白(不含信号肽)。分子质量为70~120 kDa, 理论等电点为6.3, 实验报道等电点为4.9±0.2[3]。其在血浆中的浓度约为70 μg/mL, 主要由肝细胞表达, 并分泌到血液中。

证据表明, KNG1与凝血有关[4]。敲除*Kng1*基因会导致小鼠血栓形成的时间增加[5]。前激肽释放酶通过与KNG1作用转化为血浆激肽释放酶。这会导致因子XI(由*F11*编码)的激活, 从而启动凝血共同途径的发生。据报道*kng1* rs710446与凝血因子XI和活化部分凝血活酶时间有着紧密的联系[6](表1)。除此以外, KNG1还发挥抗血管生成作用, 并对内皮细胞的增殖具有抑制作用[7-8]。

2 KNG1的结构

KNG1共有6个结构域[9](图1)。D1(domain 1)含有金属离子结合位点, 其可以和Ca^{2+}结合[10]。D2和D3属于半胱氨酸蛋白酶抑制剂家族, 其可以抑制钙蛋白酶和木瓜蛋白酶活性[11]。D3还可以与血小板内皮细胞结合, 且具有抗菌活性[12]。D4为缓激肽序

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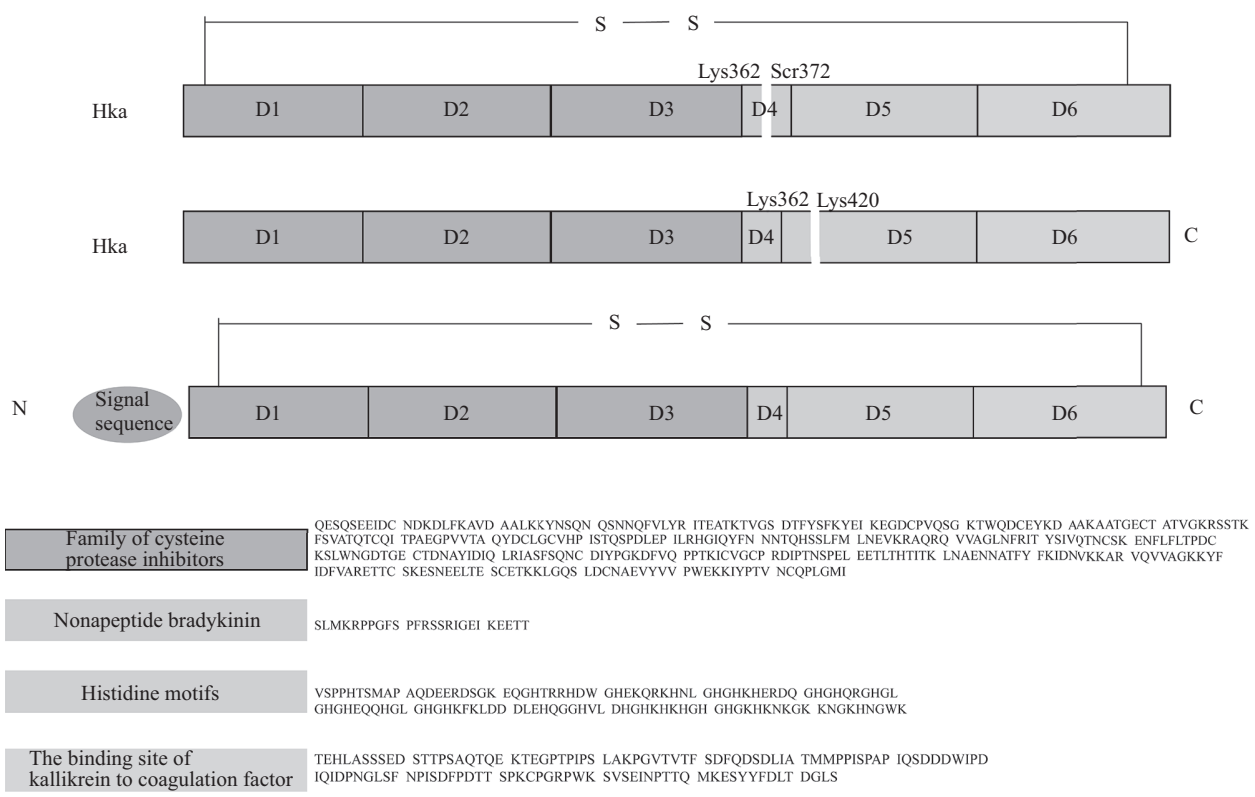
表1 KNG1单核苷酸多态性的生物学意义

Table 1 Biological significance of KNG1 single nucleotide polymorphisms

单核苷酸多态性 SNP	作用 Roles	参考文献 References
rs11924390	Associated with 25-hydroxyvitamin D in a Filipino population	[21]
rs710446	Associated with coagulation factor XI	[6]
rs2304456	Associated with irbesartan blood levels in Chinese men	[22]
rs1648711	Related to venous thrombosis	[23]
rs710446	An important risk factor for cryptogenic stroke in young Indians	[24]
rs710446	Associated with ischemic stroke susceptibility in Chinese population	[25]
rs5030082	Playing an important role in thromboembolism and stroke caused by endotoxemia	[26]
rs6796803	Associated with neuropathic pain caused by head and neck cancer	[27]



SS: 二硫键; HKa: 活性形式的激肽原; N: N-端; C: C-端; D1~D6: 结构域1~结构域6。

SS: disulfide bonds; HKa: active form of kininogen; N: N-terminal; C: C-terminal; D1-D6: domain 1-domain 6.

图1 KNG1的结构

Fig.1 Structure of KNG1

列。HK在D4的两个位置被血浆激肽释放酶切割以释放九肽缓激肽(RPPGFSPFR)和双链HKa(Active form of kininogen)(图1)。D5是细胞结合位点。有研究表明D5和Hka可能具有类似的功能。HKa和D5可以通过表皮生长因子受体(epidermal growth factor receptor, EGFR)/尿激酶型纤溶酶原激活物受体(urokinase plasminogen activator surface receptor, uPAR)相互作用从而抑制人前列腺癌细胞的迁移和侵袭。同时, HKa还可以通过阻止uPAR、EGFR与α5β1复合物的形成来抑制细胞外信号调节激酶和磷酯酰肌醇-3-激酶(phosphoinositide 3-kinase, PI3K)的激活[13]。Hka还可以调节细胞周期蛋白A从而诱导内皮细胞凋亡[14]。此外实验表明D5可以通过抑制PI3K和Akt来抑制内皮细胞迁移[15], 而以上作用都可以被铁蛋白阻断[16]。D5还可以干扰人结肠癌细胞G_1期向S期转变, 从而抑制细胞增殖[17]。也有研究

表明D5抑制癌细胞侵袭与α-肌动蛋白-4有关[18]。D3和D5可能通过uPAR、β2整合素启动的细胞内信号通路从人单核细胞释放白介素-β(interleukin-β, IL-β)[19]。KHAN等[20]进一步发现HKa可以通过IL-1β和肿瘤坏死因子β(tumor necrosis factor β, TNF-β)诱导组织因子(tissue factor, TF)表达。因此, Hka和KNG1可能成为炎症性疾病和凝血功能障碍之间的桥梁。最后, D6具有与激肽释放酶原和凝血因子XI结合的位点。AlphaFold已经可以对大部分蛋白进行结构预测, 尽管其对D1~D4结构域有较好预测 (https://alphafold.com/entry/P01042), 但对D5、D6结构域预测较差, 因此对于KNG1的空间结构仍需要更多的研究。

3 KNG1与非肿瘤疾病

3.1 KNG1与心血管疾病

研究人员对未经治疗的高血压患者的表达谱数据进行分析, 发现*Kng1*基因在未经治疗的高血压患者中具有显著作用, 并且miR-9-5P表达可能与*Kng1*有关[28]。同时也有研究发现KNG1会影响高血压患者对醛固酮的反应[29]。一些SNP位点在心血管疾病中发挥着重要作用。*Kng1* rs1648711与静脉血栓有关[23]。*Kng1* rs2304456与中国男性厄贝沙坦血药浓度有关, 其机制可能是rs2304456变异(T>G)导致KNG1蛋白表达下降, 从而使缓激肽下调, 进而影响肾素血管紧张素系统[22]。此前的研究已证明该位点可能会增加中国人群原发性高血压的发病风险[30]。近几年发现, *Kng1*变异还可能造成血管性遗传性水肿, *Kng1*第396位蛋氨酸被赖氨酸取代可能是造成遗传性血管性水肿的原因[31]。

3.2 KNG1与神经系统疾病

KNG1在缺血性卒中的作用值得我们特别关注。在*Kng*敲除鼠卒中模型中小鼠的脑梗死面积较小, 神经功能缺损也较轻, 并且不会增加小鼠脑梗死相关的出血反应。缺乏*Kng*的小鼠表现出较轻的血脑屏障损伤和水肿形成, 并且局部炎症反应减少, *Kng*的缺失可以防止中风期间病理性血栓形成, 但不会增加脑出血的风险[32]。因此, 在缺血性卒中中, 阻断*Kng*可能是一种有效的治疗方案。隐源性卒中是指即使经过广泛检查也没有明确原因的卒中, 大约有25%卒中人群病因仍不明确[33]。在印度人群中, *Kng1* rs710446是年轻人的隐源性卒中的重要危险因素(P=0.003 6)[24]。*Kng1*基因的rs710446还与缺血性卒中易感性相关(OR为1.247; 95%可信区间CI为1.050-1.481), 其机制可能与*ALOX5AP*、*THBD*和*KNG1*的相互作用有关[25]。内毒素血症可导致血栓栓塞和卒中的发生, 而*Kng1* rs503002在内毒素血症造成的血栓栓塞和卒中中发挥着重要作用[26]。除了卒中外, KNG1也可能参与其他神经系统疾病的发生发展。MARKAKI等[34]研究发现脑脊液中的KNG1水平可作为帕金森认知障碍的标志物。WEN等[35]发现先兆子痫女性血清中KNG1的下调, 可能与先兆子痫在急性炎症和防御反应中的病理生理学有关。KNG1在不宁腿综合征患者中上调, 并且这种上调和年龄、吸烟习惯等无关, 提示不宁腿综合征患者KNG1的升高可能由疾病本身引起, 且不宁腿综合征患者有发生心血管疾病的风险[36]。但是该研究病例较少, 需要更大范围的研究。

3.3 KNG1与呼吸系统疾病

特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)是一种破坏性的慢性间质性肺疾病, 其不良后果会导致呼吸衰竭, 是临床医生在重症监护病房遇到的一种慢性纤维化间质性肺炎。IPF的死亡率接近40%[37]。KNG1在IPF中显著下调, 并且与其肺部疾病(肺炎、肺结节)存在差异[38], 因此KNG1有望成为特发性肺纤维化的标志物。在肺动脉高压大鼠模型中, KNG1蛋白和mRNA表达水平都有明显的上调[39]。有研究发现, KNG1可以作为耐多药结核病的标志物, 用KNG1建立的预测模型曲线下面积达0.87, 此外, miR-199B-5p和*Kng1*表达呈负相关, miR-199B-5p水平升高可能通过转录后调节抑制*Kng1*靶基因表达, 进而降低KNG1蛋白水平, 导致凝血和纤溶系统失衡[40]。KNG1也参与了新型冠状病毒的疾病进展过程。在新冠肺炎患者中KNG1和其他凝血相关蛋白表达水平增加, 表明新冠患者可能存在凝血障碍[41]。KNG1在新冠幸存者和非幸存者之间也具有差异, 幸存者具有更高的KNG1水平[42]。在LEE等[43]的研究中新型冠状病毒感染者入院时KNG1水平与疾病严重程度呈负相关。在FRANCESCO等[44]开发的算法中, 病毒蛋白ORF3a、NS7b与人类蛋白KNG1、ECE1的相互作用在病毒致病过程中发挥着重要作用。KNG1也可作为一部分药物的作用靶点。脓毒症是由感染引起的全身性炎症反应综合征, 严重的脓毒症会导致急性肺损伤[45-46]。颗粒物是空气污染物的关键组成部分, 当我们吸入颗粒物后, 大部

分颗粒物很容易通过黏液纤毛被清除, 但是当其直径小于或等于2.5 μm时, 则会被保留在肺组织中[47]。在WANG等[48]的研究中, PM2.5可以使血浆前激肽释放酶活化, HK裂解, 缓激肽释放从而使全身炎症性反应增加, 从而造成肺损伤。研究人员发现舒芬太尼可能通过调节KNG1介导的NF-κB和NRF2/HO-1信号通路来保护肺组织免受脓毒症所致的炎症和氧化应激损伤[49]。雷公藤可以通过EDNRB/Kng1信号通路抑制香烟烟雾诱导的细胞炎症减轻慢性阻塞性肺疾病[50]。

3.4 KNG1与肾脏疾病

在早期的研究中, KNG1在小鼠肾损伤模型中上调明显[51], 但是在急性肾损伤患者中, KNG1蛋白出现了明显的下降, KNG1和RBP4联合可能用于急性肾损伤患者的预后评估[52]。在局灶节段性肾小球硬化症的生物信息学分析中*Kng1*也显著下调, 并且可能作为局灶节段性肾小球硬化症的关键基因[53]。有临床研究表明, KNG1也可能作为人早期肾损伤的标志物, 其机制可能是在血管平滑肌细胞和内皮细胞中, KNG1可以使血管重塑、缓激肽释放和一氧化氮形成, 从而损伤肾脏[54-56]。

2型糖尿病(T2DM)是一种与微血管并发症相关的代谢紊乱性疾病。糖尿病肾病经常导致终末期肾病并具有高死亡风险。T2DM的肾病患病率总体上为30%~50%, 在65岁以上的患者中更高。糖尿病肾病的进展速度是很难预测的。微量白蛋白尿被认为是终末期肾病和死亡的风险因素。然而, 它并不是糖尿病肾病的准确预测指标。此外, 在没有微量白蛋白尿的情况下T2DM患者也会发生肾功能受损。因此, 需要更可靠的标记物来更好地检测T2DM患者的肾功能障碍。为了发现新的生物标志物或治疗靶点, 尿液蛋白质组学已发展成为一个有前途的平台, 可用于鉴定不同健康状况下的排泄蛋白质和肽。在一项尿液蛋白组学的研究中, KNG1有可能作为糖尿病肾病的标志物[57]。研究人员在对I型糖尿病的*Kng1*相关位点进行分析后发现血浆激肽释放酶活性与糖尿病病程有关, 随着糖尿病肾病的进展, 血浆激肽释放酶活性降低, 而*Kng1* rs5030062和rs710446可增加血浆前激肽释放酶和/或凝血因子XI水平, 并且rs5030062和rs710446还与血浆激肽释放酶活性和eGFR增加有关[58]。这进一步增强了KNG1与糖尿病肾病有关的证据。此外, 一项大规模在欧洲人群中进行的研究表明KNG-7965 CT的T等位基因会增加糖尿病肾病的风险[59]。生物信息学研究也显示, *Kng1*在糖尿病肾病中发挥重要作用[60-61]。

3.5 其他

在葡聚糖硫酸钠诱导的炎症性肠病小鼠模型中, 与野生型小鼠相比*Kng1*$^{-/-}$小鼠疾病严重程度较轻, TNF-α、IFN-γ、IL-1β和IL-6等细胞因子水平较低。同时, 髓过氧化物酶浓度降低, 中性粒细胞和炎症性单核细胞数量减少。这些都表明, KNG1通过影响细胞因子水平和免疫浸润参与了结肠炎的发生发展[62]。葡萄糖-6-磷酸异构酶(glucose-6-phosphate isomerase, GPI)可以作为一种自身抗原诱导T细胞和B细胞产生抗自身抗体, 而抗抗体是导致关节炎发生的重要原因。研究表明GPI-抗-GPI会增加激肽释放酶活性, 并促进血浆中HK的裂解, 从而导致IL-6和IL-β水平增加。并且在关节炎小鼠模型中, 相比于HK小鼠, HK缺乏的小鼠的关节肿胀更轻微, IL-6和IL-β释放更少[63]。因此, KNG1可能通过调控IL-1β和IL-6水平影响炎症性疾病的发展。

脂多糖(lipopolysaccharide, LPS)是革兰氏阴性菌外膜的主要成分。YANG等[64]和WU等[65]发现, LPS可以与HK的D5结构域中的DHGHKHKHGHGHGKH结合, 从而阻断HK与LPS结合, 减轻内毒素血症。因此, KNG1可能成为治疗内毒素血症新的靶点。在革兰氏阳性菌的感染中, KNG1也发挥着作用。实验表明, 在链球菌感染的小鼠模型中, 与野生型小鼠相比, *Kng1*$^{-/-}$小鼠脾脏中的细菌更少, 且IL-1β、TNF-β等细胞因子减少[66]。也有研究发现, KNG1可以和肺炎链球菌结合, 但是其作用与机制尚不明确[67]。

4 KNG1与肿瘤疾病

KNG1在不同的肿瘤类型或同一肿瘤的不同亚型中发挥不同的、有时相反的调节作用。KNG1通过调控细胞周期、增殖、侵袭和转移等具有组织和进展特异性的细胞行为, 既可作为肿瘤促进因子, 又可作为肿瘤抑制因子, 但其具体作用机制尚不清楚。KNG1的功能和在癌症中的异常调节如表2所示。

4.1 KNG1与胶质瘤

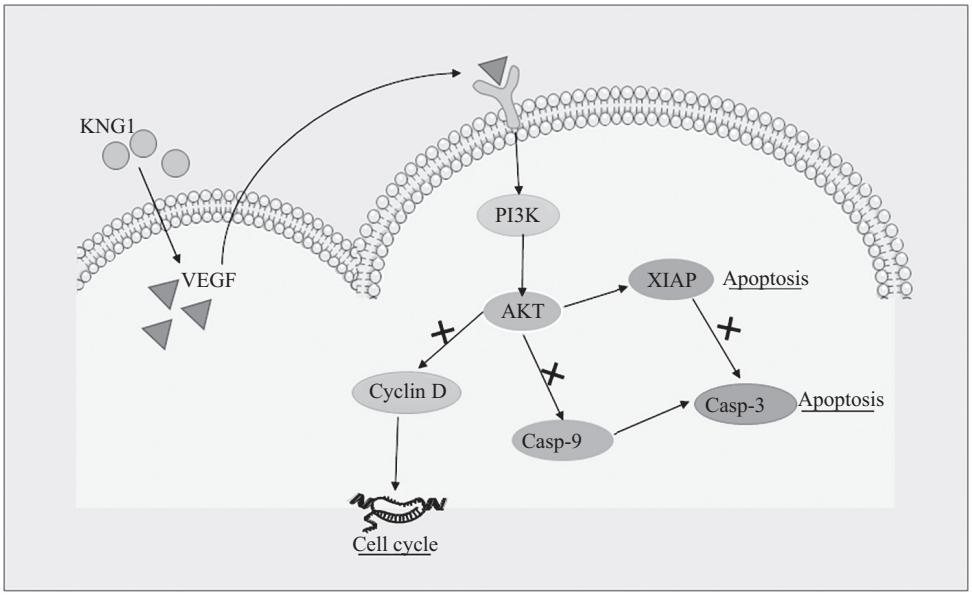
*Kng1*过表达抑制了胶质瘤细胞的活力和血管生成。研究人员利用癌症基因组图谱数据库发现*Kng1*在胶质瘤患者中低表达, 并且高表达*Kng1*的患者生存时间要长于低表达*Kng1*的患者。在细胞实

验中, *Kng1*在胶质瘤细胞中也低表达。过表达*Kng1*胶质瘤细胞以时间依赖性方式显著抑制胶质瘤细胞的活力。*Kng1*的过表达显著抑制了血管内皮生长因子(vascular endothelial growth factor, VEGF)的表达。Ki67用于评价细胞增殖的指标[68], 而X连锁凋亡抑制蛋白XIAP(X-linked inhibitor of apoptosis)可用于评价细胞凋亡[69]。KNG1的过表达还抑制了cyclinD1、ki67和XIAP的表达(图2), 增加了caspase-3和caspase-9的表达量, 表明KNG1的上调增加了胶质瘤细胞的凋亡。在小鼠实验中, *Kng1*的过表达抑制了裸鼠肿瘤的生长。在胶质瘤中, p-Akt的表达水平越高, 预后越差[70]。过表达*Kng1*会抑制p-PI3K的激活并抑制Akt的磷酸化[71]。促性腺激素释放激素激动剂已被证明对来自前列腺、乳腺、卵巢和子宫内膜的各种癌细胞株均具有直接的抗增殖作用[72]。在胶质瘤细胞LN229中, 定量蛋白质组学分析显示, 在促性腺激素释放激素激动剂处理后出现KNG1的过度表达(1.5倍)和EGFR的表达下调(2.2倍), 在进行细胞增殖实验后发现, KNG1可能通过调节EGFR通路参与调节胶质瘤的细胞增殖[73]。因此, 促性腺激素激动剂和KNG1可能对恶性胶质瘤发挥治疗作用。此外, 还有实验证明了在胶质瘤中存在*CTU1*、*KIAA1274*和*Rax ceRNAs*-miR-138-*Kng1-EGFR*的调控网络。CeRNA介导的KNG1下调会导致永生化人

表2 KNG1在不同肿瘤中的变化与作用

Table 2 Changes and roles of KNG1 in different cancers

肿瘤类型 Type of cancer	表达 Expression	作用 Roles	参考文献 References
Glioma	Decrease	Overexpressed *Kng1* inhibits proliferation of glioma cells	[71]
Renal cell cancer	Decrease/increase	Different roles in different types of renal cancer	[78,80-81]
Colorectal cancer	Increase	As an early detection biomarker	[82-83]
Hepatocellular carcinoma	Increase	To predict the prognosis of patients with liver cancer	[87-88]
Oral cancer	Increase	As a diagnostic and prognostic marker for oral cancer	[94,96]
Lung squamous cell carcinoma	Increase	Can be used as a biomarker for diagnosis	[103]
Breast cancer	Decrease	Discriminating breast cancer from healthy controls	[102]



KNG1: 激肽原-1; VEGF: 血管内皮生长因子; PI3K: 磷脂酰肌醇-3激酶; AKT: 蛋白激酶B; XIAP: X连锁凋亡抑制蛋白; Casp-3: 半胱氨酸天冬氨酸蛋白酶-3; Casp-9: 半胱氨酸天冬氨酸蛋白酶-9。

KNG1: kininogen-1; VEGF: vascular endothelial growth factor; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; XIAP: X-linked inhibitor of apoptosis protein; Casp-3: caspase-3; Casp-9: caspase-9.

图2 KNG1在胶质瘤中的作用

Fig.2 Role of KNG1 in glioma

内皮细胞和U87细胞中促血管生成EGFR信号的上调, 并刺激永生化人内皮细胞、斑马鱼和小鼠的血管生成[74]。

4.2 KNG1与肾癌

肾细胞癌占人类恶性肿瘤的2%~4%, 是最常见的泌尿系肿瘤之一。肾透明细胞癌是最常见的肾癌组织学类型, 占肾癌病例的75%。第二个最常见的肾癌亚型是乳头状肾细胞癌(papillary renal cell carcinoma, PRCC), 占肾癌的15%~20%[75-76]。KNG1在肾透明细胞癌中降低[77-79], 但是在PRCC中上调[80]。嫌色细胞癌是肾癌的特殊亚型, 生物信息学显示*kng1*在肾嫌色细胞癌中下调[81]。虽然KNG1在肾癌的不同类型中表现出不一致的调节作用, 但是没有更多的研究揭示其机制。

4.3 KNG1与结直肠癌

WANG等[82]首次发现了KNG1在结直肠癌中升高, 他们的预测模型表明KNG1对结直肠癌的诊断效能要优于癌胚抗原。有研究人员对结肠癌早期组织样本进行蛋白质组学检测后发现, KNG1在结肠癌早期就已经明显上升[83]。也有研究表明, KNG1参与了结直肠癌肝转移的转移过程[84], 但是作者并未对其详细机制进行描述。此外, KNG1可能是有结直肠癌家族史的结直肠腺瘤患者的生物标志物[85]。在小鼠的结肠癌模型中, 研究人员将CT26癌症疫苗注射于小鼠的结肠癌模型中, 随后他们发现CT26疫苗可以使KNG1表达升高, 并且升高的KNG1可以增加肿瘤浸润淋巴细胞的数量, 从而引发以Th-1为主的免疫反应进而抑制肿瘤生长[86]。

4.4 KNG1与肝癌

之前已经发现KNG1在甲胎蛋白阴性的肝细胞癌中上调[87], 由6个差异基因(*FTCD*、*MARCKSL1*、*CXCL3*、*RGS5*、*KNG1*和*S100A16*)构建的预后模型可以将肝癌患者分为两个不同的危险组(中位生存期2.46年*vs* 6.73年, $P<0.001$)[88]。法尼醇X受体(farnesoid X receptor, FXR)和维甲酸X受体(retinoid X receptor, RXR)是发挥作用的核受体, 在维持肝脏代谢的稳态中起关键作用[89]。肝细胞癌中FXR的下调与肿瘤的发生有关。KNG1已被证实可以被FXR和RXR激活[90-91]。乙型肝炎X蛋白(hepatitis B virus X, HBVX)是肝癌发生的关键因子。有研究发现FXR与KNG1表达呈正相关, 并且HBVX可以通过激活FXR调节KNG1的表达[92]。同样地, 在肝脏样本中发现了KNG1可以与乙肝病毒基因组整合[93], 这可能会导致肝癌的发生。

4.5 KNG1与口腔癌

研究人员在对口腔癌模型小鼠检测后发现在舌头早期病变期间KNG1的水平显著升高。随后在对口腔癌患者组织进行免疫组化和基因芯片分析中发现KNG1在肿瘤组织中显著升高。最后他们进行的预后分析表明, 高表达KNG1的患者生存期往往较短[94]。在口腔癌患者的唾液中也发现了KNG1的升高[95]。KNG1和MMP1是口腔癌中升高最为明显的两组蛋白, 且它们具有相关性, 并且由MMP1、KNG1、ANXA2和HSPA5四种指标联合构建的模型可以成功区分口腔癌患者和健康人群(灵敏度87.5%, 特异度80.5%)[96]。

4.6 KNG1与其他肿瘤

此前研究发现KNG1在胃癌中也出现了上调[97]。在较早的一项研究中, 研究人员发现, 在卵巢癌患尿液中KNG1蛋白显著降低[98]。糖基化是普遍存在于各类细胞中的一种常见的蛋白质翻译后修。根据糖氨基酸链接的方式, 可以把糖基化分为*N*-糖基化(天冬氨酸链接)和*O*-糖基化(丝氨酸/苏氨酸链接)。*O*-糖基化开始的第一步是*N*-乙酰基半乳糖转移酶将UDP-GalNAc上的*N*-乙酰半乳糖氨(GalNAc)以链接的方式连结到丝氨酸/苏氨酸(Ser/Thr)上。Tn抗原是一种附着在蛋白质Ser/Thr残基上的*N*-乙酰半乳糖胺(GalNAc)单糖[99]。有研究发现, 在胰腺癌Tn-糖基化的KNG1在癌症血清中升高, 其倍数变化为3.45, *P*值为0.02[100]。目前多数研究认为, Tn抗原表达会促进肿瘤细胞的恶性程度。NAPOLETANO等[101]报道胰腺癌细胞的Tn-MUC1抗原阳性表达会增加肿瘤恶性行为。但是目前, Tn-糖基化的KNG1在胰腺癌中的作用仍然未知。HER2富集型乳腺癌占所有乳腺癌的10%~15%, 且具有侵袭性强、生存时间短、预后差、复发和转移的风险增加等特点。在HER2富集型乳腺癌患者尿液中, GAJBHIEY等[102]通过2D电泳、无凝胶的同位素标记蛋白组学技术和免疫印记技术都证明了KNG1在HER2富集型乳腺癌中表达水平降低, 并且KNG1可以用于区分乳腺癌患者和健康人群。肺鳞状细胞癌患者血浆、肺泡灌洗液和尿液中的KNG1水平都显著高于健康人群。以肺泡灌洗液中的KNG1水平诊断肺鳞状细胞癌, 其曲线下面积为0.91, 因此KNG1可能在肺鳞状细胞癌的诊

断中发挥作用[103]。

5 总结与展望

KNG1在卒中、静脉血栓等凝血有关的疾病中已被广泛关注, 但是近年来研究人员也发现其参与了炎症性疾病和感染性疾病的发生发展, 例如在关节炎小鼠模型、结肠炎小鼠模型和链球菌的小鼠模型中, 敲低*Kng1*都会使细胞因子减少, 因此其可能成为凝血相关疾病与炎症性疾病之间的桥梁。在肿瘤相关疾病中, KNG1主要影响胶质瘤、肾癌、结直肠癌、口腔癌。然而, KNG1在癌症中的作用还没有被完全了解。KNG1在不同肿瘤中表达不同, 在大多数肿瘤中KNG1上调, 然而在胶质瘤中其表达下调, 并且KNG1在同一肿瘤类型中也呈现出不同的表达。KNG1在肾透明细胞癌中表达降低, 在肾乳头状细胞癌中表达上调。除此之外, KNG1还可能影响肿瘤微环境。在黑色素瘤小模型鼠中, *Kng1*$^{-/-}$小鼠的肿瘤生长更快, 并且包括MMP3、MMP9、VEGF、PlGF2、CD44和MCP1在内的几种肿瘤和间质相关蛋白的表达增加, 巨噬细胞显著减少[104], 在淋巴瘤小鼠中模型中, *Kng1*$^{-/-}$小鼠的肿瘤体积大约是野生型小鼠的2倍, 且血管密度更大[105]。因此, KNG1还可能调节更多肿瘤行为, 但目前机制尚不清楚, 更好地阐明KNG1的调节机制以及它如何通过调节基因转录抑制或维持癌症, 可能使其成为未来抗肿瘤干预的一个有吸引力的靶点。

此外, 一些SNP位点也极为重要。*Kng1* rs710446因其与凝血因子XI密切相关未来可能成为卒中和静脉血栓形成的预测因子。因此, 未来的研究应该探索KNG1中的SNP是否可以作为常见疾病发生和进展的潜在预测因子。更为重要的是, KNG1可能成为新冠肺炎患者预后的标志物, 并且与新冠肺炎患者凝血和肺水肿有关, 但是其详细机制仍不明确。因此, KNG1在新冠肺炎中的作用亟待探索。

综上所述, KNG1在多种非肿瘤疾病和肿瘤的诊断和治疗方面都有广阔的临床应用前景。然而, 在大多数疾病中, KNG1的升高或是下降的病理机制仍有待阐明。虽然目前KNG1相关的基础研究较少, 但是随着蛋白组学技术的发展, 近几年国内外对该蛋白的研究趋势明显上升, 其已经在肿瘤防治领域取得了一些令人鼓舞的进展。KNG1不仅可以作为肿瘤早期诊断和预测预后的标志物, 而且还可以通过阻断相关通路, 对肿瘤起到抑制作用。最后, 现阶段的研究大多集中于蛋白组学和临床发现阶段, 未来还需要更多的前瞻性研究来验证。相信在我们的努力下KNG1在未来会有更为广阔的应用前景。

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