NRP1在结直肠癌中的作用及干预策略研究进展

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摘要: 结直肠癌作为全球最常见的恶性肿瘤之一, 其发病率与病死率均居所有恶性肿瘤的前3位, 近年来结直肠癌患者呈现年轻化趋势。目前, 早期结直肠癌以手术为主要治疗手段, 但是术后复发转移率高达50%, 其他疗法如化疗和放疗具有严重的不良反应, 因此, 临床尚缺乏结直肠癌安全有效的治疗手段, 寻找结直肠癌的新疗法至关重要。神经纤毛蛋白-1 (neuropilin 1, NRP1) 作为跨膜糖蛋白, 在结直肠癌中高表达, 且其过度表达与结直肠癌的发生发展密切相关; NRP1参与血管生成、肿瘤生长、细胞自噬、脂代谢等, 有望成为治疗结直肠癌的潜在新靶点。本文综述了NRP1在结直肠癌中的作用, 包括其分子结构、表达、自噬及其与小分子代谢之间的关联; 阐述了NRP1在结直肠癌中发挥作用的相关调节因子, 包括血管内皮生长因子 (vascular endothelial growth factor, VEGF)、神经轴突导向因子3A (semaphorin 3A, SEMA3A)、转化生长因子β (transforming growth factor-β, TGF-β) 等; 总结了靶向NRP1的结直肠癌潜在干预策略, 以期为结直肠癌诊断和防治提供借鉴。

关键词: 结直肠癌; 神经纤毛蛋白-1; 肿瘤靶向; 抑制剂; 干预策略

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Research progress on the role and intervention strategies of NRP1 in colorectal cancer

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Abstract: Colorectal cancer (CRC) is one of the most common malignant tumors in the world, and its incidence and mortality are among the top three of all malignant tumors. In recent years, CRC is becoming more common in younger patients. Currently, surgery is the main or first treatment of early stage CRC, however, up to 50% patients have recurrence and metastasis post-surgery. While chemotherapy and radiotherapy are often used as adjuvant treatment after surgery or as main treatment options for late stage CRC, they usually induce severe adverse effects. Safe and effective treatments for CRC are still lacking. Therefore, it is essential to discover new therapies for CRC. Neuropilin 1 (NRP1), as a transmembrane glycoprotein, is reported to highly express in CRC, and its overexpression is demonstrated to be closely related to the occurrence and development of CRC. NRP1 is involved in angiogenesis, tumor growth, autophagy, and lipid metabolism, which is expected to be a potential new target for the treatment of CRC. This paper reviews the role of NRP1 in CRC, including its molecular structure, expression in CRC, as well as its connection with autophagy and metabolism. The regulatory factors of NRP1 in CRC were introduced, including vascular endothelial growth factor (VEGF), semaphorin 3A (SEMA3A), transforming growth factor-β (TGF-β), etc. The potential intervention strategies of CRC targeting NRP1 were summarized in order to provide reference for the diagnosis and prevention of CRC.

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Key words: colorectal cancer; neuropilin 1; cancer targeting; inhibitor; intervention strategy

随着现代社会发展和经济水平提高, 人们饮食结构发生了巨大改变, 消化系统恶性肿瘤发生率逐年升高。据2020年全球癌症数据统计, 全年新增癌症病例1 930万, 其中结直肠癌占10%; 全年约1 000万癌症死亡病例, 结直肠癌占9.4%[1]。结直肠癌常见于中老年人群, 且早期无特异性表现, 因此患者确诊时病情恶化较快[2], 病死率高。流行病学研究显示, 近年来结直肠癌患者呈现年轻化趋势[3]。目前结直肠癌以手术为主要治疗手段[4], 然而50%的患者在术后2年内出现复发和转移, 5年生存率仅为19%[5]。放疗与化疗作为手术的辅助疗法可降低局部复发率, 但放疗所使用的电离辐射对患者身体会造成损伤; 化疗药物不良反应明显, 如伊立替康会引起腹泻[6]、奥沙利铂会导致神经性病变[7]。靶向治疗作为新疗法逐渐成为研究热点, 研究揭示西妥昔单抗[8]和帕尼单抗[9]可靶向表皮生长因子受体 (epidermal growth factor receptor, EGFR), 针对鼠类肉瘤病毒癌基因 (Kirsten rat sarcoma viral oncogene, *KRAS*) 基因野生型的转移性结直肠癌十分有效, 但对*KRAS*基因突变型结直肠癌无效果[10]; 贝伐单抗作为靶向血管内皮生长因子 (vascular endothelial growth factor, VEGF) 的药物[11], 通过阻断VEGF的生物活性而达到抗肿瘤效果, 但贝伐单抗的不良反应明显, 会阻碍血管生成。因此, 寻找新的疾病生物标志物和潜在干预靶点对结直肠癌早期诊断和预后改善极为重要。细胞膜受体神经纤毛蛋白-1 (neuropilin 1, NRP1) 是VEGF的新型受体, 在结直肠癌患者组织中高表达且与疾病的发生发展密切相关[12]。本文就NRP1与结直肠癌关系的研究进展作论述, 系统总结了NRP1的结构、表达、生物学功能, 阐释了结直肠癌中NRP1相关调节因子的作用机制, 分析了通过靶向干预NRP1治疗结直肠癌的潜在方案与策略。

1 NRP1的结构和功能

NRP1为I型跨膜糖蛋白, 其结构分区特殊, 且不同分区通过结合相应的调节因子发挥不同的功能, 在促进肿瘤发展、影响神经发育、促进血管生成、影响免疫调节等方面发挥关键作用。最初研究人员发现NRP1在神经元中表达, 推断其是控制神经元引导和轴突生长的神经轴突导向因子3A (semaphorin 3A, SEMA3A) 的受体[13], 可影响神经发育系统的功能; 此外, NRP1作为血管生成的重要调节因子, 在维持心血管稳态的同时亦可在血管重塑和动脉生成方面发挥重要作用[14]。后期研究发现NRP1在多种肿瘤中高表达, 可通过调节信号传导和肿瘤微环境等方式促进肿瘤的发展。如NRP1与VEGF结合后通过调节肿瘤血管发育、给肿瘤提供养分而促进结直肠癌发展[15]。此外, NRP1在树突状细胞及T细胞等免疫细胞中均有表达[16], 推测NRP1在固有免疫系统方面可能发挥相应作用。

1.1 NRP1分子结构 NRP1由胞外区、跨膜区、胞质区3个部分组成[17]。胞外区可结合SEMA3A和VEGF165, 跨膜区可与神经丛蛋白 (plexin) 家族成员、血管内皮生长因子受体1 (vascular endothelial growth factor receptor 1, VEGFR1) 或VEGFR2形成寡聚受体复合物, 胞质区将细胞表面受体与内部信号网络相结合。此外, 胞外区亦可细分为5个结构域, 包括a1/a2、b1/b2和c结构域[18], 且不同结构域功能不同, SEMA3A可结合a1/a2、b1结构域, VEGF165可结合b1/b2结构域, c结构域可介导SEMA3A下游信号。总之, NRP1的不同结构域通过与多种配体结合后进行信号传递[19]。NRP1缺失c结构域、跨膜区和胞质区后将成为异构体可溶性NRP1 (soluble neuropilin-1, sNRP1), 据研究, sNRP1和NRP1有着相反的功能[20]。

1.2 NRP1的表达 NRP1在不同组织中均有表达, 但表达水平各异 (图1)。NRP1作为促癌蛋白在肝癌、胰腺癌、结直肠癌、食管癌及胆囊癌等多种肿瘤组织与细胞中高表达。研究表明, NRP1在结直肠癌细胞和组织中的表达均高于正常细胞和组织, 提示NRP1可能作为结直肠癌诊断潜在生物标志物[12]。此外, 结直肠癌患者的生存分析结果显示, NRP1阳性表达组患者与阴性表达组相比, 其生存周期明显缩短, 且肿瘤分期发展程度与NRP1表达呈相关性, 进一步证明NRP1与结直肠癌的发生发展密切相关[21]。相关研究表明, NRP1在炎症部位中有表达且具有维持免疫稳态的作用[22], 而结肠炎作为结直肠癌发生的风险因素与并发疾病[23], 推测靶向NRP1可缓解结肠炎向结直肠癌发展的不良事件。

1.3 NRP1与代谢 NRP1在结直肠癌中被异常激活, 研究证实, 降低NRP1的表达可显著抑制结直肠癌细胞的增殖[24]。本课题组前期从代谢调控角度探究NRP1与小分子代谢物之间的关联, 研究了NRP1敲低后脂质代谢的变化[25], 发现短链酰基肉碱 (乙酰肉碱和丙酰肉碱) 呈上调趋势。在脂肪酸氧化过程中, 短链酰基肉碱负责将线粒体中积累的短链和中链脂肪酸运输出去。NRP1敲低后细胞中短链酰基肉碱含量增加,

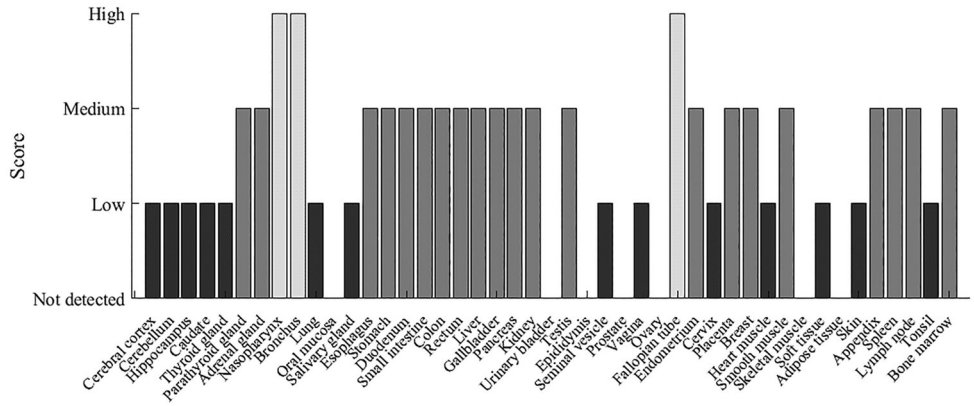

Figure 1 Neuropilin 1 (NRP1) expression in different tissues (data source: https://www.proteinatlas.org/)

在一定程度上反映了线粒体中短链和中链脂肪酸积累, 从而发挥抑制细胞增殖的作用, 其具体机制有待深入研究。

NRP1作为VEGFR1的辅助受体, 二者与VEGF-B结合后可增加跨内皮脂质转运及外周脂质摄取和储存[26]。其次, NRP1参与调节游离脂肪酸的β-氧化过程, 脂肪组织中的巨噬细胞缺乏NRP1时, 脂质代谢效率降低而转变为葡萄糖分解代谢, 该过程导致巨噬细胞新陈代谢受损[27]。

此外, NRP1可能与糖代谢紊乱疾病有关联。相关研究表明, NRP1可通过抑制核苷酸结合寡聚化结构域样受体家族3 (domain-like receptor family pyrin domain-containing 3, NLRP3)炎症小体抑制高脂膳食引起的胰岛素耐受, 此结果说明NRP1有望成为治疗糖尿病的关键靶点[28]。而糖尿病作为结直肠癌的风险因素, 会促进结直肠癌的发生与恶化[29,30]。

1.4 NRP1与自噬 在结直肠癌疾病中, 自噬是促进正常细胞向恶性细胞转化的重要开关[31]。自噬在结直肠癌发展过程中具有两面性, 早期自噬可阻止结直肠癌发展, 后期自噬的增强往往促进结直肠癌细胞的生长与存活[32]。研究表明, 自噬可增加结直肠癌中NRP1的表达, NRP1亦可促进结直肠癌细胞自噬, 敲低NRP1可增加醛酮还原酶家族1成员B10 (Aldo-keto reductase family 1 member B10, AKR1B10)的表达, AKR1B10与甘油醛-3-磷酸脱氢酶 (glyceraldehyde-3-phosphate dehydrogenase, GAPDH)相互作用可减少GAPDH的合成, 通过抑制GAPDH核转运而阻碍葡萄糖饥饿诱导的自噬通量, 进而下调自噬, 即NRP1可通过下调AKR1B10的表达来促进自噬[33]。

2 结直肠癌中NRP1相关调节因子或通路

在结直肠癌的发生发展中, NRP1作为多功能受体, 既通过与VEGF、SEMA3A、转化生长因子β (transforming growth factor-β, TGF-β)等调节因子结合而发挥相应作用, 亦可通过Wnt (Wingless-related integration site)/β-连环蛋白 (β-catenin)通路发挥调控作用 (图2)。

2.1 VEGF NRP1作为细胞膜受体, 可与多种配体结合后发挥生理调节作用。VEGF是最常见的配体之一, 其结合结构域是神经发育和血管成熟所必需的多结构域受体。VEGF结合酪氨酸激酶 (VEGFR-1和VEGFR-2)后可发挥调节血管的作用[34], VEGF有5种亚型, 分别是VEGF121、VEGF145、VEGF165、VEGF189和VEGF206, 各亚型具有不同功能, 其中VEGF165是一个重要的亚型。NRP1作为VEGF165的共受体, 在NRP1与VEGFR-2形成复合物后, 可进一步增强VEGFR-2的活性, 从而促进VEGF165与VEGFR-2的结合。此外, NRP1亦在免疫细胞和内皮细胞中表达, 且被不同亚型的VEGF-A激活后会加剧结直肠癌疾病的发展[35]。由此说明, NRP1/VEGF通路对结直肠癌的发生发展和侵袭转移具有重要意义。

2.2 SEMA3A 临床数据表明, 与正常组织相比, SEMA3A在胃肠道癌症、乳腺癌和非小细胞肺癌等中表达下调[36]。有研究表明, 激活SEMA3A可抑制肿瘤血管生成进而抑制肿瘤生长[37]。SEMA3A与NRP1结合后, 可激活plexinA1-4信号复合物, 而该信号复合物可传递SEMA3A介导的下游信号, 进而调节细胞存活、增殖和迁移[38]。研究揭示, 位于肿瘤细胞中的SEMA3A可与肿瘤相关巨噬细胞上的NRP1相结合而发挥作用, 该结合在抑制M2型巨噬细胞增殖 (促肿瘤发展)的同时, 也可促进M1型巨噬细胞 (抗肿瘤发展)增殖; 此外, 沉默NRP1后, 巨噬细胞中的SEMA3A无法磷酸化丝裂原活化蛋白激酶 (mitogen-activated protein kinases, MAPK)和蛋白激酶B (protein kinase B, AKT), 而这两个通路都与结直肠癌的发生发展密切相关, 推测NRP1表达水平介导了SEMA3A功能的发挥[39]。

2.3 TGF-β TGF-β1在肿瘤中发挥双重作用: 当肿瘤

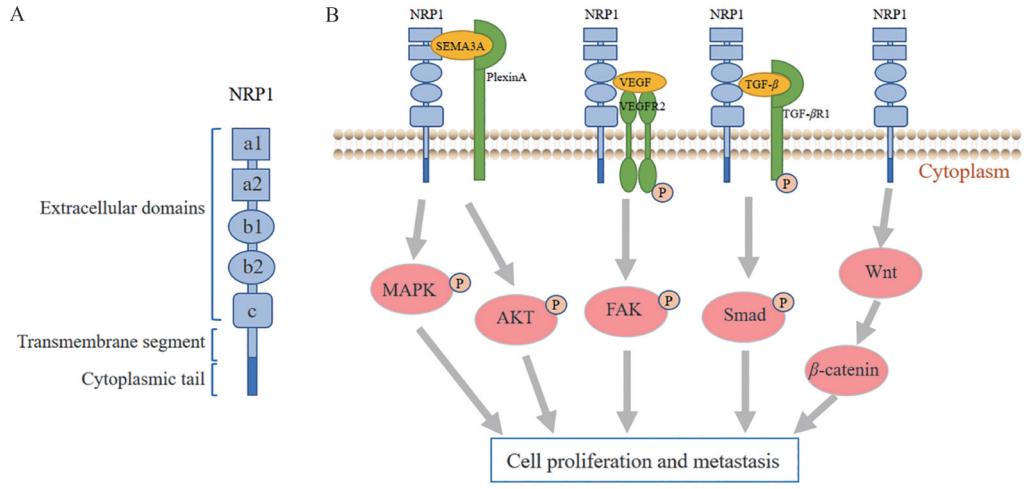

Figure 2 NRP1 structure (A) and NRP1 related regulatory factors or pathways (B). SEMA3A: Semaphorin 3A; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; MAPK: Mitogen-activated protein kinases; AKT: Protein kinase B; FAK: Focal adhesion kinase; Wnt: Wingless-related integration site

处于初期时, TGF-β1 将其阻滞于 G_1 期或延长其 G_0/S 期, 从而抑制细胞生长或防止细胞恶化; 但当肿瘤细胞处于晚期时, TGF-β1 功能丧失而无法对肿瘤细胞产生抑制作用, 甚至被异常激活转而增强肿瘤细胞侵袭转移能力[40]。研究显示, 结直肠癌细胞中 TGF-β1 功能丧失的现象较为常见[41]。NRP1 作为 TGF-β1 受体 (TGF-β1R) 的共受体, 在与 TGF-β1R 形成复合物后, 可进一步增强 TGF-β1/Smad 信号传导, 此外, NRP1 亦可激活 TGF-β1 的前体潜在形式 (LAP-TGF-β1), 通过信号传导参与肿瘤的发生发展, *NRP1* 基因表达被抑制后可降低 TGF-β1 表达从而降低癌细胞活力, 促进细胞凋亡[42]。

2.4 Wnt/β-catenin Wnt/β-catenin 通路已被证明参与结直肠癌发展进程, 该通路的激活可诱导细胞运动和细胞侵袭[43], 且对结直肠癌细胞增殖、分化和凋亡等过程具有重要影响[44]。研究表明, Wnt 信号通路的一个或多个成员在 90% 以上的结直肠癌患者体内存在突变, 主要表现为基因 *CTNNB1* (catenin beta-1) 激活突变及结肠腺瘤样息肉蛋白 (adenomatous polyposis coli, *APC*) 基因失活, 亦有可能存在基因 *SOX9* (SRY-box transcription factor 9)、*TCF7L2* (transcription factor 7 like 2)、*AXIN2* (axin 2) 和 *FBXW7* (F-box and WD repeat domain containing 7) 突变[45]。Wnt/β-catenin 信号通路的关键级联可诱导肿瘤干细胞中 NRP1 的表达, 同时该通路亦可被自分泌 VEGF/NRP1 信号通路影响, 即 VEGF-A/NRP-1 轴可激活 Wnt/β-catenin 通路, 从而促进癌细胞生长和化疗耐药[46]。此外, 相关动物实验表明, 敲低 NRP1 可影响 Wnt/β-catenin 通路进而抑制小鼠肿瘤的生长[47]。

3 NRP1 抑制剂与结直肠癌治疗

NRP1 在结直肠癌患者组织和血液中高表达, 可促进结直肠癌的发生发展。研究发现, 抑制 NRP1 表达可抑制肿瘤生长, 且 T 细胞中 NRP1 缺失后可显著增强其对肿瘤再攻击的免疫力[48], 由此猜测抑制 NRP1 亦可防止结直肠癌逃避机体免疫系统的攻击。因此, NRP1 抑制剂的筛选与功能验证引起了广泛关注。目前已有 1 个单克隆抗体类 NRP1 抑制剂进入临床 I 期试验, 2 个小分子类 NRP1 抑制剂正在进行临床前研究 (表 1)。天然小分子单体人参皂苷 Rg3 及 microRNA 等也表现出了较好的 NRP1 抑制活性。此外, 对小干扰 RNA[49]、sNRP1[20]、NRP1 抑制肽[50] 的研究也正在进行中。

3.1 MNRP1685A MNRP1685A 作为一种针对 NRP1 的单克隆抗体, 已在临床试验中表现出良好效果, 且作为单一药物给药时耐受性良好, 但

Table 1 Research progress on NRP1 inhibitors. Information on clinical trials is available at https://www.clinicaltrials.gov/

Inhibitor	Type	Mechanism	Therapeutic action	Research stage
MNRP1685A	The human monoclonal antibody	MNRP1685A blocks binding of VEGF to the b1b2 domain of NRP1 on vascular endothelial cells	Reducing tumor-related angiogenesis and vascular remodeling	A phase I study
EG00229	Small molecule ligand	EG00229 blocks binding of VEGF-A to the b1 domain of NRP1	Targeting angiogenesis, tumor growth and metastasis	A preclinical study
EG01377	Small molecule ligand	EG01377 inhibits the formation of NRP1-VEGF complex by binding to NRP1	Anti-angiogenesis, anti-migration and anti-tumor	A preclinical study

MNRP1685A可能存在诱导急性炎症的风险, 将地塞米松作为术前用药可抑制急性炎症, 猜测机制为地塞米松诱导白介素10 (interleukin 10, IL-10) 升高后可介导免疫耐受, 从而抑制肿瘤逃避免疫攻击[51]。MNRP1685A靶向NRP1的VEGF结合结构域, 通过阻断VEGF与NRP1b1/b2结构域的结合以减少肿瘤相关的血管生成和血管重塑。同时, MNRP1685A亦可与血小板结合, 减少血栓形成风险。MNRP1685A与贝伐单抗 (抗VEGF单克隆抗体) 联用时, 可显著提高贝伐单抗抑制肿瘤生长的作用[52]。猜测相关机制为贝伐单抗结合VEGF的同时, MNRP1685A与NRP1结合, 两者共同作用从而达到进一步抑制肿瘤增殖的效果。

3.2 EG00229 科研人员在2009年报道了NRP1的第1个小分子配体EG00229[53], 该小分子旨在与NRP1的VEGF-A165结合口袋相互作用, 抑制NRP1表达从而拥有靶向血管生成、肿瘤生长和转移的能力, 进一步减缓肿瘤发展; EG00229亦可通过SMAD3 (small mothers against decapentaplegic 3)/AKT阻断典型TGF-β信号, 逆转免疫调节肽引起的免疫表型。虽然小分子抑制剂EG00229的抑制效果仍需进一步加强, 但其作为一个较好的工具药, 为今后开发更有效的抗NRP1药物提供新起点, 为新型抗结直肠癌药物的研发提供宝贵经验。

3.3 EG01377 近年来, 科研学者在上述化合物EG00229基础上设计了一组新型的NRP1抑制剂, 该抑制剂主要靶向于精氨酸结合袋附近的特定残基, 并在该组抑制剂中发现了EG01377[54]。EG01377与NRP1可稳定结合且具有较好的生物活性和体内稳定性, 其抑制NRP1−VEGF复合物形成的同时, 亦能较明显地抑制VEGF驱动的血管生成、细胞迁移、肿瘤侵袭性; 体外实验结果显示, EG01377具有抗血管生成、抗迁移和抗肿瘤作用。不仅如此, EG01377还可通过减少调节性T细胞中TGF-β的产生, 从而导致抗肿瘤免疫反应的增强。综上所述, EG01377通过阻断NRP1从而调节VEGF介导的信号转导, 并进一步影响结直肠癌细胞的运动和侵袭。

3.4 人参皂苷Rg3 人参皂苷Rg3作为中药人参的有效抗肿瘤活性成分之一, 现有研究表明其可抑制内膜异位症中*NRP1*基因表达, 从而抑制内膜异位症的发展[55]。此外, 人参皂苷Rg3亦可阻断NRP1与纤维连接蛋白1 (fibronectin 1, FN1) 的相互作用[56], 进而抑制胃癌发展。因此, 推测人参皂苷Rg3可通过抑制NRP1发挥抗结直肠癌作用, 具体作用机制有待深入研究。

3.5 MicroRNAs MicroRNAs作为一类内源性小分子RNA, 由内源性发卡结构转录产物衍生而来, 其通过碱基配对方式与靶mRNA结合, 进而抑制靶mRNA的翻译或剪切, 即microRNAs可在转录后水平负调控靶基因的表达。相关证据表明microRNAs可用于结直肠癌疾病的诊断与防治[57]。亦有研究表明microRNA-9[58]和microRNA-338[59]对*NRP1*的基因水平可发挥负调控作用, 推测microRNA-9和microRNA-338均可通过抑制NRP1发挥抗结直肠癌效果。

4 结语与展望

NRP1作为结直肠癌的潜在干预新靶点, 在血管生成、细胞迁移、肿瘤侵袭等多种生理病理学过程中发挥关键调节作用, 具有广阔的研究前景。但是, 为何NRP1会在结直肠癌中高表达, 是否存在其他调节因子与NRP1共同作用、促进结直肠癌的发生发展, 如何设计安全有效的NRP1抑制剂对结直肠癌进行干预? 这些问题都亟待解释。最新研究揭示, NRP1在呼吸道、血管和神经元等组织中高表达, 与新冠病毒 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) 结合可增强病毒对宿主细胞的感染力[60-62], 使得NRP1成为治疗新型冠状病毒肺炎 (coronavirus disease 2019, COVID-19) 的新途径, 这吸引了大量研究人员将研究工作聚焦到NRP1上。随着对NRP1的深入研究, 其生物学功能会逐步被揭示, 更多靶向NRP1的抑制剂会被开发出来, 这对于NRP1介导的结直肠癌治疗具有重要推动意义。

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References

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA Cancer J Clin, 2021, 71: 209-249.

[2] Leijssen LGJ, Dinaux AM, Amri R, et al. The impact of a multivisceral resection and adjuvant therapy in locally advanced colon cancer [J]. J Gastrointest Surg, 2019, 23: 357-366.

[3] Lipsyc-Sharf M, Zhang S, Ou FS, et al. Survival in young-onset metastatic colorectal cancer: findings from Cancer and Leukemia Group B (Alliance)/SWOG 80405 [J]. J Natl Cancer Inst, 2022, 114: 427-435.

[4] Brouwer NPM, Bos ACRK, Lemmens VEP, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients [J]. Int J Cancer, 2018, 143: 2758-2766.

[5] Centelles JJ. General aspects of colorectal cancer [J]. ISRN Oncol, 2012, 2012: 139268.

[6] Okunaka M, Kano D, Matsui R, et al. Evaluation of the expression profile of irinotecan-induced diarrhea in patients with colorectal cancer [J]. Pharmaceuticals, 2021, 14: 377.

[7] Fujita S, Hirota T, Sakiyama R, et al. Identification of drug transporters contributing to oxaliplatin-induced peripheral neuropathy [J]. J Neurochem, 2019, 148: 373-385.

[8] Bridgewater JA, Pugh SA, Maishman T, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial [J]. Lancet Oncol, 2020, 21: 398-411.

[9] Kast J, Dutta S, Upreti VV. Panitumumab: a review of clinical pharmacokinetic and pharmacology properties after over a decade of experience in patients with solid tumors [J]. Adv Ther, 2021, 38: 3712-3723.

[10] Wrafter PF, Connelly TM, Khan J, et al. The 100 most influential manuscripts in colorectal cancer: a bibliometric analysis [J]. Surgeon, 2016, 14: 327-336.

[11] Ottaiano A, Scala S, Santorsola M, et al. Aflibercept or bevacizumab in combination with FOLFIRI as second-line treatment of mRAS metastatic colorectal cancer patients: the ARBITRATION study protocol [J]. Ther Adv Med Oncol, 2021, 13: 1758835921989223.

[12] Niland S, Eble JA. Neuropilins in the context of tumor vasculature [J]. Int J Mol Sci, 2019, 20: 639.

[13] Kolodkin AL, Levengood DV, Rowe EG, et al. Neuropilin is a semaphorin III receptor [J]. Cell, 1997, 90: 753-762.

[14] Plein A, Fantin A, Ruhrberg C. Neuropilin regulation of angiogenesis, arteriogenesis, and vascular permeability [J]. Microcirculation, 2014, 21: 315-323.

[15] Wang H, Li F, Liu HF, et al. Expression of neuropilin-1 and VEGF and its relationship with prognosis in colon cancer [J]. Chin J Cancer Prev Treat (中华肿瘤防治杂志), 2020, 27, 445-450.

[16] Kang JY, Gil M, Kim KE. Neuropilin1 expression acts as a prognostic marker in stomach adenocarcinoma by predicting the infiltration of Treg cells and M2 macrophages [J]. J Clin Med, 2020, 9: 1430.

[17] Chuckran CA, Liu C, Bruno TC, et al. Neuropilin-1: a checkpoint target with unique implications for cancer immunology and immunotherapy [J]. J Immunother Cancer, 2020, 8: e000967.

[18] Lampropoulou A, Ruhrberg C. Neuropilin regulation of angiogenesis [J]. Biochem Soc Trans, 2014, 42: 1623-1628.

[19] Plein A, Calmont A, Fantin A, et al. Neural crest-derived SEMA3C activates endothelial NRP1 for cardiac outflow tract septation [J]. J Clin Investig, 2015, 125: 2661-2676.

[20] Panigrahy D, Adini I, Mamluk R, et al. Regulation of soluble neuropilin 1, an endogenous angiogenesis inhibitor, in liver development and regeneration [J]. Pathology, 2014, 46: 416-423.

[21] Wang H, Xie RJ, Liu LF, et al. The expression of neuropilin-1 and relationship with prognosis in colon cancer [J]. Mod Med J Chin (中国现代医药杂志), 2018, 20: 1-3.

[22] Delgoffe GM, Woo SR, Turnis ME, et al. Stability and function of regulatory T cells is maintained by a neuropilin-1-semaphorin-4a axis [J]. Nature, 2013, 501: 252-256.

[23] Liu YT, Sun Y. Advances in mechanisms for inflammation-associated colon carcinogenesis and chemoprevention [J] Acta Pharm Sin (药学学报), 2022, 57: 1273-1281.

[24] Qi YT. The Effect of Neuropilin-1 on Biological Behavior of Colon Cancer Cell Line HT-29 (Neuropilin-1 对结肠癌细胞系 HT-29 生物学行为的影响) [D]. Tangshan: North China University of Science and Technology, 2016.

[25] Lv Y, Hou X, Zhang Q, et al. Untargeted metabolomics study of the *in vitro* anti-hepatoma effect of saikosaponin d in combination with NRP-1 knockdown [J]. Molecules, 2019, 24: 1423.

[26] Dabravolski SA, Khotina VA, Omelchenko AV, et al. The role of the VEGF family in atherosclerosis development and its potential as treatment targets [J]. Int J Mol Sci, 2022, 23: 931.

[27] Wilson AM, Shao Z, Grenier V, et al. Neuropilin-1 expression in adipose tissue macrophages protects against obesity and metabolic syndrome [J]. Sci Immunol, 2018, 3: eaan4626.

[28] Dai X, Okon I, Liu Z, et al. Ablation of neuropilin 1 in myeloid cells exacerbates high-fat diet-induced insulin resistance through NLRP3 inflammasome *in vivo* [J]. Diabetes, 2017, 66: 2424-2435.

[29] Del Puerto - Nevado L, Minguez P, Corton M, et al. Molecular evidence of field cancerization initiated by diabetes in colon cancer patients [J]. Mol Oncol, 2019, 13: 857-872.

[30] Petrelli F, Ghidini M, Rausa E, et al. Survival of colorectal cancer patients with diabetes mellitus: a meta-analysis [J]. Can J Diabetes, 2021, 45: 186-197.

[31] Burada F, Nicoli ER, Ciurea ME, et al. Autophagy in colorectal cancer: an important switch from physiology to pathology [J]. World J Gastrointest Oncol, 2015, 7: 271.

[32] Amaravadi R, Kimmelman AC, White E. Recent insights into the function of autophagy in cancer [J]. Genes Dev, 2016, 30: 1913-1930.

[33] Li W, Liu C, Huang Z, et al. AKR1B10 negatively regulates autophagy through reducing GAPDH upon glucose starvation in colon cancer [J]. J Cell Sci, 2021, 134: jcs255273.

[34] Braile M, Marcella S, Cristinziano L, et al. VEGF-A in cardiomyocytes and heart diseases [J]. Int J Mol Sci, 2020, 21: 5294.

[35] Al-Shareef H, Hiraoka SI, Tanaka N, et al. Use of NRP1, a novel biomarker, along with VEGF-C, VEGFR-3, CCR7 and SEMA3E, to predict lymph node metastasis in squamous cell carcinoma of the tongue [J]. Oncol Rep, 2016, 36: 2444-2454.

[36] Toledano S, Nir-Zvi I, Engelman R, et al. Class-3 semaphorins and their receptors: potent multifunctional modulators of tumor progression [J]. Int J Mol Sci, 2019, 20: 556.

[37] Neufeld G, Mumblat Y, Smolkin T, et al. The role of the sema-

phorins in cancer [J]. Cell Adh Migr, 2016, 10: 652-674.

[38] Sakurai A, Doci C, Gutkind JS. Semaphorin signaling in angiogenesis, lymphangiogenesis and cancer [J]. Cell Res, 2012, 22: 23-32.

[39] Wallerius M, Wallmann T, Bartish M, et al. Guidance molecule SEMA3A restricts tumor growth by differentially regulating the proliferation of tumor-associated macrophages [J]. Cancer Res, 2016, 76: 3166-3178.

[40] Mikuła-Pietrasik J, Rutecki S, Książek K. The functional multipotency of transforming growth factor *β* signaling at the intersection of senescence and cancer [J]. Cell Mol Life Sci, 2022, 79: 196.

[41] Lv X, Xu G. Regulatory role of the transforming growth factor-*β* signaling pathway in the drug resistance of gastrointestinal cancers [J]. World J Gastrointest Oncol, 2021, 13: 1648.

[42] Li HM, Wang XX, Wu ML, et al. siRNA targeting *NRP-1* gene silencing inhibited proliferation of cervical cancer cells through Wnt, ROS and TGF-*β*1 pathway [J]. Cell Mol Immunol (中国免疫学杂志), 2018, 34: 1626-1631.

[43] Dong X, Liao W, Zhang L, et al. RSPO2 suppresses colorectal cancer metastasis by counteracting the Wnt5a/Fzd7-driven noncanonical Wnt pathway [J]. Cancer Lett, 2017, 402: 153-165.

[44] Wang Q, Zhang S, Feng GS. Research progress of Wnt/*β*-catenin signaling pathway in colorectal cancer [J]. Med Recapit (医学综述), 2017, 23: 907-911.

[45] Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer [J]. Nature, 2012, 487: 330-337.

[46] Zhang L, Wang H, Li C, et al. VEGF-A/neuropilin 1 pathway confers cancer stemness *via* activating Wnt/*β*-catenin axis in breast cancer cells [J]. Cell Physiol Biochem, 2017, 44: 1251-1262.

[47] Liu W, Wu T, Dong X, et al. Neuropilin-1 is upregulated by Wnt/*β*-catenin signaling and is important for mammary stem cells [J]. Sci Rep, 2017, 7: 10941.

[48] Acharya N, Anderson AC. NRP1 cripples immunological memory [J]. Nat Immunol, 2020, 21: 972-973.

[49] Raskopf E, Vogt A, Standop J, et al. Inhibition of neuropilin-1 by RNA-interference and its angiostatic potential in the treatment of hepatocellular carcinoma [J]. Z Gastroenterol, 2010, 48: 21-27.

[50] Jiang SX, Whitehead S, Aylsworth A, et al. Neuropilin 1 directly interacts with Fer kinase to mediate semaphorin 3A-induced death of cortical neurons [J]. J Biol Chem, 2010, 285: 9908-9918.

[51] Weekes CD, Beeram M, Tolcher AW, et al. A phase I study of the human monoclonal anti-NRP1 antibody MNRP1685A in patients with advanced solid tumors [J]. Invest New Drugs, 2014, 32: 653-660.

[52] Patnaik A, LoRusso PM, Messersmith WA, et al. A Phase Ib study evaluating MNRP1685A, a fully human anti-NRP1 monoclonal antibody, in combination with bevacizumab and paclitaxel in patients with advanced solid tumors [J]. Cancer Chemother Pharmacol, 2014, 73: 951-960.

[53] Jarvis A, Allerston CK, Jia H, et al. Small molecule inhibitors of the neuropilin-1 vascular endothelial growth factor A (VEGF-A) interaction [J]. J Med Chem, 2010, 53: 2215-2226.

[54] Powell J, Mota F, Steadman D, et al. Small molecule neuropilin-1 antagonists combine antiangiogenic and antitumor activity with immune modulation through reduction of transforming growth factor beta (TGF*β*) production in regulatory T-cells [J]. J Med Chem, 2018, 61: 4135-4154.

[55] Song ZY, Fu K, Hu LY, et al. The influence of ginsenoside Rg3 on *ID-1* and *NRP-1* gene expression in endometriotic tissues [J]. Chin Rem Clin (中国药物与临床), 2011, 11: 768-771.

[56] Wu C, Zeng M, Liao G, et al. Neuropilin-1 interacts with fibronectin-1 to promote epithelial-mesenchymal transition progress in gastric cancer [J]. Onco Targets Ther, 2020, 13: 10677-10687.

[57] Peng J, Lv HJ, Ding XX, et al. Research progress of microRNA in colon cancer diagnosis and Chinese medicine prevention and treatment [J]. J Med Theory Pract (医学理论与实践), 2021, 34: 3713-3714, 3718.

[58] Xu D, Chen X, He Q, et al. MicroRNA-9 suppresses the growth, migration, and invasion of malignant melanoma cells *via* targeting NRP1 [J]. Onco Targets Ther, 2016, 9: 7047-7057.

[59] Ding Z, Zhu J, Zeng Y, et al. The regulation of neuropilin 1 expression by miR-338-3p promotes non-small cell lung cancer *via* changes in EGFR signaling [J]. Mol Carcinog, 2019, 58: 1019-1032.

[60] Davies J, Randeva HS, Chatha K, et al. Neuropilin-1 as a new potential SARS-CoV-2 infection mediator implicated in the neurologic features and central nervous system involvement of COVID-19 [J]. Mol Med Rep, 2020, 22: 4221-4226.

[61] Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity [J]. Science, 2020, 370: 856-860.

[62] Daly JL, Simonetti B, Klein K, et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection [J]. Science, 2020, 370: 861-865.