Notch 信号通路在肿瘤微环境中的调控作用

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摘　要:肿瘤细胞与肿瘤微环境(tumor microenvironment,TME)之间通过多种信号通路相互作用,其中 Notch 信号被认为是重要的信号通路之一。现已证实 Notch 信号与 TME 之间的相互作用参与调节肿瘤的血管生成、肿瘤干细胞干性的维持、免疫细胞的浸润和对治疗的抗性。此外,Notch 信号还介导许多分子的分泌,影响 TME 中的细胞功能。大量研究表明,Notch 信号在 TME 中的作用与不同肿瘤中 Notch 的促癌和抑癌特性有关。该综述讨论了 Notch 信号在调节 TME 不同组分之间的相互作用中发挥的重要作用,还从治疗的角度讨论了 Notch—TME 相互作用的结果。

关键词:Notch 信号通路;肿瘤;肿瘤微环境
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Regulation of Notch Signaling Pathways in Tumor Microenvironment

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Abstract:Tumor cells interact with the tumor microenvironment(TME) through multiple signaling pathways,among which Notch signaling pathway is considered as important one. The interactions between Notch signaling and TME have been shown to regulate angiogenesis,tumor stem cell maintenance,infiltration of immune cells,and resistance to therapy. In addition,Notch signaling also mediates the secretion of many molecules to affect the function of cells in TME. A large body of studies have shown that the role of Notch signaling in TME is related to the promotion or suppression in different tumors. In this review,the regulating function of Notch signaling in TME and the perspective of Notch-TME interaction in tumor treatment are discussed.

Key words:Notch signaling;tumor;tumor microenvironment

Notch 信号是一条高度保守的信号通路，参与调节细胞生长、增殖和炎症反应等重要进程。在哺乳动物中,包含 3 个 delta-like 配体(Dll1,Dll3 和 Dll4)和 2 个 jagged 配体 (Jag1 和 Jag2)。配体通过与 Notch 的 4 种受体(Notch1~4)的结合诱导 Notch 受体的切割,释放 Notch 胞内结构域(Notch intracellular domain,NICD) 进入细胞核内。NICD 与 CSL(centromere-binding factor 1/suppressor of hairless/Lag1)转录因子的相互作用募集转录共激活因子(Co-A)MAML 代替转录共阻遏物(Co-Rs),激活下游靶基因(*HES*,*HEY* 等),进而发挥其功能。Notch 信号通过依赖 CSL 转录的激活介导经典信号的传导并参与肿瘤的发生及发展[1]。

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肿瘤微环境（tumor microenvironment，TME）包括肿瘤周围的血管、免疫浸润细胞、成纤维细胞和细胞外基质等。肿瘤的进展、对治疗的抗性、侵袭和转移与肿瘤细胞和 TME 相互作用有关[2]。肿瘤细胞与 TME 之间通过多种旁分泌信号相互作用，其中 Notch 信号被认为是重要的信号通路之一。Notch 信号在肿瘤细胞中的促癌或抑癌作用已被广泛认知[1]，其旁分泌信号可以调节基质和肿瘤之间的异型相互作用，反之亦然。此外，Notch 信号还介导许多分子的分泌影响 TME 中的细胞功能。Notch 在 TME 中发挥的作用与 Notch 在不同肿瘤中的促癌和抗癌特性相关，见表 1(Table 1)。因此，研发靶向 Notch 信号通路的肿瘤治疗方法需要详尽了解 Notch 在 TME 的作用。

1 Notch 信号介导的肿瘤血管形成

肿瘤可诱导血管新生，为肿瘤细胞提供营养。Notch 信号通过调节内皮生长因子受体 2(VEGFR2)影响内皮细胞(epithelial cells，ECs)向尖端细胞与茎细胞的分化选择，调节血管出芽[16]。由于 Dll4 和 Jag1 在控制出芽式血管生成方面具有相反功能[17]，因此 ECs 中 Dll4 和 Jag1 表达的平衡对肿瘤血管结构的形成具有重要的意义。在前列腺癌中，ECs 中过表达的 Jag1 通过 Notch4/Hes1 诱导肿瘤血管的增加，并且抑制肿瘤组织的细胞凋亡；而 ECs 中 Jag1 功能丧失则诱导肿瘤细胞凋亡增加，肿瘤生长减缓[18]。有研究还表明 ECs 中 Jag1 激活局部周细胞前体细胞的 Notch 信号并诱导周细胞分化[19]。ECs 中过表达的 Dll4 降低肿瘤血管的密度，限制肿瘤的生长和转移[20]；Dll4 抗体可增加肿瘤血管密度，但肿瘤大小及重量反而降低，这可能与生成的血管灌注不良有关[7]。然而，在急性 T 淋巴细胞白血病(T-ALL)中，ECs 表达的 Dll4 激活肿瘤细胞的 Notch3，使肿瘤细胞从缺乏血管生成能力的休眠状态开始诱导血管增加[7]。在肿瘤移植模型中，Dll4 抗体可降低肿瘤细胞的 Notch 活性，表明 ECs 表达的 Dll4 激活相邻肿瘤细胞的 Notch 信号[21]。在结肠癌中，邻近血管激活肿瘤细胞的 Notch 信号，促进肿瘤细胞的转移[4]。最近有研究表明，Jag1 不是通过拮抗 Dll4 而是诱导 Dll4 的生成来增加血管生成[22]。因此，Notch 信号通过与肿瘤的异型相互作用调控肿瘤血管生成。

2 Notch 信号介导的肿瘤免疫

免疫细胞参与 TME 的免疫浸润，但受到多种调节机制的抑制。目前研究表明，Notch 信号参与调节淋巴细胞、DC、Th 和 Treg 细胞的分化和功能，见表

Table 1 The function of Notching signaling in the TME

Receptor	Ligand	Signal-sending cell	Signal-receiving cell	Effects on the tumor	Tumor type	References
ND	sJag1	Endothelial cells	Tumor cells	Increase tumor stem cell phenotype	Colorectal cancer	[3]
Notch1	Dll4	Endothelial cells	Tumor cells	Increase metastasis formation	Colorectal cancer	[4]
Notch1	Jag1	Endothelial cells	Tumor stem cells	Self-renewal of tumor stem cells	Glioblastoma	[5]
Notch2	Jag1	Endothelial cells	Tumor cells	Increase resistance of tumor cells	B cell lymphoma	[6]
Notch3	Dll4	Endothelial cells	Tumor cells	Escape from dormancy	T-ALL	[7]
Notch3	Jag1	Tumor cells	Endothelial cells	Increase tumor angiogenesis and tumor growth	Lung cancer	[8]
Notch1	ND	Tumor cells	Macrophages	Trans-endothelial tumor cell migration	Breast cancer	[9]
ND	Jag1	Tumor cells	Bone marrow stromal cells	Increased secretion of IL-6	Multiple myeloma	[10]
ND	Jag1	Tumor cells	Stroma	Increased number of inflammatory foci and formation of a reactive stroma	Prostate cancer	[11]
Notch1 Notch4	Dll4	Myeloid cells	Tumor cells	Tumor progression	Lung cancer, melanoma	[12]
Notch3	Jag1	Fibroblasts	Tumor cells	Resistance to chemotherapy	Breast cancer	[13]
Notch3	Jag1	Fibroblasts	Endothelial cells	Increase angiogenesis	Oral squamous cell carcinoma	[14]
ND	Jag1	Mesenchymal stem cells	Tumor cells	Induction of EMT	Pancreatic cancer	[15]

Notes：ND：not determined；sJag-1：soluble Jag1；EMT：epithelial-mesenchymal transition；T-ALL：T cell-acute lymphoblastic leukemia

Table 2 The function of Notch signaling in the tumor immune infiltration

Cell type	Notch pathway member involved	Function in tumor immunity	Effect of Notch signaling	References
DC	Dll1	Anti-tumor	Induction of anti-tumor T-cell responses	[23]
M1 macrophages	Dll1	Anti-tumor	Increase antigen presenting activity	[24]
M2 macrophages	Jag1	Pro-tumor	Induction of differentiation	[25]
$CD8^+$ T cells	Dll1/Notch2	Anti-tumor	Enhancing anti-tumor response	[26–27]
MDSC	Jag1/2	Immunosuppression	Induction of T cell tolerance	[28]
Myeloid-derived $CD11b^+$ cells	Jag2	Immunosuppression	Induction of EMT in cancer cells	[29]

Notes: DC: dendritic cells; MDSS: myeloid-derived suppressor cells

2(Table 2)。研究 Notch 信号在免疫浸润过程中是如何被调控的，对于阐明 Notch 信号在肿瘤免疫调控中的作用具有重要意义。

Notch 信号对于细胞毒性 T 细胞 (cytotoxic T cell,CTL)活化的调节非常重要。幼稚 $CD8^+$细胞的活化需要 Dll1 与 Notch1 或 Notch2 的结合以表达颗粒酶 B 和 IFN-γ[26]。肿瘤可以通过在造血环境中降低 Dll1 和 Dll4 的水平来抑制宿主 T 细胞的发育和功能，而恢复造血环境中的 Dll1-Notch 通路可以恢复 CTL 的功能[30]。多价 Dll1 可诱导 T 细胞的分化和增强抗原特异性细胞毒性，抑制肿瘤生长[31]。这些研究都表明 Notch 信号在调节 CTL 的抗肿瘤活性中的积极作用。然而，在结肠癌患者中，即使抑制 $CD8^+$T 细胞的 Notch 信号，T 细胞反而会通过降低 PD-1 的表达，从而增强细胞毒活性。因此，Notch 信号在特定环境下的功能需要进一步阐明[32]。

Notch 信号对肿瘤相关巨噬细胞(tumor-associated macrophage,TAMs)的分化也很重要。敲除单核细胞的 CSL 可阻断 TAMs 的分化及与 TAMs 相关的免疫抑制功能[33]。在乳腺癌模型可以检测到 Notch1 和 Notch2，而在肺癌模型中则检测到 TAMs 表达 Dll1 和 Dll4 [24,33]。过表达 Jag1 的乳腺癌细胞与巨噬细胞共培养增加 TAMs 标记，用 γ-分泌酶处理后，这种变化则消失 [25]。Notch 信号增加促炎巨噬细胞(M1)表型，缺失 Notch 信号的巨噬细胞的抗原呈递活性降低[24]。此外，过表达 N1ICD 的巨噬细胞降低 TAMs 的功能，从而抑制肿瘤生长[34]。因此，巨噬细胞的极化依赖于内在的 Notch 信号，而其 Notch 信号通过与 TME 中表达 Notch 配体的其他细胞相互作用而被调节。

TME 中的其他免疫细胞也受 Notch 信号的影响。在结肠癌中，表达 CD11b 的髓系细胞积累在肿瘤细胞上皮—间质转化(EMT)区域，通过表达 Jag2 诱导肿瘤细胞的 Notch 信号和 EMT[29]。Notch 信号会损害 Tregs，减弱其免疫抑制功能[35]。此外，毛囊干细胞中 Tregs 表达 Jag1 可诱导 Notch 信号，促进细胞增殖[36]。然而，Tregs 表达的配体调节肿瘤干细胞的作用仍有待研究。

3 Notch 信号与成纤维细胞的相互作用

肿瘤相关成纤维细胞(cancer-associated fibroblasts,CAFs)参与疾病的发生、发展和转移[37]。成纤维细胞中 Notch 的缺失可能参与肿瘤的发生：Notch1 是成纤维细胞中衰老分泌小体的主要调节因子，其缺失可能使衰老相关的分泌表型向促炎表型极化[38,39]。另外，Notch 的激活参与成纤维细胞的活化。前列腺癌的肿瘤细胞表达的 Jag1 诱导成纤维细胞分化为 CAFs[11]。CAFs 分泌 IL-6 诱导乳腺癌细胞的 Notch 活化[40]。CAFs 还分泌 CCL2 维持肿瘤干细胞干性 [41]。多项研究表明 Notch3 与 CAFs 存在重要关联：肝癌 CAFs 诱导 Notch3 表达，促进肿瘤干细胞增殖[42]。乳腺癌 CAFs 表达 Jag1，可以与肿瘤细胞中的 Notch3 相互作用并调节肿瘤抗性[13]。口腔鳞状细胞癌刺激 CAFs 表达 Notch3，诱导 CAFs 参与血管生成，从而促进肿瘤生长[23]。另外，黑色素瘤中 CAFs 表达的 Notch1 控制着黑色素瘤干细胞的可塑性和干性，从而调节黑色素瘤的侵袭性[43]。Notch 介导的肿瘤细胞和间充质之间的相互作用也参与肿瘤的治疗耐受。因此，肿瘤细胞和 CAFs 之间的相互作用部分地由 Notch 信号控制。

4 Notch 信号调节 TME 与肿瘤干细胞之间的相互作用

Notch 信号通过 TME 中 CAFs、ECs 和细胞外基

质等调节肿瘤干细胞(cancer stem cell,CSC)干性[44]。抑制胶质母细胞瘤的 Notch 信号，导致内皮细胞的减少,进而破坏肿瘤干细胞的微环境[45]。血管所表达的配体可以激活 CSC 的 Notch 信号[5,46]。黑色素瘤中 CAFs 表达的 Notch1 调控肿瘤干细胞的可塑性和干性,从而调节黑色素瘤的侵袭性[43]。乳腺癌成纤维细胞分泌 CCL2 诱导乳腺癌细胞 Notch1 的表达，以维持干细胞的干性 [41]。在不同的肿瘤中,Jag1 在调解 CSC 与 TME 之间的相互作用中起重要作用。结肠癌 ECs 分泌可溶性 Jag1 维持 CSC 的自我更新[3]。在 APC 缺陷的肠癌模型中,Jag1 还参与干细胞增殖和微环境的形成[47]。抑制骨肉瘤细胞中的 Jag1,会使得其干细胞表型受到抑制，进而限制肿瘤的生长[48]。因此,Jag1 是参与维持 CSC 干性的主要 Notch 配体,它可能诱导特定转录程序发挥特殊作用，而其他配体是否参与干细胞表型的维持还有待探索。

5　TME 中 Notch 信号与其他信号通路的交流

TME 中其它信号通路通过影响 Notch 配受体的表达来实现对 Notch 的动态调节。如 Notch1 信号和 CXCL12/CXCR4 之间的交流可能有助于胶质瘤干细胞的自我更新和侵袭[49]。B 细胞淋巴瘤细胞分泌 FGF4 诱导邻近 ECs 表达 Jag1，继而激活淋巴瘤细胞的 Notch2 [6]。Jag1 是乳腺癌和结肠癌中 Wnt 信号的靶标 [50,51]。TME 中 IL-6/STAT3 通路参与调节 Notch 信号[52]。乳腺癌基质细胞表达的 Jag1 诱导 CSC 通过RIG-1/STAT1 通路表达 Notch3,增加肿瘤细胞对治疗的抗性[13]。肝癌细胞和 CAFs 之间、结肠癌细胞和间充质干细胞之间以及结肠癌细胞和骨髓来源的抑制性细胞 (myeloid-derived suppressor cells,MDSCs) 之间都存在 IL-6/STAT3/Notch 信号间的交流[53-55]。TME 与 Notch 之间信号交流的另一个重要通路是 TGF-β 通路。乳腺癌中抑制 TGF-β 导致 Jag1 表达的降低 [56]。前列腺癌细胞中 Jag1 的上调引起前列腺癌基质中 TGF-β 的上调,导致间质再次被激活[11]。肿瘤细胞中骨髓细胞依赖的 Notch 信号的激活与 TGF-β 的信号交流导致 TGF-β 依赖的 pSMAD2/3 信号的增强[12]。因此,Notch 配体和受体通过与 TME 中其他信号通路的信号交流,进行动态调节。

6　抑制 TME 中的 Notch 信号进行肿瘤治疗

目前针对 Notch 信号的抑制剂主要包括 3 种：γ-分泌酶抑制剂(GSI)、靶向配受体的抗体以及靶向

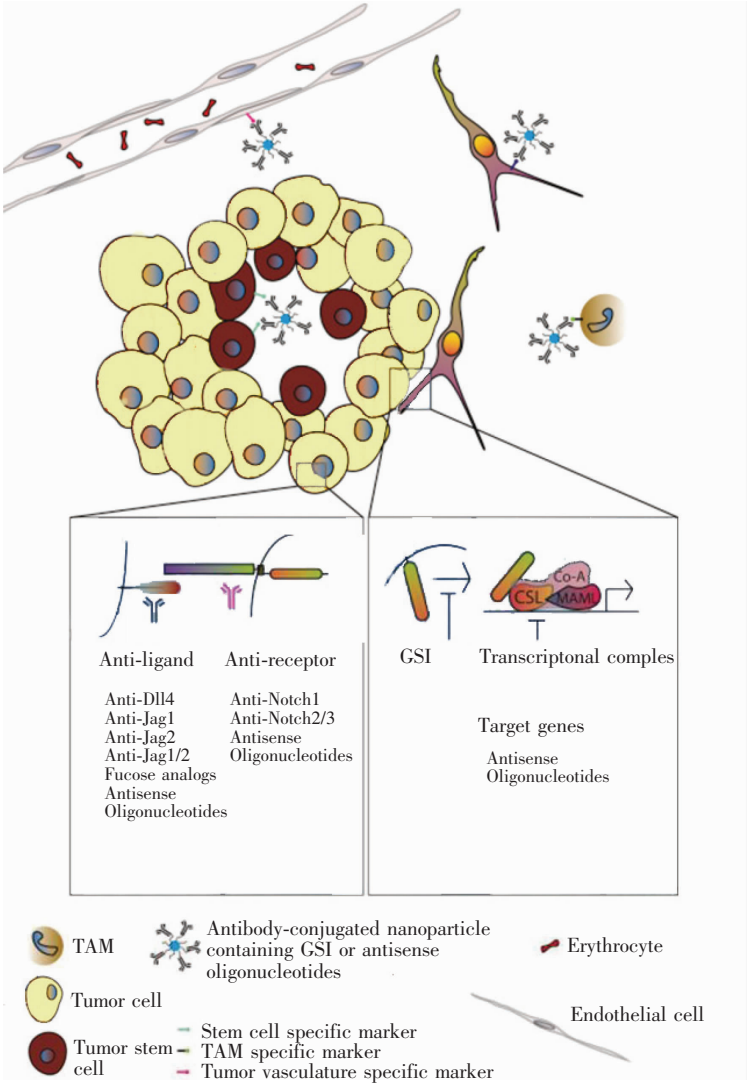

Figure 1　Different approaches of inhibiting Notch signaling[1]

转录激活的复合物，见图 1(Figure 1)[1]。除了靶向肿瘤血管系统的 Dll4 抗体，大多都靶向肿瘤细胞。然而，由于 TME 中 Notch 配受体的广泛表达，任何方法都将靶向肿瘤细胞和 TME，所以对体内抑制 Notch 信号的疗效需谨慎分析，抑制 Notch 信号的部分影响见表 3 (Table 3)。GSI 影响 Notch 配受体的结合，导致肿瘤血管生成减少 [57]。如前所述，Dll4 和 Jag1 在调节血管生成具有相反的作用，因此靶向 Jag1 与 Dll4 对肿瘤血管具有不同的作用。抗 Dll4 治疗会导致非增生性的血管生成，而抗 Jag1 抗体具有相反的作用，可导致血管生成正常化[58]。用 Notch1 类似物干扰 Jag1 与 Notch1 的结合能减少血管生成的萌芽和周细胞的覆盖，而干扰 Dll4 则导致肿瘤血管增生高度萌芽 [59]。另外，GSI 治疗会靶向 ECs，导致 ECs 死亡[8,45,60]。值得注意的是，抗 Dll4 治疗迫使休眠肿瘤细胞(DTCs)重新进入细胞周期。最近发现非经典 Notch 信号也会调节血管屏障，使其出现新的复杂层，而用抗 Dll4 或 GSI 治疗，会影响该过程并增加血管通透性[61]。

Table 3　Effects of Notch inhibition in the TME

Inhibitor used	Effect on the tumor microenvironment	Reference
GSI (DAPT)	endothelial cell death	[8]
GSI (MRK-003)	Endothelial cell death	[60]
GSI (DAPT)	Angiogenesis inhibition	[57]
GSI (DAPT)	Enhanced anti-tumor immunity	[62]
GSI	M2 polarization of macrophages	[24]
GSI (MK-0762)	Increased cancer stem cells	[63]
DAPT	Increased cytotoxicity of T cells	[32]
N1 decoy blocking Jag	Reduced sprouting vessel;pericytes coverage	[59]
N1 decoy blocking Dll	Vasculature hypersprouting	[59]
Anti-Dll4 antibody	Vasculature hypersprouting	[21]
Anti-Notch1 NRR	Angiogenesis inhibition	[64]
Anti-Notch2/3 (tarextumab)	Impaired pericyte functions	[65]
Anti-Jag1/2 (CTX014)	MDSC inhibition	[28]

抑制 Notch 信号影响肿瘤免疫。GSI 导致 TAMs、MDSCs 和 Tregs 减少[62]，M1 巨噬细胞极化需要 Notch 信号的参与，所以抑制 Notch 信号也可能限制先天抗肿瘤免疫应答的效能[24]。与野生型相比，Notch 缺陷型巨噬细胞抑制肿瘤生长效率较低[24]。多价 Dll1 诱导 T 淋巴细胞分化和增强抗原特异性细胞毒性[31]。Jag1/2 抗体抑制 Notch 信号，降低肿瘤内 MDSCs 的积累和耐受性 [66]。然而，抑制肿瘤的 Notch 信号也会增强 Tregs 功能，阻断 Tregs 中 Notch 信号导致移植物抗宿主病的调节表型增强[35]。此外，在实验性自身免疫性脑脊髓炎中，Dll4 中和抗体诱导 Tregs 增加[67]。虽然以上结论仍需要在肿瘤中得到进一步证实，但抑制 Notch 可能在某些情况下会加强免疫抑制。

7　展　望

Notch 信号在 TME 中的作用是呈网状互相关联的，仅针对该通路中任何单一靶点进行治疗都可能存在缺陷。因此，研究 TME 中 Notch 信号在肿瘤恶性进程中的作用应全面考虑多种组成成分。今后的主要任务就是阐明 Notch 信号复杂调控网络的机制，从而研究不同 Notch 信号异常所导致的特定病理情况，设计出更有针对性的治疗方案。

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