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KCTD9的结构、功能及在人类疾病中起到的作用

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摘 要

KCTD9 (新型钾通道相关基因)，是钾通道四聚化结构域(KCTD)基因家族的成员之一；因其N端保守的BTB结构域与电压门控钾通道具有序列相似性而得名，可以与CUL3相互作用介导靶蛋白的泛素化，并在NK细胞生长发育和功能发挥过程中发挥重要作用。起初的研究始于发现它在重型乙型肝炎中呈高表达，后续发现他还在几种恶性肿瘤中如肺癌、结直肠癌、乳腺癌发挥着重要的抗肿瘤作用。近年来关于KCTD9的研究报道逐渐增多，但对它的综述表述几乎没有，基于此我们对KCTD9的结构、功能以及在人类疾病中发挥的作用作了综述，并介绍了其所属KCTD家族的结构、功能及家族内成员在人类疾病中发挥的作用。

关键词

KCTD家族，KCTD9，CUL3，肺癌，结直肠癌，ACLF，人类疾病

Structure, Function, and Role of KCTD9 in Human Diseases

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Abstract

KCTD9 (novel potassium channel-related gene) is a member of the potassium channel tetradomain

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(KCTD) gene family. It is named for its N-terminal conserved BTB domain, which shares sequence similarity with voltage-gated potassium channels. KCTD9 can interact with CUL3 to mediate the ubiquitination of target proteins and plays an important role in the growth, development, and function of NK cells. Initial studies began with the discovery of its high expression in severe hepatitis B, followed by findings of its important antitumor effects in several malignant tumors, such as lung cancer, colorectal cancer, and breast cancer. In recent years, reports on KCTD9 have increased, but there are almost no comprehensive reviews of it. Based on this, we provide a review of KCTD9's structure, function, and role in human diseases, and introduce the structure, function, and role of its family members in human diseases.

Keywords

KCTD Family, KCTD9, CUL3, Lung Cancer, Colorectal Cancer, ACLF, Human Diseases

1. KCTD 家族

人类基因组编码 183 个包含 BTB 结构域的蛋白质，并根据结构域共同特征划分为四个大家族：ZBTB 家族(BTB-锌指蛋白；43 个成员)、KLHL 家族(BTB-BACK Kelch-pro 蛋白；49 个成员)、T1/Kv 家族(T1 K^+通道整联膜蛋白；27 个成员)和 KCTD 家族(钾通道四聚化结构域蛋白；25 个成员) [1]。KCTD 家族由单个短形式 n 端 BTB 结构域和可变性较强的 c 端序列组成，因其保守 n 端序列含有的 brick-a-brack，Tram-track，Broad 复合体(BTB/POZ)结构域与可以介导电压门控钾通道亚基四聚化的 T1/BTB 结构域相似而得名[1]-[3]，家族成员们基于 BTB 结构域多数表现为五聚体形式少数为四聚体形式[2] [4]，通过氨基酸序列将他们划分为 8 组，广泛分布于细胞质、细胞核中而且参与很多不同的生物功能过程，比如蛋白质的降解、增殖或转录的抑制、人类遗传疾病风险、睡眠稳态和 G 蛋白偶联受体的调节[2] [5]。

2. KCTD9 的结构特点及功能

KCTD9 (新型钾通道相关基因)，是钾通道四聚化结构域(KCTD)基因家族的一名成员，其结构由 N 端的保守 BTB 结构域介导形成了与传统 BTB 蛋白的二聚体不同的独特对称五聚化结构，并且可以与 CUL3 (E3 连接酶)相互作用形成稳定的 5:5 复合物，介导相应靶蛋白泛素化[1] [4] [6] [7]。对 KCTD9 的初步深入研究源于其被发现在病毒性暴发性肝炎小鼠模型肝 NK 细胞、$CD8^+$ T 细胞、$CD4^+$ T 细胞和重型乙型肝炎患者 PBMC(外周血单核细胞)中表达上调且与肝损害程度正相关，其高表达主要作用为活化 NK 细胞产生更多的 INF-γ 等细胞因子、增加细胞毒性来介导免疫相关炎症反应[8] [9]。后续通过建立 KCTD9 缺陷小鼠模型研究发现：KCTD9 免疫缺陷小鼠体内介导 NK 细胞发育成熟的转录因子如 Ets1、Nfil3、Eomes 和 Id2 表达受阻从而引起了 NK 细胞的成熟受损，同时 NK 细胞的效应功能也受到损害表现为 IFN-γ、脱颗粒和颗粒酶 B 产生下降以及体外实验中对肿瘤细胞的毒性减弱[7]，说明 KCTD9 通过影响上述转录因子表达以及相应细胞因子分泌在介导 NK 细胞发育成熟和效应功能表达过程中不可或缺，具体详尽的分子靶点调控需尚需进一步研究，但 KCTD9 在 NK 细胞成熟过程中的作用是确定的，推测可能与 KCTD9 独特的五聚化结构有关。

3. KCTD9 与人类疾病

3.1. KCTD9 与 ACLF

慢性乙型肝炎(CHB)是一种由乙型肝炎病毒(HBV)感染引起的全球危害性疾病，据 WHO 数据统计显示：2019 年全球感染慢性乙型肝炎患者人数高达 2.96 亿人次[10]，ACLF(急性慢性肝衰竭/慢加急性肝衰竭/爆发性肝衰竭)是 CHB 慢性期发生的急性肝脏衰竭，死亡率高达 50%~70% [11]-[13]。而在 HBV 感染引起的 ACLF 患者的外周血和肝脏 NK 细胞中发现 KCTD9 的表达水平上调，体外细胞实验发现 KCTD9 通过抑制 NKG2A 受体的产生促进 NK 细胞活化提高细胞毒性与杀伤力，从而介导炎症反应加重肝衰竭[14]。相关的小鼠体内实验也证明，KCTD9 在爆发性肝衰竭小鼠模型中表达上调，且加重肝脏损伤，降低 KCTD9 表达后可以抑制 NK 细胞活化降低细胞毒性来改善小鼠的肝功能，提高存活率[12]，且通过抗肝衰竭化合物(AHFC)处理爆发性肝衰竭小鼠模型后，KCTD9 基因表达下降，相关免疫损伤得到控制[15]。由此说明 KCTD9 通过活化 NK 细胞介导炎症反应的方式在 ACLF 中产生重要的作用，以此为研究方向可提供新的治疗策略，降低 ACLF 的死亡风险。

3.2. KCTD9 与肺癌

肺癌是全球范围内危害性极高且防治困难的恶性肿瘤之首，根据国际癌症研究机构(IARC)最新的 2022 年全球癌症统计数据显示：肺癌是目前世界范围内生存率(12.4%)和死亡率(18.7%)排名均第一的癌症，且死亡率是排名第二位的结直肠癌(9.3%)的三倍，其五年生存率明显低于其他类型的癌症[16]-[18]。在肺癌治疗相关研究中，一种中药制剂康莱特(薏苡仁提取物/CSE)被广泛用于肺癌的辅助治疗中，可以起到缓解病症，提高患者生活质量，延长生存时间以及减少化疗毒副反应的作用，而且安全性得到肯定[19]-[21]。通过相关体外细胞实验也发现，CSE 可以抑制肺腺癌细胞如 A549 和 HCC827 细胞的侵袭能力[22]。研究发现这种抗肿瘤作用与本文所述基因 KCTD9 密切相关，相比于正常组织而言，KCTD9 在肺腺癌中的 mRNA 和蛋白表达水平明显下降，而用 CSE 处理之后 KCTD9 表达水平明显提高，且 KCTD9 是 CSE 减少 PD-L1 (T 细胞活性的负调节因子) [23]的产生来增强人 $CD8^+$ T 细胞增殖能力和杀伤作用的靶点，具体而言 CSE 通过 KCTD9 介导的 TOP2A 蛋白泛素化修饰过程降低 PD-L1 的产生在肺癌发生发展中发挥抑制肿瘤增值、侵袭等恶性行为和免疫逃逸的抗肿瘤作用，且敲低肺癌细胞中 KCTD9 表达之后可以逆转上述抗肿瘤效应，促进了肿瘤免疫逃逸[22] [24]。所以 KCTD9 在肺癌中的抗肿瘤效应是确定的，上述提到 KCTD9 与 CUL3 相互作用可介导相应靶蛋白泛素化，推测 KCTD9 介导的 TOP2A 泛素化与其密切相关，以此为切入点研究 CUL3、KCTD9、TOP2A 的相互作用及对下游相关分子靶点的调控在未来有望作为肺癌新的治疗靶点。

3.3. KCTD9 与结直肠癌

结直肠癌是全球范围内严重危害人类健康安全的恶性肿瘤之一，根据 IARC 报道的最新数据显示，其发病率为 9.6%，仅次于肺癌(12.4%)和女性乳腺癌(11.6%)排名第三；死亡率(9.3%)更是高居第二位，仅次于肺癌(18.7%)，是消化道肿瘤中发病率和死亡率排名第一的癌症[18]。结直肠癌的发生发展过程与 Wnt 信号传导通路有密切的关系[25]，Wnt 信号传导通路是正常细胞生长发育，增殖分化不可或缺的一部分，由经典的 Wnt/β-catenin 信号传导通路以及非经典的 Wnt-PCP (平面细胞极性)通路、Wnt-Ca^{2+}信号通路组成，形成复杂的细胞间信号传导网络[26]，在胚胎孕育、组织与器官的发育和再生、干细胞的维持与分化的精准调控等正常生理过程中发挥着不可或缺的作用[27]-[29]；但是该通路的异常激活也是造成结直肠癌细胞的产生、增殖和转移促进其发生发展的关键因素之一[26] [30] [31]。而且在以往经典 Wnt 通路促

进结直肠癌结论的基础上，近期有研究发现 Wnt 配体可以通过协同激活经典和非经典通路形成复杂的信号通路网促进结直肠癌的进展[32]。Yao 等人的研究发现 KCTD9 的蛋白表达水平在结直肠癌中呈下调趋势，并探究了 KCTD9 抑制结直肠癌进展的具体分子机制：首先他们证实 ZNT9(锌转运蛋白 9)是 Wnt/β-catenin 信号传导、EMT 的正调节因子，而 KCTD9 可以与其相互作用，一方面竞争性抑制了 ZNT9 与 β-catenin 的相互作用降低了 Wnt 通路激活成分如：c-Myc、cyclin D1、MMP-7 蛋白的表达从而抑制了经典的 Wnt/β-catenin 通路的传导；另一方面抑制了上皮标记物 N-cadherin、SNAIL 和 vimentin 的表达来抑制结直肠癌细胞的 EMT 过程，这两种效果共同发挥抑制结直肠癌增殖和转移的作用[30]。相关的体外细胞实验以及裸鼠皮下成瘤实验也证明了 KCTD9 基因抑制结直肠癌的进展[30] [33]此外还有不同的预后模型分析均显示 KCTD9 作为一种保护因子与结直肠癌患者的预后呈正相关[33]-[35]，在以上基础上围绕 KCTD9 这一基因研究有望研发出新型有效的临床药物，为治疗结直肠癌提供了新的研究方向。

4. KCTD 家族相关疾病

随着对 KCTD 家族的广泛深入研究，发现他们与很多人类疾病的发生发展有着密切的联系并且作用不尽相同。在此对与他们相关性较强的疾病做了简要总结概括：KCTD1 突变引起头皮－耳－乳头(SEN)综合征[36]；KCTD2 可抑制神经胶质瘤的发生[37]；KCTD3 介导发育性癫痫性脑病[38]；KCTD4 促进食管癌转移[39]；KCTD5 促进三阴性乳腺癌的恶性进展以及不良预后[40]；KCTD6 [41]、KCTD11 [42]、KCTD21 抑制髓母细胞瘤的发生；KCTD7 可引起神经发育障碍的进行性肌阵挛性癫痫(PME3/EPM3)；KCTD8 抑制肝细胞癌进展[43]；KCTD9 抑制结直肠癌与肺癌的进展以及介导暴发性肝炎引起的肝损害，见下文详述；KCTD10 通过抑制 Notch 信号通路对胚胎血管生成和心脏发育起关键作用[44]，是肝细胞癌肿瘤抑制因子[45]；还可以通过介导 KCTD13 泛素化抑制神经发育障碍疾病的发生[46]；KCTD11 抑制肺癌[47]、肝细胞癌[48]、前列腺癌[49]、随母细胞瘤等多种癌症的发生发展；KCTD12 的经典报道为调节 GABA(B)受体的功能[50]，后来发现它与神经障碍性疾病如双相情感障碍、抑郁症等相关[51]，并且在结直肠癌[52]、黑色素瘤[53]、乳腺癌[54] [55]中的下调促进了他们的进展，可能作为未来开展治疗新靶点。KCTD13 主要因其基因定位(16p11.2)与癫痫、自闭症以及精神分裂症密切相关[2]；早期关于 KCTD15 的报道主要涉及抑制神经嵴的形成[56]，近期报道其还在几种恶性肿瘤中发挥不同的作用：抑制结直肠癌[57]以及髓母细胞瘤[58]的进展，在 her2^{+}阳性乳腺癌[59]以及儿童 B 细胞急性淋巴细胞白血病[60]、外周血和急性髓性白血病[61]中高表达；KCTD17 近期报道与运动障碍相关[62]并且可以促进肝细胞癌的进展[63]；KCTD19 基因突变可导致男性不育[64] [65]；KCTD20 可促进非小细胞肺癌进展[66]。对于 KCTD 家族成员功能的探究以及与人类疾病尤其是恶性肿瘤的相关机制研究对未来这些疾病的治疗、预防提供了新的依据。

5. 讨论与总结

KCTD 家族是根据人类基因组编码的 183 个包含 BTB 结构域蛋白质的共同特征划分的四个大家族之一，广泛分布于细胞质与细胞核中并发挥不同的生理功能，KCTD9 是 KCTD 家族的成员之一，他在人类重型乙型肝炎患者组织样本中高表达，后通过暴发性肝炎等相关小鼠体内模型探讨发现，其高表达主要通过促进 NK 细胞的活化介导 TNF-γ 等细胞因子的产生及细胞毒性的提高引起了免疫系统相关性炎症引起了与其表达水平呈正相关的肝损伤。而且 KCTD9 还可以在甲型流感病毒(IAV)复制过程中作为宿主蛋白参加多种生理过程，很有可能协助 NP (IAV 核蛋白)转移到细胞核，用于病毒 RNA 的复制和转录促进甲型流感的发展[67]。后续通过对 KCTD9 的深入研究发现它可以通过抑制经典的 Wnt/β-catenin 通路的传导以及介导 TOP2A 蛋白泛素化修饰过程分别在结直肠癌和肺癌中发挥抗肿瘤效应。还有研究通过筛

选异常甲基化基因的差异表达并利用公开数据库验证筛选出 KCTD9 在乳腺癌中呈低表达状态并与不良的临床结果相关[68]。本文还总结了KCTD家族成员在密切相关的人类疾病中发挥的作用或饰演的角色，希望能对 KCTD9 和它所在 KCTD 家族的深入研究以及多种临床相关疾病的诊疗有所助益。

6. 挑战与展望

基于对 KCTD9 与 KCTD 家族的了解，虽然 KCTD9 已经被发现可以作为肿瘤抑制因子在几种恶性肿瘤包括结直肠癌、肺癌、乳腺癌中发挥抗肿瘤作用，但是以 KCTD9 为作用靶点、有效且安全的临床药物尚未被研发出来，并且相关研究较少，想要实现从基础实验研究到临床药物研发阶段的转换存在一定的挑战性，尚有几个关键性问题需要解决比如：KCTD9 是否可作为治疗性靶点？其在癌症中的功能是否具有成药性？KCTD9 调控的下游通路中哪些节点可被小分子干预以进一步深入研究？以 KCTD9 为靶点药物开发的临床前安全性与毒性评价又如何？但是通过相关成熟的实验技术我们相信可以逐步攻克相关的关键问题，比如类器官模型或 PDX (人源肿瘤异种移植)评估 KCTD9 敲除/过表达对治疗响应的影响；磷酸化蛋白质组学(phospho-proteomics)技术筛选 KCTD9 依赖的信号网络；通过体外毒性筛选、体内动物毒理学研究评估药物的安全性与毒性。相信不久的未来有望开发出新型有效的抗肿瘤药物。不仅如此，KCTD9 在重型乙型肝炎及暴发性肝炎介导肝损伤的机制也是基于活化 NK 细胞并且药物实验方面已经以小鼠为模型逐步开展，并有一定的研究支持，相对于肿瘤拮抗作用药物研发具有一定挑战性而言，以 KCTD09 为作用靶点开发出有效降低肝炎患者肝损伤来降低重型肝炎特别是爆发性肝炎的死亡率较为可观，但仍需要继续努力以研发出有效且安全的临床药物，并且相信在未来 KCTD9 有望成为新兴的热门研发药物靶点。

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