

野生型胃肠间质瘤分子机制研究进展

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背景资料

胃肠间质瘤(gastrointestinal stromal tumor, GIST)是一类起源于胃肠道间叶组织的肿瘤, 主要发生于消化系统, 多数存在KIT或PDGFRA基因突变, 无KIT和PDGFRA基因突变的GIST称为野生型GIST(WT-GIST)。

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Progress in understanding of molecular mechanisms of wild-type gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors of the gastrointestinal tract, 80%-95% of which have KIT and PDGFRA gene mutations. GISTs without gene mutations, including KIT and PDGFRA gene mutations, are called wild-type GISTs (WT-GISTs). The development of

a molecular drug targeting tyrosine kinase inhibitor (TKI) has changed the therapeutic of GISTs with gene mutations; however, WT-GISTs are not sensitive to TKI. The molecular basis and mechanism of these characteristics should be elucidated.

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Key Words: Wild type gastrointestinal stromal tumor; Molecular mechanism; Genetic mutation

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摘要

胃肠道间质瘤(gastrointestinal stromal tumor, GIST)是消化系最常见的间叶源性肿瘤, 80%-95%GIST存在KIT或PDGFRA基因突变, 未突变者称为野生型GIST(WT-GIST)。目前证实, 突变型GIST对酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)分子靶向治疗有效。但WT-GIST通常对TKI类药物不敏感, 其分子理论基础、发生机制需明确阐述。

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关键词: 野生型胃肠间质瘤; 分子机制; 基因突变

核心提要: 胃肠间质瘤(gastrointestinal stromal tumor, GIST)的主要发生机制是KIT和PDGFRA基因突变, 针对上述基因突变的治疗已较成熟,

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但对野生型GIST(WT-GIST), 缺乏发病机制的研究和探索, 药物治疗多年来无重大突破, 迫切需要引起重视。

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0 引言

目前研究证实, 胃肠间质瘤(gastrointestinal stromal tumors, GIST)的主要发生机制是酪氨酸激酶受体KIT(v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog)和血小板源性生长因子受体 α 多肽PDGFRA(platelet derived growth factor receptor alpha)基因突变, 约80%-95%胃肠间质瘤存在KIT或PDGFRA基因突变, 未检测到KIT或PDGFRA基因突变的GIST称为野生型GIST(wild-type GIST, WT-GIST). 以甲磺酸伊马替尼为代表的酪氨酸激酶抑制剂(tyrosine kinase inhibitors, TKI)分子靶向药物的研制, 改变了GIST的治疗模式, 但WT-GIST对TKI类药物不敏感, 甚至耐药. 与突变型GIST相比, WT-GIST的发病年龄更年轻, 肿瘤相对更小, 梭形细胞型多见, CD117、DOG-1阳性表达率更低. 上述特点的分子理论基础、发生机制尚未阐明, 对WT-GIST治疗及预后所知甚少, 这些问题需在全面认识WT-GIST后才能解决. 对WT-GIST的进一步分析, 预示GIST未来将进行重新分型. 为此, 本文对WT-GIST分子机制研究进展进行综述.

1 WT-GIST定义

WT-GIST为一类异质性肿瘤, 形态学符合GIST, 免疫组织化学表达或不表达CD117、CD34、DOG-1, 基因检测未发现KIT或PDGFRA突变^[1]. 美国国家综合癌症网络胃肠间质瘤诊疗指南中推荐对KIT基因外显子11、外显子9、外显子13、外显子17及PDGFRA基因外显子18、外显子12进行检测^[2], 而现有研究证实KIT/PDGFRA共44个外显子, 故实际中有38个外显子未被常规检测^[3]. Huss等^[4]报道了部分WT-GIST患者复查中发现KIT基因外显子8的突变. Dufresne等^[5]在WT-GIST中也证实KIT基因外显子10的突变. 我国一项研究, 也在WT-GIST中检测到KIT突变和PDGFRA突变^[6]. 但普遍

认为上述6种基因突变发生率高, 将44个基因全部纳入检测的实用性需要更多报道、发现后再次评定.

2 WT-GIST分子机制

WT-GIST可能的发病机制有: 琥珀酸脱氢酶B(succinate dehydrogenase B, SDHB)基因缺失、原癌基因蛋白质BRAF(rapidly accelerated fibrosarcoma B)突变、I型神经纤维瘤病(neurofibromatosis type I, NF1), 转录调控因子家族(ETS transcription factor 1, ETV1)等.

2.1 SDH缺陷型GIST SDH基因缺失的GIST称为SDH缺陷型GIST, 约50%的WT-GIST存在SDHB基因缺失, 见于90%儿童和10%成人野生型GIST^[7], 尤以女性多见, 如为SDHB缺陷导致SDHB基因启动子过度甲基化, 表现为Carney三联征, 即多发胃间质瘤、副神经节瘤、肺软骨瘤三主征^[8], 而Carney Stratakis综合征, 一种具有多发胃间质瘤、副神经节瘤倾向的遗传性疾病中SDH各亚型突变均有报道^[9]. 该型WT-GIST大多以多灶性病变分布于胃内(尤其胃窦部), 值得注意的是, SDH缺陷型GIST不依据肿瘤大小及核分裂相进行良恶性判断, 多伴淋巴结转移, 但为惰性临床过程^[10].

SDH基因编码的蛋白质以SDH复合物的形式存在于正常机体细胞线粒体内, 参与电子传递链, 完成琥珀酸像延胡索酸的转换^[11]. 该复合物由4种亚单位(SDHA、SDHB、SDHC及SDHD)以及装配因子、铁硫蛋白和辅酶Q构成. 当机体细胞发生变异, SDH表达缺失, SDH复合物失活, 促进肿瘤细胞形成. 目前SDH基因缺失导致肿瘤形成的具体机制尚未完全明确. 认为可能与琥珀酸聚集导致缺氧诱导因子(hypoxia inducible factor 1 α , HIF1- α)稳定性增强^[12-14], 激活血管内皮生长因子(vascular endothelial growth factor, VEGF)相关. 也有研究认为: 基于SDH缺陷型GIST较突变型GIST细胞DNA甲基化水平升高^[15], microRNA异常甲基化, 故与甲基化相关. 最新研究发现: SDHB缺陷型GIST中检测到胰岛素类似物生长因子1受体(insulin-like growth factor receptor 1, IGF-1R)RNA或蛋白的高表达, 因此, IGF-1R活化可能是SDHB缺陷型野生GIST的发病机制^[16-18], linsitinib作为IGF-1R高选择性的小分子抑制剂^[19], 正处于临床研究中, 期待成为

■ 研究前沿

目前, WT-GIST亟待解决的问题: (1)缺乏重要相关基因探索方向、有效药物研究; (2)众多相关基因如何有效应用于临床.

■ 相关报道

本文引用文献包含了胃肠间质瘤领域较为经典的几篇文章, 同时涵盖了近年来有关WT-GIST分子机制的最新研究, 包括动物试验、药物试验等。

SDHB缺失的野生型GIST个体化治疗选择。

胰岛素样生长因子(insulin-like growth factor, IGF)系统参与细胞周期调控及多种病理过程, 尤其是对恶性肿瘤发生起关键调节作用^[20]。IGF系统包括受体IGF-1R(IGF-1 receptor)、IGF-2R, 配体IGF-1、IGF-2以及相关结合蛋白IGF-BP(IGF-binding proteins)。IGF-1、IGF-2表达及其强度被认为与肿瘤的预后明显相关^[21,22]。IGF受体与配体结合, 参与细胞酪氨酸残基磷酸化, 转导信号, 触发抗凋亡和促增生通路^[23]。

Wei等^[24]发表的一篇个案, 报道了1例SDH缺陷型GIST女性患者伊马替尼治疗期间, 复发2次的特殊病史。该病例于第2次手术中行二代全基因测序, 发现病损细胞几乎全部检测到抑癌基因*TP53*(tumor protein P53)杂合突变。提示二代测序在靶向治疗前的重要评价作用, 可以避免长期无效药物治疗。同时提示SDH缺陷型GIST可能存在其他基因突变或者基因转变。不同于大部分SDH缺陷型GIST惰性表现, 伴异基因突变后, 肿瘤生物学行为更具侵袭性。但*TP53*基因乃至其他基因突变在SDH缺陷型GIST中的作用, 尚需要大量数据分析。

2.2 *BRAF*基因突变 *BRAF*属于丝氨酸/苏氨酸蛋白激酶RAF家族成员, 通过MAPK(mitogen activated protein kinase)信号通路调节细胞周期及细胞增殖^[25,26]。*BRAF*基因最常见的活化突变位于第15号外显子, DNA链上胸腺嘧啶取代腺嘌呤(T-A), 使氨基酸残基第600位上缬氨酸转化为谷氨酸(V600E), 常见于甲状腺乳头状癌和黑色素瘤。*BRAF*在KIT下游突变, 活化V600E, 从而使细胞在缺乏KIT指导下持续增殖, 故存在*BRAF*突变的GIST对酪氨酸激酶抑制剂不敏感, 亦或原发耐药^[27]。*BRAF*突变型GIST更易发生于女性, 多见于小肠, 常为梭形细胞型, 肿瘤显示出高度恶性倾向, 但在体积小(≤ 5 mm)或无核分裂活性的GIST也可发生*BRAF*突变。目前认为KIT/PDGFR与*BRAF*表达呈负相关。一项大宗数据研究^[28]显示, 127例野生型GIST中有7例存在*BRAF* V600E突变, 所有*BRAF*突变GIST均为野生型。Hostein等^[29]分析了321例GIST患者, 其中70例为野生型GIST, 同样有7例野生型GIST检测到*BRAF* V600E突变, KIT/PDGFR突变患者中未发现*BRAF*突变。KIT、PDGFR和*BRAF*均阴性的GIST称为

“三阴性GIST”, 足以见得*BRAF*在GIST基因研究中的重要地位。但Miranda等^[30]报道了1例伊马替尼耐药患者同时表达KIT和*BRAF*, 通过体外实验发现*BRAF*可影响KIT阳性伊马替尼敏感病例对该药的反应, 这也说明*BRAF*突变可能为酪氨酸酶抑制剂原发耐药机制, 同时也推测, *BRAF*抑制剂或可作为GIST患者新的治疗药物。近期, 首例*BRAF*突变并转移的GIST患者接受*BRAF*抑制剂dabrafenib治疗的一期试验, 该患者既往曾接受MEK抑制剂治疗, 使用dabrafenib达疾病稳定(缓解17%)8 mo后出现进展, 再次行全基因检测发现*PIK3CA*、*CDKN2*突变, 考虑*BRAF*抑制剂治疗中可能诱发新的基因突变, 导致二次耐药^[31]。美国食品药品监督管理局批准了3项靶向*BRAF* V600E药物(vemurafenib、dabrafenib、trametinib)在野生型*BRAF*突变的GIST患者进行临床研究, 后续结果值得期待。

2.3 NF1相关性GIST I型神经纤维瘤病(neurofibromatosis type I, NF1)相关性GIST:神经纤维瘤病为一种常见的常染色体显性遗传病^[32], 致病基因为17号染色体上*NF1*抑癌基因, 其编码的NF1蛋白是RAS激酶的负向调节因子, 该蛋白丢失激活了RAS及其下游激酶, 包括MEK-MAPK通路, 加之后续GIST特异性转录网络主调节基因*ETV1*的过度表达, 可能为NF1-GIST的发生机制^[33]。与正常人群相比, NF1患者GIST发病率更高, 发病年龄更年轻, 好发于小肠(包括十二指肠)。NF1患者常发展成多个原发性肿瘤, 有时与小肠Cajal细胞增生相关。部分NF1相关性GIST表达S-100蛋白, 组织学上以单纯梭形细胞形态多见, 肿瘤细胞免疫组织化学CD117呈强阳性表达。大部分NF1相关性GIST体积小, 核分裂活性低, 预后较好。Gasparotto等^[34]研究纳入22例入组前无NF1疾病诊断及临床表现的KIT/PDGFR/*BRAF*/SDH阴性GIST患者, 上述患者称为“四阴性GIST”, 发现大部分患者病变位于小肠, 女性患者偏多, 60%(13/22)“四阴性”GIST存在*NF1*基因突变, 包括错义突变、无义突变、诱导蛋白截断、剪接位点附近的突变、缺失。日本一项多中心研究纳入了1528例GIST患者, 根据NIH诊断标准确诊了18例NF1, 研究同样发现NF1患者并存GIST时, 具有多发于小肠、低核分裂相、梭形细胞多见等特点, 与单纯GIST

对比, 发病年龄、性别、肿瘤大小、复发倾向均未发现明显差异, 与多项报道相同, 该研究同样发现NF1-GIST中绝大部分为野生型, 并对伊马替尼耐药^[35]. 瑞典癌症中心流行病学统计显示, NF1患者GIST终身患病率为7%^[36], 可见, 对NF1患者需重视伴发GIST的风险.

2.4 ETV1基因突变 ETS(E26 transformation specific or E-twenty-six)家族是最大的信号依赖转录调控因子家族之一^[37,38], ETV1为ETS家族成员, 在乳腺癌、黑色素瘤、前列腺癌中表达, ETV1基因可与其他基因融合产生嵌合体蛋白导致细胞恶变. Chi等^[39]发现ETV1在GIST细胞中存在异常表达, 显著高于其他肿瘤组织. 动物模型中ETV1亦呈强表达, 敲除ETV1后, GIST起源细胞ICC出现缺失^[40], 故可认为ETV1参与GIST形成, 但ETV1在WT-GIST中表达是否具有特异性, 目前尚无足够证据证实. ETV6-NTRK3融合基因最早在婴儿纤维肉瘤中描述, 是12号染色体ETV6外显子与15号染色体NTRK3外显子发生的融合^[41]. 回顾文献, 仅有1例ETV6-NTRK3融合基因GIST, 该病例为1例44岁男性直肠GIST, 细胞学形态为上皮细胞形, 具有较高核分裂相, 表达CD117、DOG1, 基因缺乏KIT、PDGFRA、BRAF突变, 无SDHB缺陷, 为“四阴性GIST”, 手术后无病生存期>44 mo^[42]. 该文献提出: ETV6-NTRK3融合基因可能通过促进IGF1R下游级联活化、替代细胞核内IRS1通路, 实现GIST一部分发展. ETV1及其基因融合在控制WT-GIST发生、发展过程尚需要更多数据支持, 目前没有该基因的靶向药物治疗研究.

2.5 KRAS基因突变 KRAS(kirsten rat sarcoma viral oncogene homolog)是Kirsten大鼠肉瘤病毒细胞同源癌基因^[43], 与HRAS、NRAS同属RAS家族成员, KRAS编码胞内蛋白, 参与细胞增殖、分裂的信号传递, 控制GTP酶活化, KRAS突变后干扰了正常GTP酶功能. 改变了RAS-RAF-MAPK信号传导通路, 从而导致细胞过度增殖, 进一步形成肿瘤^[44]. KRAS突变常见于结肠癌、胰腺癌、肺腺癌^[45]. 仅有一些个案报道证实KRAS在GIST中存在突变, KRAS突变在GIST发生中的作用机制仍不清楚, 现有资料并未显示KRAS突变在野生型GIST中表达率高于突变型GIST. 一项514例GIST的大样本队列研究, 包含117例WT-GIST, 通过标准

PCR核酸扩增、Sanger直接检测PCR蛋白产物方法, 均未发现KRAS基因12、13号密码子在WT-GIST中的突变^[46], 推测KRAS在WT-GIST中表达阳性率极低, 也预示该基因突变可能并未参与WT-GIST发生.

2.6 其他机制 一项国内研究发现, WT-GIST二代测序最常见的5个基因突变依次为抑癌基因TP53、ROS1融合基因、NF1、ATRX(α -thalassemia/mental retardation syndrome X linked gene)和KIT, 但没有证实上述突变是否与GIST的发生相关^[6], 仍需要研究证实上述基因与GIST的相关性. Hechtman等^[47]分析了无SDHB缺陷的8例WT-GIST存在ARID1A(AT-rich interactive domain 1A gene)、TP53和KRAS等基因突变. ARID1缺失突变可增加AKT磷酸化及PI3K/AKT通路的活化, 从而使肿瘤细胞增殖, 针对该基因的靶向药物未来可能开启WT-GIST治疗新篇章. TP53突变提示无进展生存期缩短, 预后差. 降钙素受体样受体基因(calcitonin receptor like receptor gene, CALCLRL)是一种G蛋白耦联受体, 在血管瘤和胶质瘤中强表达^[48,49]. 现有研究发现CALCLRL作为肾上腺素及降钙素基因相关肽受体(calcitonin receptor like receptor, CRLR)在WT-GIST中过度表达^[50]. 另外, 22型胶原 $\alpha 1$ (collagen type X X II alpha 1, COL22A1)属于胶原蛋白家族成员, 作为细胞黏附配体分布于组织接合部位, 从而黏附皮肤上皮细胞和成纤维细胞, 该配体也在野生型GIST中过度表达^[51]. 上述两种蛋白受体的发现, 或可作为诊断WT-GIST的标记, 但报道仅包含几例患者, 大量数据仍缺乏.

3 结论

WT-GIST可能的发病机制包括SDHB基因缺失、原癌基因BRAF突变、NF1疾病相关、ETV1基因突变等, 目前研究对上述4种机制有比较详细的阐述. 另有众多报道分析了WT-GIST发生、发展的可能分子机制, 但目前没有统一观点, 诸多问题需要更多经验和探索.

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创新盘点

本文详细总结了目前对WT-GIST较为认同的观点及新近发现的分子机制研究进展, 具有较高参考意义.

■应用要点

通过对WT-GIST分子机制的明确阐述, 能够灵活有效指导临床和对科研工作中对相关基因的探索。

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同行评价

本文对于临床进一步认识野生型GIST具有参考价值, 并为今后的治疗提供一定线索。

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