doi: 10.3978/j.issn.2095-6959.2018.04.024
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2018.04.024

·综述·

KIT 基因双突变在胃肠道间质瘤中的作用

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[摘 要] 胃肠道间质瘤(gastrointestinal stromal tumors，GISTs)是胃肠道最常见的间叶源性肿瘤，KIT/PDGFRA基因是其驱动基因，伊马替尼是GISTs的一线靶向药物。长期靶向药物治疗GISTs常发生复发、耐药和转移，分子测序发现存在KIT基因双突变。GISTs中KIT或PDGFRA双突变率约为61.3%，多数研究提示双突变抑制伊马替尼与ATP区的结合，激活下游增殖通路，引起耐药及肿瘤转移；但也有文献提示KIT/PDGFRA基因双突变对伊马替尼更敏感或阻滞肿瘤的生长，表现出双相作用。

[关键词] KIT基因；双突变；胃肠道间质瘤

Role of KIT gene double mutation in gastrointestinal stromal tumors

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Abstract Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. The KIT/PDGFRA gene is the driver gene, and imatinib is a first-line target drug for GISTs. Relapse, drug resistance and metastasis of GISTs often occur in the long-term treatment of target drug. Molecule sequencing shows the double mutation in KIT gene. The double mutation of KIT or PDGFRA in GISTs is about 61.3%. The results of most studies suggest that double mutation of KIT gene inhibits the combination of imatinib and ATP domain of KIT, which activates the proliferation pathways in downstream, and causes the drug resistance and tumor metastasis. However, there are opposite conclusions that double mutation of KIT/PDGFRA gene is more sensitive to imatinib or blocks the growth of GISTs. These results shows that the double mutation of KIT gene has double phase effect on GISTs.

Keywords KIT gene; double mutation; gastrointestinal stromal tumor

收稿日期 (Date of reception)：2018–02–09
通信作者 (Corresponding author)：张声，Email: zhgshg@126.com
基金项目 (Foundation item)：福建省自然科学基金 (2015J01452)。This work was supported by Fujian Provincial Natural Science Foundation, China (2015J01452).

胃肠道间质瘤(gastrointestinal stromal tumors，GISTs)是胃肠道最常见的间叶源性肿瘤[1]，发病率为10%~35%[2-3]，占全部胃肠道恶性肿瘤中的比例<1%。美国国立卫生研究所(NIH)[4]按危险程度分级标准(肿瘤大小、核分裂象以及肿瘤发生部位)将其分为极低危、低危、中危和高危4个级别，其中直径<2 cm且核分裂象≤5个/50高倍视野(high power field，HPF)的GISTs定义为“极低危险性”，直径≤2 cm的GISTs称为小GIST(small-GIST)[5]，直径>2 cm的GISTs称为显著GIST(overt-GISTs)。临床显著GISTs患者中性别无明显差异，而在小GIST中男性更常见[6-7]。GIST临床症状常表现为吞咽困难、疲劳、腹痛、胃肠道出血或梗阻，最常见的发病部位为胃(50%~60%)、小肠(30%~35%)、直肠5%、食管<1%，约5%发现于胃肠道外，如网膜、肠系膜、腹膜后[8]。GISTs常转移到肝和腹膜(25%~30%)[9]，也有报道[10]转移到肺部和胸腔。小GIST的细胞形态温和，间质玻璃样变明显，临床表现及预后明显好于显著GIST，呈惰性自限性增生性表现[11-12]。

约77%的GISTs存在KIT驱动基因突变[1,13-14]，少数病例涉及一些原癌基因的突变，如PDGFRA(约6.5%)，SDH酶复合体(5%)，神经纤维瘤蛋白(1.3%)，Braf(2%)，RAS(罕见)和PIK3CA(罕见)，主要存在于临床显著GISTs。KIT驱动基因激活主要是由于与其配体干细胞因子结合后导致受体二聚化和激酶激活，刺激RAS/MAPK，PI3K/AKT/mTOR和JAK/STAT3信号，调节细胞增殖、黏附、迁移和凋亡等生物学过程。突变的KIT二聚化和激活是一种非配体依赖性行为[15]，自动抑制状态被破坏，导致细胞增殖不受调控而引起肿瘤发生。

伊马替尼甲磺酸是ATP结合区竞争性抑制剂，阻碍BCR-ABL，KIT和PDGFRA的激活，能显著抑制GISTs的生长，是手术不能切除或转移性GISTs的一线治疗药物[16]。KIT基因二次突变常导致长期治疗的患者发生耐药[17-24]、复发和转移，肿瘤平均进展期为12个月[25]。但也有相反的结论：一项小鼠实验研究[26]发现KIT基因双突变的肿瘤明显小于单突变的肿瘤，中位生存期延长。提示KIT基因双突变对肿瘤的作用存在双相性。笔者使用“gastrointestinal stromal tumors”“KIT”“double mutation”或“secondary mutation”或“two hit”检索词在PubMed上进行文献检索，综述KIT基因双突变对GISTs发生和发展的作用。

1 KIT 基因的分子结构

KIT原癌基因定位于人4q12-13cDNA，全长5 230 bp，开放阅读框长2 931 bp，包含21个外显子，编码的蛋白产物KIT分子质量为145 kD(1 D=1 U)，包含976个氨基酸，属于III型酪氨酸激酶生长因子受体(Src基因家族)。

KIT结构包括细胞外配体结合区、跨膜结构域、胞内酪氨酸激酶结构域[27]。胞内激酶区被激酶插入区分隔为近膜区段和远端区段(Distal)。近膜区段对激酶结构域起负调控作用，相当于KIT蛋白信号转导通路中的闸门。当两个KIT受体分子与配体干细胞因子分子形成二聚体时，蛋白构型发生改变，近膜区段负调控作用解除，激酶激活，蛋白从自动抑制状态转为激活态。

2 KIT 基因突变与肿瘤

KIT基因突变导致其表达模式和内部激酶结构发生变化[28]，使自动抑制状态解除，不依赖配体自动磷酸化，激活下游增殖通路，导致细胞增殖不受调控引起肿瘤的发生。黑色素瘤中KIT基因突变率为5%[29]，主要为肢端和黏膜黑色素瘤[30]，其突变率高达39%和36%，常伴KIT基因扩增[31-32]；女性生殖道黑色素瘤KIT基因突变也高达36.4%[33]。最常见的突变为外显子11 L576P和外显子13 K642E胚系突变[29,34]，驱动PI3K激活引起MAPK通路的活化，促进黑色素细胞增殖[35]。

在造血系统肿瘤中，KIT突变主要发生于近膜区二聚化结构域(外显子9)、近膜区段(外显子11)、ATP结合区(外显子13)和激活环(外显子17)。肥大细胞增生症的KIT突变主要为外显子17 D816V，其次为外显子9的AY502-503串联复制[36]。约63%的急性髓细胞性白血病存在KIT蛋白表达，M0和M1约69%，M5约21%[37]，M4常见KIT突变t(16;16)和t(8;22)的inv(16)或M2b，胚系突变主要影响外显子17 D816和N822位点，核心结合因子相关性急性髓系白血病(core binding factor acute myeloid leukemia，CBF-AML)常发生于外显子8 D419位点[38]，主要激活KIT下游信号PI3K和MAPK通路[39]。

在生殖细胞肿瘤中，26%精原细胞瘤存在KIT突变[40]，常见于外显子17 D816V和N822K，30%单侧卵巢无性细胞瘤存在外显子17 N822K突变[41-42]。35%~87%上皮性卵巢肿瘤存在KIT基因突变[43-44]。37.5%纵膈精原细胞瘤中发现KIT外显子17 K818R，D820V和N822K突变。KIT突变后通过激

活RAS/MEK/MAPK等通路导致细胞持续增殖[45]。

GISTs KIT突变率为75%~85%[46]，主要为外显子11(65%)，其次为外显子9(8%)，13(1%)，外显子17(1%)和外显子8(<1%)[38,46-48]。外显子11的突变包括点突变、串联复制、缺失和插入，缺失突变占66.15%，点突变占18.46%，插入突变占6.15%，点突变伴缺失突变占9.23%[49]，其中550~561及570~580密码子区为突变的热点区域，以框内缺失突变最常见，占70%~80%，病理类型主要为胃的梭形细胞亚型[50]，缺失突变的无进展生存期明显短于其他外显子11突变类型，其557和/或558缺失与恶性行为相关[51-52]。

编码细胞外区域的外显子9突变中最常见为AY502-503的6个核苷酸复制，占10%~15%，病理类型常见为小肠梭形细胞亚型，胃部罕见[50]。ATP结合区和激活环的突变少见，主要为外显子13 K642E和exon17 Y823D，N822K，常发生于肠道[53]。有学者[54]认为外显子13 K642E的突变可能为胚系来源，约70%的外显子17突变主要为N822K[53]，偶见外显子17 S821F突变[55]。突变可能干扰近膜片段自动抑制功能。

KIT突变类型与复发风险关系的研究[56]发现外显子11串联复制突变及特定点突变如W557R，V559A或L576P，复发风险较低，可不行辅助治疗。外显子9 AY503-503串联复制和外显子11 W557-K558缺失突变，在肿瘤核分裂指数低时也属低复发风险。外显子13和17突变也无较高的复发风险，而外显子17中较常见的N822K突变可能为中等复发风险[53]。纯合子外显子11的突变与恶性行为相关，转移风险超过50%，平均生存期为33个月[57]。

3 KIT 基因双突变与 GISTs

KIT可发生双突变，包括原发性和继发性(表1)。原发性双突变即在同一基因上同时存在两个突变；继发性双突变为第1次仅发现1个突变，经过一段时间后在同一基因上再发第2次突变。双突变可出现于同一外显子或不同外显子。目前对原发性双突变的文献报道较少。

3.1 KIT 基因双突变的频率、位点及类型

KIT基因双突变以继发性多见(表2)，90%的GISTs原发突变是半合子，存在1个野生型和1个突变型的等位基因，绝大多数继发性双突变都发生于原发突变的等位基因，位于不同的外显子[64]。1例报道同一外显子的原发双突变为外显子11 W557G/Y578C[58]。继发性双突变是非随机分布的[64]，最常见的继发性双突变为激活环区外显子17(54.5%)，其次为激酶I区外显子13(38.3%)，少数发生于激酶II 外显子14(13.4%)，继发性双突变热点区为外显子13 V654A，激酶II区外显子14 T670I和激活环的外显子17 C809G，D816H，D820A/E/G，N822K/Y，Y823D[46,65-68]。原发突变主要为外显子11(70.7%)和外显子9(39.2%)[24]。

表1 部分文献中报道的具体双突变基因型及其生物学行为

Table 1 Specific double-mutant genotypes and biological behavior reported in literature

双突变基因型	原发外显子	继发外显子	生物学行为
W557G/Y578C[58]	外显子11	—	对伊马替尼敏感
V560D/A829P[59]	外显子11/17	—	对伊马替尼敏感
V560D/M724A[60]	外显子11/14	—	可抑制PI3K但不抑制KIT磷酸化
V558△/T669I[26]	外显子11	外显子14	肿瘤减小、惰性生长
553-559del+V654A[61]	外显子11	外显子13	肝转移
V560D/K558N+V654A[62]	外显子11/13	外显子13	腹膜转移，肝转移
V559A+V654A[63]	外显子11	外显子13	盆腔转移

表2 继发双突变热点区及其无进展生存期

Table 2 Secondary double mutation hot spot and progression-free survival

突变位点	突变频率/%	常见基因型	无进展生存期/月
外显子13	38.3	V654A	2.3
外显子14	13.4	T670I	2.3
外显子17	54.5	C809G，D816H，D820A/E/G，N822K/Y，Y823D	7.8

3.2 KIT 基因双突变与 GISTs 的耐药性

研究[22-24,64,69,70]发现61.3%~80%进展期GISTs发生KIT或PDGFRA继发性双突变导致对伊马替尼耐药。继发性双突变通过特异性改变ATP结合激酶区的结构或稳定受体的活性构象，抑制或阻断伊马替尼的结合，导致GISTs对伊马替尼耐药[71]。

与原发突变相比，外显子13和17的继发性双突变引起磷酸化KIT(p-KIT)，p-AKT，PCNA和Bcl-2，且双突变中的p-AKT不能被伊马替尼抑制[20]。而双突变外显子11 V560D/外显子14 M724A能直接阻断PI3K与pY721(PI3K与KIT的结合位点)的结合，但不能抑制KIT的磷酸化[60]。提示通过阻断下游分子通路改善耐药需抑制KIT的磷酸化才能达到提高药物敏感性的目的。

舒尼替尼和索拉替尼能有效抑制对伊马替尼耐药的exon13和14继发性双突变引起的KIT磷酸化[72-74]，而达沙替尼对外显子13或14继发性双突变无效。在激活环区域的突变中，尼罗替尼对外显子9/17或11/17突变比舒尼替尼有更好的抑制作用，达沙替尼作用较小或没有作用，索拉替尼可拮抗外显子17继发性双突变的磷酸化，尼罗替尼可使外显子11/17双突变的疾病稳定期延长至12个月[74]。目前尚未发现能作用于所有的KIT双突变的抑制剂，PI3K/AKT是KIT下游主要的信号通路，可考虑使用PI3K抑制剂联合酪氨酸激酶抑制剂(TKI)抑制PI3K激活并消除KIT磷酸化。

有研究[58]报道1例原发性KIT基因外显子11 W557G/Y578C双突变对伊马替尼敏感，该患者核分裂象为60个/50HPF，肿物直径>5 cm，属于高风险GIST，使用伊马替尼治疗后反应良好。分析发现W557G/Y578C双突变后KIT蛋白磷酸化可被伊马替尼抑制。另1例双突变外显子11 V560D/外显子17 A829P患者亦被报道[59]对伊马替尼敏感，其IC_{50}值仅高于V560D单突变(IC_{50}=100 nmol/L) 2~3倍，提示V560D/A829P可能是比较少见的保留对伊马替尼敏感性的双突变。尽管双突变与耐药相关，但上述2例双突变者却对伊马替尼敏感。W557G/Y578C是外显子11上同一个外显子不同位点的双突变，二者单突变时所致的磷酸化可被伊马替尼减少70%，即使双突变也未改变对伊马替尼的敏感性。推测可能是两者的双突变均位于外显子11从而不影响伊马替尼结合ATP结合区(外显子13，14)，或者双突变后对药物敏感性发生叠加所致。

4 KIT 基因双突变与 GISTs 其他生物学行为的关系

4.1 双突变与肿瘤的生长

KIT基因继发性双突变后肿瘤平均进展期为12个月[25]，主要见于耐药和转移，导致肿瘤细胞增长不受控制。但也有相反的报道。Bosbach等[26]构建了一个同时携带$KIT^{V558\triangle}$(外显子11，发现于家族性GISTs)和KIT^{T669I}(外显子14对应人类KIT T670I，发现于伊马替尼耐药GISTs)的双突变小鼠，以单突变$KIT^{V558\triangle}$小鼠为对照，结果显示双突变小鼠$KIT^{V558\triangle:T669I}$较单突变$KIT^{V558\triangle}$中位生存时间延长(14个月)；双突变小鼠的肿瘤直径小于单突变的肿瘤，3个月龄小鼠中双突变肿瘤直径为单突变的1/5[(1.4±0.1) mm vs (7.0±0.3) mm，P<0.001]；盲肠自身长度明显短于单突变小鼠[(13±2) mm vs (24±2) mm，P=0.003]。提示并非所有的双突变均促进肿瘤生长，特定的突变型也具有一定的阻滞生长的作用，但其机制不清，是否为双突变阻断了主要的下游通路如PI3K/AKT或双突变使KIT激活态结构被关闭或隐藏，下游增殖通路停止或启动凋亡通路，有待于进一步研究。

4.2 KIT 基因双突变与 GISTs 的转移

KIT基因双突变与GISTs转移密切相关。Utsunomiya等[61]报道1例原发突变外显子11 553-559del在伊马替尼治疗4年后复发，发生肝转移，显示为继发性突变外显子13 V654A。另一项研究[62]发现伊马替尼治疗GISTs数月后发生肝转移和左腹膜后复发，使用二线药物舒尼替尼治疗，腹膜后复发的肿瘤被抑制，而肝转移瘤仍处于增长的状态，分子检测发现肝转移瘤既存在原发性双突变外显子11 V560D/外显子13 K558N，又存在继发性双突变外显子13 V654A，Ki-67指数更高，超过单突变的50%。1例先后发生肝转移和盆腔转移的GIST，采用伊马替尼治疗后肝转移瘤缩小，而盆腔转移瘤继续增大；测序发现肝转移瘤仍保持单突变外显子11 V559A，而盆腔转移瘤存在双突变外显子11 V559A/外显子13 V654A[63]。这些结果提示外显子13 V654A可能是一个强进展型基因型，对伊马替尼耐药后该突变再次强烈促进KIT磷酸化，引起KIT相关下游信号通路瀑布式激活，肿瘤在短时间内迅速进展与侵袭转移。

4.3 KIT 基因双突变与 GISTs 患者的预后

KIT基因继发性双突变的GISTs患者的中位无进展生存期明显低于无双突变者[75]。外显子17继发性双突变者无进展生存期短于外显子13和14双突变者，分别为2.3个月和7.8个月[75]。

5 结语

近年来涉及KIT基因双突变的研究仅停留于对复发、耐药和转移的GISTs进行基因检测以及对临床药物治疗的选择，对KIT基因双突变与GISTs细胞增殖关系的研究较少。目前的研究结果提示KIT基因双突变可能具有双相作用，涉及RAS/MAPK，PI3K/AKT/mTOR，JAK/STAT3信号通路的调节，调控细胞增殖、黏附、迁移和凋亡等，期望深入研究生物学过程发现某一位点的双突变可关闭下游激活通路或开启凋亡信号通路，阻滞肿瘤生长或对靶向治疗敏感，延长患者的生命。

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本文引用： 孟琳, 张声. KIT基因双突变在胃肠道间质瘤中的作用[J]. 临床与病理杂志, 2018, 38(4): 830-836. doi: 10.3978/j.issn.2095-6959.2018.04.024

Cite this article as: MENG Lin, ZHANG Sheng. Role of KIT gene double mutation in gastrointestinal stromal tumors[J]. Journal of Clinical and Pathological Research, 2018, 38(4): 830-836. doi: 10.3978/j.issn.2095-6959.2018.04.024