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述评 EDITORIAL

胃肠道间质瘤的分子学机制及靶向治疗

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Gastrointestinal stromal tumors: Molecular pathogenesis and targeted therapy

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Abstract

The autophosphorylation of KIT protein, resulting from gain-of-function mutations of the *c-kit* or PDGFR gene, is the most important molecular mechanism involved in the pathogenesis of gastrointestinal stromal tumors (GISTs). Imatinib is a small molecule tyrosine kinase inhibitor and is effective in the treatment of GISTs. KIT is a convenient target in GISTs, and inhibition of this receptor with imatinib (Gleevec, STI571) in GISTs has shown dramatic efficacy. Unfortunately, resistance to imatinib is a significant clinical problem. Further understanding of the molecular pathogenesis of GISTs is therefore important and may lead to the identification of novel drug targets. This review will focus on recent advances in the understanding of molecular mechanisms involved in the pathogenesis of all types of GISTs. The molecular biological characteristics of each type of GISTs will also be discussed.

Key Words: Gastrointestinal stromal tumors; Molecular pathogenesis; Targeted therapy

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摘要

C-kit/PDGFRA基因发生功能获得性突变和因此引发的KIT蛋白自主磷酸化是胃肠道间质瘤(gastrointestinal stromal tumors, GISTs)发生过程中最具特征性的分子机制. 这一发现使得imatinib靶向治疗GISTs成为可能并取得重大疗效, 但研究发现不同类型的GISTs对imatinib治疗的反应也不尽相同, 并且随着其临床应用的增加, 耐药性及不良反应也随之出现, 迫使imatinib临床停药或改为二线用药. 因此, GISTs是由不同生物学机制引发的一组疾病, 本文就GISTs的分子生物学机制及靶向治疗药物作一综述.

关键词: 胃肠道间质瘤; 分子机制; 靶向治疗

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0 引言

胃肠道间质瘤(gastrointestinal stromal tumors, GISTs)是一组由未分化、梭形或上皮样细胞组成的最常见的消化道间叶源性肿瘤(gastrointestinal mesenchymal tumor, GIMT)[1-3], 年发病率为10-15/1 000 000[4,5], 无明显区域及性别差异[5]. 诊断主要依赖免疫组织化学检测特异性表达的*c-kit*(CD117)、Dog-1和CD34. 早期、局限的GISTs主要依赖手术治疗, 但术后复发率高且对放疗、化疗不敏感. 近年来, 针对GISTs发病机制的靶向治疗药物imatinib问世, 成为了GISTs治疗的一把利剑, 但随着越来越多的GISTs患者接受imatinib治疗, 人们发现imatinib的疗效与GISTs的临床及生物学特征有关, 并且其耐药性

■背景资料
随着越来越多的胃肠道间质瘤(GISTs)患者接受imatinib治疗, 人们发现imatinib的疗效与GISTs的临床及生物学特征有关, 并且其耐药性的出现大大降低了其疗效. 基于近年其发病率有逐年增高的趋势, 明确肿瘤生物学特性与靶向药物治疗间的关系对药物耐药机制的寻找和新的靶向药物的开发具有重要意义.

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■研发前沿
尽管与传统的放化疗相比, 全新的靶向治疗模式能避免损伤正常组织而更高效、更具选择性地杀伤肿瘤细胞, 且口服给药更显便捷; 但是, 在长期的临床应用过程中, TKI也出现一些问题.

的出现大大降低了其疗效. 基于近年其发病率有逐年增高的趋势, 明确肿瘤生物学特性与靶向药物治疗间的关系对药物耐药机制的寻找和新的靶向药物的开发具有重要意义. 本文就近年来研究发现的GISTs分子学特征及靶向治疗的研究进展作一综述.

1 胃肠道间质瘤的分子学特征

1.1 配体非依赖的受体信号通路的激活

1.1.1 *c-kit*基因的突变: 人们对GISTs分子生物学特征的认识是由Hirota等[6]发现GISTs中存在*c-kit*基因突变开始的. *c-kit*基因是HZ4猫科肉瘤病毒*kit*癌基因的同源物, 位于人染色体4q11-12, 共有21个外显子组成[7]. 其编码的KIT受体蛋白属于III型酪氨酸激酶受体家族, 由976个氨基酸组成, 包括3个基本结构区: 由5个免疫球蛋白样结构域构成的胞外配体结合区、胞内酪氨酸蛋白激酶活性区以及连接这2个区域的跨膜区. 正常情况下KIT受体胞外区的第1、2、3结构域与其配体干细胞因子(stem cell factor, SCF)结合, 使胞外区第4、5结构域结构发生改变[8,9], 受体从细胞膜上解离、迁移、聚集, 形成二聚体, 进而促发酪氨酸激酶及其效应分子磷酸化, 调控KIT的下游底物包括MARK、JAK/STAT等多条信号转导通道, 产生一系列的级联反应[10], 最终活化胞质内的转录因子, 调控基因表达、控制细胞生长、增殖和分化. 当*c-kit*基因发生突变时则无需SCF配体参与, 自主形成二聚体, 活化酪氨酸激酶即激活配体非依赖的信号通路, 致使肿瘤细胞的持续增殖和抗凋亡信号的失控, 引发恶性肿瘤. 在CD117阳性的GISTs中, *c-kit*基因总突变率为76.1%, 突变形式主要表现为点突变、缺失, 偶见插入突变, 范围可涉及一个或多个密码子. 其中约67.1%的突变发生在编码近膜区的exon11, 绝大多数位于外显子近端的密码子Gln550-Glu561之间[11-13], 最常见的是密码子Trp557和Lys558的缺失. 此外, 还有约20%-30%为错义突变, 几乎都独立发生在近端的Trp557、Val559、Val560和远端的Leu576. 其次是编码胞外区的exon9的突变, 突变率为7.1%, 突变类型主要是编码Ala502-Tyr503的6个核苷酸的复制[14]. 此外也有编码酪氨酸激酶区Ⅰ的exon13、14及酪氨酸激酶区Ⅱ的exon16、17突变的报道, 所占比例分别为1.3%和0.6%[11]. 影响GISTs预后的因素很多, 目前主要将肿瘤的大小及有丝分裂计数作为主要的危险度分级指标[15], 但许多研究发现*c-kit*基因突变主要发生于恶性倾向较大的GISTs, 恶性倾向较小GISTs罕有突变, 且突变位点与预后有关[16-19]. 一般认为发生于exon11的Trp557和Lys558的缺失多预后不良, 发生于胃部的错义突变的病例预后好于发生缺失突变的病例, 而在小肠却无此差异[20-22], 因此提示*c-kit*基因的突变与GISTs预后存在密切关系[23]. 对此, 我们也做过类似研究, 结果显示发生在exon11的总突变为41.5%, 低于恶性组(54.8%)[24,25]. 此外, *c-kit*基因突变与GISTs的组织学分型及发生部位也存在一定的联系, 即发生*c-kit*基因突变的GISTs多表现为梭形细胞型[19,26], 且exon11的突变多导致胃部GISTs, 而exon9的突变多见于小肠[11].

1.1.2 PDGFRA基因的突变: 随着GISTs分子生物学特征研究的深入, 2003年Heinrich等[27]又在40例*c-kit*突变阴性的GISTs中检测到了15例PDGFRA基因的活化突变(35%), 提示PDGFRA突变可能是GISTs发生的另一分子机制. 血小板源性生长因子受体(platelet derived growth factor receptor, PDGFR)包括α和β两种, 编码基因分别为PDGFRA和PDGFRB, 各自与其配体血小板源性生长因子(platelet derived growth factor, PDGF)的α和β两个链结合, 从而发挥调节细胞生长、分化的作用. PDGFRA基因位于*c-kit*基因的下游(4q12)[28], 其蛋白产物PDGFRa也属于III型酪氨酸蛋白激酶家族. 与*c-kit*基因突变相同, PDGFRA基因突变也是功能获得性突变, 在缺乏配体结合的情况下, 自主二聚化激活配体非依赖信号通路, 引起ICC的转化亦或是通过激活野生型KIT蛋白在细胞中的共表达[29]. PDGFRA基因突变主要发生在编码酪氨酸激酶区Ⅱ的exon18和编码跨膜区的exon12, 发生率分别为5.6%和1.5%[30-32]. 点突变是exon18最常见的突变形式, 突变集中在841-847位点, 主要为D842V突变, 其次为缺失突变. 本实验组对上海长海医院2006-2007年间25例GISTs病例进行检测, 亦发现5例存在PDGFRA突变的病例中有4例均位于上述热点位置.

与*c-kit*基因突变一样, PDGFRA突变的GISTs也有其独特的临床特征. 相较于*c-kit*突变的GISTs, 大多数PDGFRA突变的肿瘤生物学行为呈良性, 预后良好, 且PDGFRA缺失或缺失加点突变比单纯点突变更多地显示出恶性生物学行为. 在发生部位上, 超过95%的PDGFRA突变的GISTs发生于胃、肠系膜或者网膜, 在病理形

态上, 大多数PDGFRA突变的GISTs表现为上皮细胞, 少数为混合型[32]. 但也有学者认为PDGFRA突变的GISTs多发生于后腹膜且具有高度侵袭性[33]. 因此PDGFRA基因突变与GISTs预后的关系仍需大样本的长期观察.

1.2 配体依赖的SCF/KIT受体信号通路的激活 大约仍有14%的GISTs未检测到*c-kit*和PDGFRA基因突变, 称为野生型GISTs(wild-type GISTs). 但在这些野生型GISTs中却存在着KIT酪氨酸激酶被激活的情况, 因此有专家认为可能是与IGF1R、BRAF或KRAS等其他基因的突变导致KIT配体SCF的自分泌或旁分泌[34], 引起“配体依赖的受体信号通路激活”有关, 包括下游PI3K信号通路, 激活最终效应蛋白Akt调节细胞抗凋亡作用[35], 而并非*c-kit*或PDGFRA突变所致. 关于这部分野生型GISTs中KIT酪氨酸激酶的激活, 国外基础研究证实为野生型KIT受体的激活, 特别是Tabone-Eglinger等[36]在共聚焦显微镜下观察到GISTs中突变型KIT受体蛋白主要积聚在内质网或高尔基体(突变型KIT), 而野生型KIT受体蛋白多定位于细胞膜表面(野生型KIT), 这为野生型GISTs中配体依赖的SCF/KIT受体信号途径的激活提供了良好的佐证. 更重要的是, 国外学者发现绝大多数GISTs是*c-kit*杂合性突变, 而这些病例中仍然有野生型KIT蛋白的表达[37], 并且*c-kit*基因的突变状态与KIT下游磷酸化程度并不相关, 他们将此现象归因于配体依赖的SCF/KIT信号通路也是GISTs的发病机制[38]. 对此, 我们的研究也发现, 无论是否存在*c-kit*/PDGFRA基因突变, 几乎所有的GISTs组织中都存在KIT受体的激活及其配体SCF的高表达, 其中KIT突变阴性的GISTs主要表现为野生型KIT受体(145 kDa), KIT突变阳性的GISTs同时存在野生型KIT受体(145 kDa)和突变型受体(125 kDa).

在靶向药物imatinib(glivec、gleevec、STI-571)治疗GISTs取得重大疗效的同时, 临床研究却表明, 相较于突变型GISTs, 大部分imatinib对野生型GISTs无抑制作用[39], 仅12%的野生型GISTs能够获得部分缓解. 更重要的是, 我们的研究发现长时间的imatinib作用会引起配体SCF的表达增强从而促进GISTs中野生型KIT的活化, 从而导致imatinib治疗无效. 类似研究也证实GISTs中存在SCF的自分泌途径[40], 且imatinib无法抑制配体依赖SCF/KIT通路的KIT受体磷酸化[41], 这也是imatinib治疗GISTs后产生耐药的主要原因[39,42-44].

2 胃肠道间质瘤的靶向治疗及耐药

GISTs是一种对传统化放疗高度抗拒的肿瘤, 手术是首选治疗方案, 但手术只是局限性治疗GISTs的手段, 即使完整切除肿瘤原发灶, 仍有50%的患者在2年内复发或转移, 且复发率呈逐年上升趋势. 对于这些已复发、转移和不能手术的GISTs患者, 人们发现以imatinib为代表的小分子酪氨酸激酶抑制剂(tyrosine kinase inhibitors, TKI)可以特异性阻断酪氨酸激酶的激活, 从而有效诱导GISTs肿瘤消退[45]. 目前对GISTs患者采用外科手术联合靶向药物治疗的治疗模式已达成共识.

2.1 典型的治疗GISTs酪氨酸激酶抑制剂类药物

2.1.1 含嘧啶结构的酪氨酸激酶抑制剂: imatinib为苯氨嘧啶的衍生物[46,47], 最初主要用于慢性粒细胞性白血病(chronic myelogenous leukemia, CML)的治疗, 后将其应用于GISTs, 发现80%患者的病情得到控制[48-50]. 其抗肿瘤的机制是因其分子结构类似于ATP, 能够竞争性地结合KIT蛋白的ATP结合位点, 阻滞酪氨酸激酶的磷酸化, 抑制下游信号通路的传导, 从而阻止细胞的增殖和肿瘤的形成. 有研究证实imatinib能够有效抑制KIT蛋白的活化及抑制存在*c-kit*突变的GISTs细胞系增殖[22,51], Ⅰ期和Ⅱ期临床药物试验也发现每日给予400 mg imatinib治疗的有效率可达70%以上[52,53], 随后进行的Ⅲ期临床试验也肯定了每日400 mg的给药剂量的安全性和有效性[54,55]. 更重要的是, 几乎所有的大型临床试验均发现, imatinib能够使70%-85%的晚期GISTs患者的中位无进展生存时间延长到20-24 mo, 并使晚期GISTs患者的中位总生存期延长至36 mo[54,55]. 但imatinib只能与活化状态的ATP结合位点结合, 有其局限性, 故仅为高效而非特效的抗肿瘤药[56]. 且不同的基因突变位点对imatinib治疗敏感性不同, 发生*c-kit*的exon11突变型GISTs一般对imatinib敏感, 而exon9突变以及PDGFRA突变型GISTs对imatinib不敏感, 特别是在野生型GISTs病例中, 有限剂量的imatinib无法完全抑制除KIT或PDGFRA之外的其他酪氨酸激酶通路的开放, 使细胞增殖信号绕过imatinib的抑制而下传, 造成细胞增殖. 我们的研究也发现imatinib会促进GISTs中SCF的表达, 而导致配体依赖的SCF/KIT途径的信号通路的开放, 使其发生耐药成为必然. imatinib的不良反应除贫血、白细胞减少、疲劳、水肿、皮肤潮红及胃肠道反应外[54], 还有心力衰竭等心血管毒性反应[57-59].

2.1.2 含吲哚结构的酪氨酸激酶抑制剂: sunitinib

■相关报道

有报道表明, GISTs的imatinib敏感性与分子伴侣热休克蛋白90(HSP90)、IGF1R及其配体IGF1和IGF2、胰岛素样生长因子相关蛋白3(IGFBP-3)、组蛋白H2AX有关, 与相关抑制剂合用, 下调HSP、IGF1R、IGF1、IGF2及IGFBP-3, 亦或使H2AX上调, 都能使imatinib介导的细胞凋亡反应性增强, 但与临床的相关性还需进一步阐明.

■同行评价
本文对GISTs的分子学特征及其类型, 靶向治疗药物的原理机制及耐药情况进行了综述, 从基础到临床应用较全面, 有一定指导意义.

是一种新型含吲哚结构的口服多靶点酪氨酸激酶受体抑制剂, 临床所用的是*L*-苹果酸盐. 与imatinib相比, 能阻断更多个酪氨酸激酶受体, 更强效抑制PDGFRA、KIT和血管内皮生长因子受体[60]. 这提示他不仅能在分子水平上抑制KIT酪氨酸激酶的活性, 还能干扰肿瘤细胞发展形成新生血管的能力, 阻止新生血管的生长. 同时, 与imatinib相似, sunitinib的临床疗效与基因突变位点有关. 但不同的是, 他对KIT的exon9突变者效果最好, 对exon13和14突变者也有疗效, 对exon11突变者的效果欠理想[61]. 因此适用于imatinib治疗失败或不能耐受的GISTs患者[20,50,62]. 高血压、出血及血栓栓塞是其主要不良反应.

2.1.3 含噻唑结构的酪氨酸激酶抑制剂: masitinib (AB1010)是苯基-氨基噻唑型TKIs. 相较于imatinib有更强的阻断KIT激酶活性和选择性, 他能阻断表达野生型及近膜区*c-kit*突变的GISTs肿瘤细胞的增殖. Ⅰ期临床实验表明每天12 mg/kg的剂量为有效[63]. 除此之外, masitinib对其他的酪氨酸、丝氨酸和苏氨酸激酶阻断活性较差. 这种高选择性预示着masitinib比其他TKIs具有更加安全的效用[64]. 事实上, 在动物体内实验, 几乎检测不到masitinib诱导产生的心脏或遗传性毒性. 所以, masitinib是一种强效且高选择性的酪氨酸激酶阻滞剂, 并且呈低毒性[65,66].

2.1.4 增加酪氨酸激酶抑制剂敏感性研究: 有报道表明GISTs的imatinib敏感性与分子伴侣热休克蛋白90(hot shocking protein-90, HSP90)[67]、IGF1R及其配体IGF1和IGF2[67,68]、胰岛素样生长因子相关蛋白3(IGFBP-3)[69]、组蛋白H2AX[70]有关, 与相关抑制剂合用, 下调HSP、IGF1R、IGF1、IGF2及IGFBP-3, 亦或使H2AX上调, 都能使imatinib介导的细胞凋亡反应性增强, 但与临床的相关性还需进一步阐明.

2.2 靶向治疗的优缺点 尽管与传统的放化疗相比, 这种全新的靶向治疗模式能避免损伤正常组织而更高效、更具选择性地杀伤肿瘤细胞, 且口服给药更显便捷. 但是, 在长期的临床应用过程中, TKI也出现一些问题.

首先是耐药性的出现. 在治疗的最初6 mo内肿瘤进展称为原发性耐药, 治疗6 mo后出现耐药为继发性, 发生耐药的机制主要为基因的二次突变. 但Janeway、Théou-Anton和Negri等[38,40,71]学者研究证实肿瘤细胞还可通过SCF/KIT自-旁分泌所引起的“配体依赖的受体信号通路的激活”来逃离药物的靶向治疗. 我们也做过类似研究, 发现几乎所有的GISTs组织中都存在野生型KIT受体(145 kDa)的激活, 且imatinib能刺激SCF表达, 激活大量野生型KIT受体引发肿瘤.

其次, 不能长期、有效控制GISTs的发展达到根治. 尽管TKI治疗GISTs取得巨大成功, 但是罕有TKI治疗GISTs达到完全缓解(CR: 是指肿瘤完全消失, 在4 wk后得到确证)病例的报道, 这主要是肿瘤通常不止一处突变, 而不同的TKI只能针对其中的一种或者几种突变起作用, 无法抑制所有类型突变所导致的受体活化[72]. 同时在应用TKI控制病变的患者中应持续用药, 如一旦停止治疗, 大部分患者病情会在短期内迅速进展[73], 对此, 有专家认为是TKI的应用大大增加*c-kit*二次突变的概率[74].

最后是安全性的提高. 因目前用于治疗GISTs的TKI为多靶点抑制剂, 能抑制细胞内多条信号传递途径, 其分子机制可能导致潜在的不良反应[75]. KIT同时还存在于造血细胞、黑素细胞等正常细胞中, 故在应用过程中不可避免出现正常细胞出现的骨髓抑制、胃肠道反应等.

3 结论

随着分子生物学技术不断、快速地推动生命科学的发展, 人类对于肿瘤的研究也随之进入了后基因组时代, 尤其是新型生物及靶基因治疗等无创治疗逐渐取代既往有创的手术及放化疗在肿瘤治疗中的应用, 更是现代肿瘤研究中的重大突破. 但是TKIs治疗GISTs过程中的缺陷是其本质所决定的, 并且改变剂型或增加药物剂量都不能解决, 尤其是对SCF/KIT自-旁分泌所导致的肿瘤, 很难获得有效、理想、安全的酪氨酸靶向抑制药物, 这使得GISTs的靶向治疗再一次面临难以逾越的鸿沟, 直至应用二聚化受体阻断抗体戴默赛特(Dimercept, Herstatin)在小鼠实验中成功拦截HER同源及异源二聚体的形成并抑制所有HER受体(HER1/EGFR、HER2/ErbB2、HER3/ErbB3和ErbB4)引发的信号连锁反应, 有望弥补赫赛汀(Herceptin)耐药的不足, 为肿瘤分子靶向治疗开拓了一片全新的前景[76]. 应用这一研究思路, 阻断KIT-dimer的形成可以同时阻断配体依赖和配体非依赖的两条信号通路, 从而解决imatinib耐药性使GISTs的分子靶向治疗达到根治.

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• 消息 •

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