·综　述·

软组织肉瘤的分子靶向治疗研究进展

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［摘要］　软组织肉瘤是一类起源于间叶组织的罕见恶性肿瘤，在中国，软组织肉瘤的发病率为1.15/10万人每年，且呈上升趋势。根据世界卫生组织分类，这种恶性肿瘤包含了超过100种不同的组织学亚型，许多分子畸变普遍存在于一些特定的亚型中，但很少有可用于治疗的靶点。软组织肉瘤的一线治疗方案仍然局限于传统的外科手术和化疗，而不是利用分子标志物作为靶点进行治疗。随着对不同组织学亚型发病潜在的分子、基因组机制的了解，促进了软组织肉瘤靶向治疗的发展。将对目前研究较多的软组织肉瘤亚型的靶向治疗进展作一综述。

［关键词］ 软组织肉瘤；靶向治疗；分子通路；靶点

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Advances in molecular targeted therapies for soft tissue sarcomas

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［**Abstract**］ Soft tissue sarcomas (STS) are rare malignant tumors arising from mesenchymal tissues and have an overall incidence of about 1.15/100 000 per year. According to the World Health Organization classification, over 100 distinct histological subtypes have been categorized, many molecular aberrations are prevalent within specific sarcoma, and very few are therapeutically targeted. Instead of utilizing molecular markers as targets, first-line sarcoma treatment options are still limited to traditional surgery and chemotherapy. Current understanding of the underlying molecular and genomic mechanisms of different histology subtypes have led to encouraging development of targeted therapy for STS. In this review, we explained and summarized the current molecular targeted therapies in development for the most common studied subtypes of soft tissue sarcoma.

［**Key words**］ Soft tissue sarcomas; Targeted therapies; Molecular pathways; Target

软组织肉瘤是一类罕见的肿瘤，尽管其治疗效果在过去几十年内得到了很大提升，但软组织肉瘤的治疗和新药研发仍是一大难题。单药多柔比星是目前治疗晚期软组织肉瘤的首选方法，对于二线治疗和后期治疗尚无标准，目前临床上最常用于软组织肉瘤的靶向药物主要有：血管靶向药物、以信号转导通路分子为靶点的药物以及免疫靶向药物，而不同组织学亚型对各种靶向药物的敏感性存在明显差异。

1　平滑肌肉瘤

平滑肌肉瘤（leiomyosarcoma，LMS）是常见的软组织肉瘤之一，占所有软组织肉瘤的10%~20%，常发生在子宫、四肢、小肠及腹膜后[1]。由于半数以上的早期患者在治疗后复发，LMS需要更多新的治疗方法，在既往研究中，抗血管生成药物对LMS有良好的疗效，主要包括小分子酪氨酸激酶抑制剂及单克隆抗体。帕唑帕尼是一种多靶点酪氨酸激酶抑制剂，在其用于治疗软组织肉瘤的首次多层设计Ⅱ期研究中，LMS队列中41例患者在接受治疗12周时的无进展生存率（progression-free rate，PFR）为44%[2]，在另一项回顾性研究中，帕唑帕尼作为第2或第3线治疗药物，LMS组临床获益率超过40%，非子宫平滑肌肉瘤患者中位总生存期（overall survival，OS）达12.9个月，子宫平滑肌肉瘤患者则为16.5个月[3]。对于蒽环类药物治疗后进展的LMS患者，接受索拉非尼治疗在6个月时PFR为38.4%[4]，

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有研究报道索拉非尼联合达卡巴嗪也是一种有效、安全的治疗方案[5-6]，与索拉非尼结构相似的瑞戈非尼，也可改善晚期LMS患者的无进展生存期（progression-free survival，PFS）[7-8]。此外，舒尼替尼用作一线治疗时具有活性[9]，但用作子宫平滑肌肉瘤的第二或第三线治疗时效果不佳[10]。另一种强效多靶点酪氨酸激酶抑制剂安罗替尼，具有优于舒尼替尼、索拉非尼的抗血管生成作用[11-12]，先前的一项Ⅱ期临床研究探索了安罗替尼在常规治疗失败后的软组织肉瘤中的活性，26例LMS患者在治疗12周时PFR为69.23%[13]。单克隆抗体中，有研究发现奥拉单抗联合多柔比星对比多柔比星单药可显著改善晚期软组织肉瘤的中位OS，且该研究纳入的患者中有38%诊断为LMS[14]，但目前研究发现贝伐珠单抗、西妥木单抗在该病中疗效不太理想[15-17]。除上述的血管靶向药物外，细胞周期蛋白依赖性激酶（cyclin-dependent kinase，CDK）4/6抑制剂帕博西林、抗程序性死亡受体1（programmed cell death protein 1，PD-1）单克隆抗体纳武单抗也可能对其有效[18-19]。

2 脂肪肉瘤

脂肪肉瘤（liposarcoma，LPS）约占所有成人肉瘤的20%，是一组异质性很高的恶性肿瘤，形态学上分为4个亚型：分化良好型、去分化型、黏液样、多形性脂肪肉瘤，目前的治疗方式包括手术、放化疗，但80%的病例发生复发[20]，目前已在LPS中发现较多靶点，其中在高分化及去分化LPS中均发现存在CDK4扩增，Zhang等[21]给异种移植人类LPS的小鼠口服CDK4抑制剂，发现肿瘤生长被抑制甚至出现肿瘤消退，这为临床应用开发提供了理论依据。美国食品药品管理局批准的第一个CDK4抑制剂帕博西林，在有CDK4扩增及视网膜母细胞瘤肿瘤抑制蛋白（retinoblastoma protein，pRb）表达的晚期高分化/未分化LPS患者中，治疗12周时PFR为66%，中位PFS为4.5个月[22]，另一项对60例晚期LPS患者使用帕博西林的研究也得到了相似结果[23]。此外，部分抗血管生成药物也显示出活性，接受帕唑帕尼治疗的转移性LPS患者在12周时PFR为68.3%，且在24周时有39%的患者保持无进展，44%的患者的肿瘤得到了控制（部分反应或疾病稳定），中位PFS为4.4个月，中位OS为12.6个月[24]，但在另外两项Ⅱ期研究中，帕唑帕尼对LPS疗效有限[2, 25]。在安罗替尼的Ⅱ期研究中LPS队列12周时的PFR为53.83%[13]，研究者发现舒尼替尼对LPS有效，接受单药舒尼替尼治疗时，中位PFS为3.9个月，中位OS为10.1个月[9]。除上述小分子抑制剂以外，LPS患者还可能从奥拉单抗、西妥木单抗的治疗中获益[14-15]。

3 滑膜肉瘤

滑膜肉瘤（synovial sarcoma，SS）占青壮年软组织肉瘤的10%~20%，多发生在四肢，最常见的远处转移灶是肺，广泛的外科切除加辅助或新辅助放疗是其主要治疗手段。然而，该病有早期和晚期复发的倾向，其特点是18号染色体与X染色体发生平衡易位，这在任何其他人类肿瘤中都没有发现[26]。在过去的几年里，尽管人们花了很多精力来设计更有效、毒性更小的治疗SS患者的方法，但帕唑帕尼仍是唯一经批准用于治疗标准细胞毒性药物治疗失败后的软组织肉瘤的靶向药物。在一项Ⅱ期临床研究中，37例SS患者在治疗12周时的PFR为49%，在后续的Ⅲ期临床试验中，相比其他组织学亚型，SS组的中位PFS和OS更有前途，但由于数量相对较少，在该亚型中并未观察到差异有统计学意义[2, 27]。帕唑帕尼联合异环磷酰胺的Ⅰ期临床试验报道了两例SS患者获得部分缓解[28]。除帕唑帕尼外，临床中新的靶向治疗药物，如安罗替尼、瑞戈非尼、索拉非尼也显示出有希望的结果。在安罗替尼的Ⅱ期研究中，47例SS患者第12周时PFR为63.83%[13]，研究小组进一步进行了ⅡB期研究，试验组的整体反应率和疾病控制率都显著高于对照组[29]。尽管单药索拉非尼在SS组的疗效非常有限[30]，但联合达卡巴嗪时，获得了令人鼓舞的结果[6]。一项探索瑞戈非尼对蒽环类药物耐药的软组织肉瘤患者疗效的Ⅱ期研究中，SS队列中瑞戈非尼组与安慰剂组对比，中位PFS分别为5.6和1.0个月[7]。CDK4抑制剂帕博西林在SS细胞系的体外实验中能有效地抑制pRb磷酸化，导致增殖阻滞，这表明CDK4/6抑制剂可能是一种潜在的治疗方法[31-32]。此外，SS还可能在免疫治疗中获

益，一项帕姆单抗治疗软组织肉瘤的Ⅱ期研究中，1例SS患者出现反应[33]，Robbins等[34]发现以肿瘤-睾丸抗原-1（NY-ESO-1）为靶点的免疫治疗在SS中疗效显著，18例患者中有11例获得客观疗效。

4　横纹肌肉瘤

横纹肌肉瘤（rhabdomyosarcoma，RMS）是一种众所周知的儿科疾病，在成人中，它占所有恶性实体瘤的不到1%，横纹肌肉瘤可发生于全身各部位，头部、颈部、泌尿生殖系统、躯干和四肢相对常见。该肿瘤有三个主要的组织学亚型为：胚胎性、腺泡型和多形性横纹肌肉瘤[35]。到目前为止，RMS的靶向治疗进展仍不乐观，以往的一项研究显示RMS细胞系对胰岛素样生长因子（insulin-like growth factor，IGF）1的小分子抑制剂敏感[36]，但单药西妥木单抗在RMS队列的第12周无进展生存率仅为12%，最终因无效而在第一阶段结束之后关闭[15]。后来Guenther等[37]发现使用雷帕霉素靶蛋白抑制剂PI103联合有丝分裂原激活蛋白激酶激酶（mitogen-activated protein kinase kinase，MEK）抑制剂UO126对RMS细胞系有高度协同触发凋亡的活性，而只使用一种药物时未能引起细胞死亡。此外，一项阿帕替尼对Ⅳ期软组织肉瘤疗效的回顾性研究中，给药一个月后有8例患者达到部分缓解，其中1例为RMS（共纳入2例）[38]。有病例报道称克唑替尼在有间变性淋巴瘤激酶（anaplastic lymphoma kinase，ALK）基因融合突变的肉瘤患者中观察到活性[39]，虽然RMS中也查见了*ALK*基因突变，但这些改变不同于易位，在临床前试验中，ALK抑制剂似乎对横纹肌肉瘤无效[40-41]。

5　血管肉瘤

血管肉瘤（angiosarcoma，AS）是一种内皮细胞来源的软组织肉瘤，最常见的发病部位为头颈部皮肤，尤其是头皮。最近的一些研究发现血管靶向药物在控制AS方面显示出希望[42]。这些药物包括帕唑帕尼、索拉非尼、贝伐珠单抗等。帕唑帕尼的一项回顾性研究中，AS是临床获益率较高的组织学亚型[3]，而且帕唑帕尼对血管内皮生长因子受体2（vascular endothelial growth factor receptor 2，VEGFR2）水平升高的皮肤AS患者疗效更佳，VEGFR2高表达组的中位OS为7.2个月，而低表达组仅为2.3个月[43]。Mehren等[44]开展的索拉非尼治疗晚期软组织肉瘤的Ⅱ期研究中，AS组患者有更长时间的临床获益，中位PFS为5个月，索拉非尼在蒽环类药物治疗后进展的患者中，AS组也比其他组织学亚型控制更好[4]。有研究[5]还发现，索拉非尼联合达卡巴嗪治疗接受过二线及以上化疗的5例AS，结果在6个月时均未出现进展。一项关于贝伐珠单抗在AS（23/30例）和上皮样AS（7/30例）患者中的Ⅱ期研究表明，9%的AS患者出现部分缓解，48%保持病情稳定，中位PFS为6.5个月，而且这些患者对贝伐珠单抗的耐受性良好[45]。除血管靶向药物外，在化疗后进展的AS中使用依维莫司有较高的疾病控制率[46]，也有病例报道称个别AS患者在接受帕姆单抗后出现部分缓解[47-48]。

6　尤文肉瘤

尤文肉瘤（Ewing's sarcoma，ES）是一种与神经外胚层相关的恶性肿瘤，常发生在儿童和青壮年中，男性多见，常见的原发部位有椎旁区、胸壁及下肢，其发病与血管内皮生长因子、IGF等通路相关，这些特征为靶向治疗研究提供了方向[49]。一项血管内皮生长因子抑制剂阿帕替尼治疗软组织肉瘤的回顾性研究中，ES组的中位持续反应时间为2.0个月，客观缓解率为70%[50]。学者们还发现ES患者体内IGF信号通路有所上调，从而促进肿瘤发生、发展，但西妥木单抗单药在ES中仅观察到有限的活性[15,51]，当与哺乳动物雷帕霉素靶蛋白抑制剂（替西罗莫司）联合时则疗效可观[52]，随后研究者进行了进一步研究，在17例ES患者中，有5例发生了超过20%的肿瘤消退，且持续8~27个月[53]，IGF-1受体表达情况不能预测这种联合治疗的临床结果[54]。目前，ES的免疫靶向治疗成果不甚理想，一项Ⅱ期研究中，13例患者接受帕姆单抗治疗均无客观反应[33]。

7　腺泡状软组织肉瘤

腺泡状软组织肉瘤（alveolar soft part sarcoma，ASPS）十分罕见，占全部软组织肉

瘤不足1%，常见于成人下肢及儿童头颈部。很多患者以肿瘤出现肺或脑转移为首发症状，特异性染色体易位导致转录因子E3（transcription factor E3，TFE3）与腺泡状软组织肉瘤候选基因（candidate gene for alveolar soft part sarcoma，ASPSCR1）发生融合，最近发现ASPSCR1-TFE3融合蛋白具有促进血管生成和细胞增殖的作用，提供了一种有前途的治疗靶点[55]。血管靶向药物安罗替尼，在常规治疗失败后的ASPS患者中的第12周PFR为76.92%[13]，进一步研究发现，ASPS是生存期增加最多的组织学亚型，安罗替尼组中位PFS为18.23个月，对照组仅3个月[29]。血管内皮生长因子受体酪氨酸激酶抑制剂西地尼布对ASPS具有显著的单药活性，还可导致与血管生成相关的基因下调[56-57]。此外，也有报道称舒尼替尼、阿帕替尼、帕姆单抗对ASPS具有可观的活性[58-60]。

8 孤立性纤维瘤

孤立性纤维瘤（solitary fibrous tumor，SFT）是一种纤维母细胞间质肿瘤，几乎在每个解剖部位都可见。目前手术切除仍是治疗的金标准，放疗和传统化疗药物的疗效有限[61]。近年研究发现，帕唑帕尼在作为一线治疗转移性SFT时疗效可观，中位OS为13.3个月，46%的患者达到部分缓解，36%维持疾病稳定[62]，作为二线或三线治疗时，中位OS为13.2个月[3]。另外索拉非尼也可能是一种有效的药物，在5例转移性或不可切除的SFT患者中，2例患者实现了超过9个月的疾病控制[63]。另一血管靶向药物，舒尼替尼在治疗晚期SFT的研究中，中位PFS为6个月，中位OS为16个月[64]，此外，伊马替尼在具有t（17；22）染色体易位的纤维肉瘤中有较好的临床反应[65]。

9 胃肠道间质瘤

胃肠道间质瘤（gastrointestinal stromal tumor，GIST）是胃肠道最常见的间质肿瘤，由*KIT*基因突变驱动，虽然手术切除是最佳的治疗方法，但以酪氨酸激酶抑制剂为基础的靶向治疗已经彻底改变了治疗选择：伊马替尼可作为晚期转移性患者的一线治疗；术后高危患者的辅助治疗；切除前缩小大肿瘤的新辅助治疗制剂[66-67]。但耐药性的出现改变了一些治疗方案，包括延长用药时间，增加药物剂量或改用二线药物。其他较新的酪氨酸激酶抑制剂，如舒尼替尼和瑞戈非尼，可能为伊马替尼耐药的患者提供一些治疗选择[68]。在伊马替尼和索拉非尼治疗失败的高级别GIST中，瑞戈非尼具有显著的活性，临床获益率达79%[69]，原发性*KIT*1号外显子突变及琥珀酸脱氢酶缺乏的患者获益更显著[70]。另外，西地尼布在进展期GIST的Ⅱ期临床研究中，11例患者有8例持续疾病稳定超过4个月[56]。

10 未分化多形性肉瘤

未分化多形性肉瘤（undifferentiated pleomorphic sarcoma，UPS）曾称为恶性纤维组织细胞瘤（malignant fibrous histiocytoma，MFH），是一种罕见的梭形细胞肿瘤，可发生于身体任何部位[71]。19例UPS患者在接受安罗替尼治疗后，12周时PFR为47.37%[13]，而使用舒尼替尼治疗的患者，中位PFS为4.2个月，中位OS为13.6个月[9]。此外，阿帕替尼对其可能有效[38]，一项回顾性研究中，UPS队列的中位持续反应时间为5.6个月[50]，既往的一些研究还发现奥拉单抗[14]、利达福罗莫司[72]对UPS有效。

11 其他类型

软组织肉瘤的组织学亚型众多，除上述几种亚型，部分软组织肉瘤因发病率低、相关的临床研究缺乏，其相应的靶向治疗效果仅在个别案例中有报道。隆突性皮肤纤维肉瘤（dermatofibrosarcoma protuberans，DFSP）是一种罕见的间质性肿瘤，起源于真皮，特点是携带17号和22号染色体易位，伊马替尼是目前治疗不可切除或转移性DFSP的首选药物[73]。炎性肌纤维母细胞瘤（inflammatory myofibroblastic tumor，IMT）是一种临床表现多样的间质肿瘤，患者多为儿童及青少年，50%的IMT患者存在*ALK*基因重排[74]，Butrynski等[39]发现克唑替尼在这类患者中表现出活性。血管周围上皮样细胞瘤（perivascular epithelioid cell tumor，PEComa）可见于全身各处[75]，前体细胞目前尚不清楚[76]。其结节性硬化症基因突变所致的雷帕霉素靶蛋白通路激活，为PEComa患者的靶向治疗提供了机会[77]，既往报道称雷帕霉素靶蛋白抑制剂西罗莫司及替

西罗莫司对这类患者具有可观的疗效[77-78]。

12 结语

由于软组织肉瘤的遗传、组织学多样性，成人软组织肉瘤的治疗需要多学科的方法来达到最佳的效果。在过去的30年里，与其他恶性肿瘤相比，软组织肉瘤的靶向治疗及免疫治疗进展相对缓慢。但这一趋势正在改变，进一步的发展和研究终将改变软组织肉瘤的治疗策略和治疗选择。最后，作者已将目前研究相对较广泛的软组织肉瘤及其对应的靶向治疗药物对照表归纳于表1。

表 1 软组织肉瘤的靶点、靶向药物

Tab. 1 Soft tissue sarcoma type, target and medicine

Sarcoma type	Target	Medicine
LMS	VEGFR, PDGFR	Pazopanib
	VEGFR, PDGFR, c-Kit	Sorafenib
	VEGFR, PDGFR, BRAF, FGFR	Regorafenib
	VEGFR, PDGFR, FGFR, c-Kit	Anlotinib
	PDGFR	Olaratumab
LPS	CDK4	Palbociclib
	VEGF, PDGFR, KIT, FLT-3	Sunitinib
	VEGFR, PDGFR	Pazopanib
SS	VEGFR, PDGFR	Pazopanib
	VEGFR, PDGFR, FGFR, c-Kit	Anlotinib
	VEGFR, PDGFR, BRAF, FGFR	Regorafenib
RMS	VEGFR	Apatinib
	mTOR + MEK	PI103+UO126
AS	VEGFR, PDGFR	Pazopanib
	VEGFR, PDGFR, c-Kit	Sorafenib
	VEGF	Bevacizumab
	mTOR	Everolimus
ES	VEGFR	Apatinib
	PDGFR + mTOR	Cixutumumab+sirolimus
ASPS	VEGFR, PDGFR, FGFR, c-Kit	Anlotinib
	VEGFR, c-Kit	Cediranib
	VEGFR	Apatinib
	VEGF, PDGFR, KIT, FLT-3	Sunitinib
SFT	VEGFR, PDGFR	Pazopanib
	VEGFR, PDGFR, c-Kit	Sorafenib
	VEGF, PDGFR, KIT, FLT-3	Sunitinib
	PDGFR, c-kit	Imatinib
GIST	PDGFR, c-kit	Imatinib
	VEGF, PDGFR, KIT, FLT-3	Sunitinib
	VEGFR, PDGFR, BRAF, FGFR	Regorafenib
	VEGFR, c-Kit	Cediranib
	VEGFR, PDGFR, FGFR, c-Kit	Anlotinib
	VEGF, PDGFR, KIT, FLT-3	Sunitinib
UPS	VEGFR	Apatinib
	PDGFR	Olaratumab
	mTOR	Ridaforolimus

VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; BRAF: *B-Raf* and *v-Raf* murine sarcoma viral oncogene homolog B; FGFR: Fibroblast growth factor receptor; SCFR/c-Kit: Mast/stem cell growth factor receptor; FLT-3: Fms-like tyrosine kinase 3; mTOR: Mammalian target of rapamycin; CDK4: Cyclin-dependent kinase 4; MEK: Mitogen-activated protein kinase kinase

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