

人源肿瘤异种移植模型在罕见癌症中的应用进展

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摘 要: 随着早期诊疗、靶向药物和免疫疗法的普遍应用, 大部分常见癌症的5年生存率都有较明显的提升。相比于常见癌症, 罕见癌症由于其发病率较低, 长期缺乏足够的关注度。然而, 基于庞大的人口总数, 罕见癌症的发病数依然是不容忽视的, 但有效治疗手段的缺失使得罕见癌症患者的预后不佳。罕见癌症的研究难点之一在于癌种群体分散, 样本量较小, 难以进行相关的临床研究。而患者来源的异种移植模型可有效保存患者样本, 高度模拟原发肿瘤, 是研究罕见癌症的有利工具。就罕见癌症的概念和人源肿瘤异种移植模型在不同类别的罕见癌症如腺样囊性癌、胆管癌、肛管癌、恶性间皮瘤、罕见妇科癌症、睾丸癌、黑色素瘤、恶性胚胎肿瘤、脊索瘤、胃肠胰神经内分泌肿瘤、肾上腺皮质癌、胶质母细胞瘤、血液系统恶性肿瘤中的应用进展进行综述, 以期探索罕见癌症发病机制及开发更具有前景的抗罕见癌症药物提供参考。

关键词: 罕见癌症; 人源肿瘤异种移植模型; 腺样囊性癌; 胆管癌; 肛管癌; 恶性间皮瘤; 罕见妇科癌症; 睾丸癌; 黑色素瘤; 恶性胚胎肿瘤; 脊索瘤; 胃肠胰神经内分泌肿瘤; 肾上腺皮质癌; 胶质母细胞瘤; 血液系统恶性肿瘤

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Application of patient-derived xenografts model in rare cancers

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Abstract: With the prevalence of early diagnosis and treatment, targeted drugs and immunotherapy, the 5-year survival rate of most common cancers has improved more significantly. Compared with common cancers, rare cancers have long lacked sufficient attention due to their lower incidence. However, based on the large population, the incidence number of rare cancers is still not negligible, but the lack of effective treatments makes the prognosis of patients with rare cancers poor. One of the difficulties in the research of rare cancers is the dispersed cancer population and small sample size, which makes it difficult to conduct relevant clinical studies. Patient-derived xenograft models, on the other hand, can effectively preserve patient samples and highly mimic primary tumors, making them a favorable tool for studying rare cancers. In this paper, we review the concept of rare cancers and the progress of the application of patient-derived xenograft models in different categories of rare cancers, such as adenoid cystic carcinoma, cholangiocarcinoma, squamous cell carcinoma of the anal canal, malignant mesothelioma, rare gynecological cancers, testicular cancer, melanoma, malignant embryonal tumors, chordoma, gastroenteropancreatic neuroendocrine neoplasms, adrenocortical carcinoma, glioblastoma, and hematologic malignancy, with the aim of providing an opportunity to explore the pathogenesis of rare cancers and to develop more promising and effective models for the study of rare cancers. We hope to provide reference for exploring the pathogenesis of rare cancers and developing more promising anti-rare cancer drugs.

Key words: rare cancers; patient-derived xenograft model; adenoid cystic carcinoma; cholangiocarcinoma; anal canal cancer; malignant mesothelioma; rare gynecological cancers; testicular cancer; melanoma; malignant embryonal tumors; chordoma; gastrointestinal and pancreatic neuroendocrine tumors; adrenocortical carcinoma; glioblastoma; hematological malignant neoplasm

罕见癌症的定义目前还没有统一标准, 美国国家癌症研究所(NCI)将每年发病率低于15/10万的癌症定义为罕见癌症, 根据该定义, 除肺癌、乳腺

癌、子宫癌、卵巢癌、肾癌、膀胱癌、前列腺癌、结肠癌、直肠癌、黑色素瘤和非霍奇金淋巴瘤外的成人癌症和全部的儿科癌症均为罕见癌症^[1]。而欧洲国

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家将患病率低于6/10万的癌症定义为罕见癌症^[2]。根据欧洲国家的定义,日本、韩国和中国台湾地区的相关机构对近些年的患者进行统计,发现上述地区的罕见癌症发病率与欧洲国家相近^[3]。尽管作为一个整体,罕见癌症约占所有癌症诊断和死亡数量的25%,但是具体到单个病种,其发病率较低,患者又分散在各个地区,给临床研究带来了很大困难^[4]。由于缺乏诊疗指南和有针对性的治疗药物,同常见癌症的患者相比,罕见癌症患者的平均5年相对生存率明显较低(65% vs 47%)^[2]。因此,罕见癌症研究领域迫切需要更多的关注和开发更多的治疗手段。

由于细胞系存在着无法模拟肿瘤微环境、长期培养易丢失原发特征、交叉污染等不足,基于细胞系的抗肿瘤研究实际转化有很大的不确定性,因此,可以一定程度上模拟肿瘤微环境并保持原发部位肿瘤特征的患者来源的异种移植(PDXs)模型近年来得到越来越多的研究和应用^[5-8]。通过将患者手术或活检中获取的肿瘤组织剪切为2~3 mm³的组织块或消化为单细胞悬液,然后移植到免疫功能缺陷的小鼠腋下、背部、肾包膜等处,从而建立PDXs模型。PDXs模型充分保留了人源肿瘤的结构特征,包括各类型细胞间及细胞与基质间的相互作用等,使其在模拟人体肿瘤组织增殖、侵袭、转移、血管生成、免疫抑制等方面具有独特优势。随着样本的积累和技术的进步,包含罕见癌症在内的PDXs模型也逐渐丰富起来,为了资源共享,欧洲的EurOPDX联合会以及美国NCI均建立了相应的患者衍生模型库(PDMR),可为各国的研究人员提供多种不同的PDXs模型,以便在机制探索和药物开发中获得高质量数据,从而推动更有前景的抗罕见肿瘤药物的发现^[9]。

目前根据罕见癌症的发生部位,可分为12个家族:头颈部肿瘤、消化道肿瘤、胸部肿瘤、女性生殖系统肿瘤、泌尿和男性生殖系统肿瘤、皮肤癌和非皮肤黑色素瘤、胚胎肿瘤(以各类母细胞瘤为主)、肉瘤、神经内分泌肿瘤、内分泌肿瘤、中枢神经系统肿瘤和血液系统恶性肿瘤^[10]。本文对PDXs模型在不同罕见癌症中的应用进展情况进行综述,以期探索罕见癌症发病机制及开发更具有前景的抗罕见癌症药物提供参考。

1 PDXs模型在不同罕见癌症中的应用

1.1 腺样囊性癌

腺样囊性癌是一种罕见的、具有高复发率和远

处转移率的侵袭性癌症,发病率约4.5/10万,通常起源于头颈部的唾液腺^[11-12]。虽然疾病进程缓慢,且手术和放疗对其有一定作用,但针对转移性的腺样囊性癌尚无有效的化疗药物^[13]。Moskaluk等^[14]进行23次移植尝试,成功建立了17个腺样囊性癌PDXs模型,并通过免疫组化生物标志物和RNA微阵列分析发现PDXs模型高度保留了供体肿瘤的特征,而MYB基因的重排或融合可能是导致腺样囊性癌发生发展的重要因素。Andersson等^[15]发现VX-970通过抑制MYB的下游ATM和Rad3相关(ATR)激酶的方式,减缓了腺样囊性癌相关PDXs模型的肿瘤生长。Prabakaran等^[16]发现将放疗和鼠双微体同源基因2(MDM2)抑制剂AMG 232联用可以增强对P53野生型腺样囊性癌PDXs模型的肿瘤生长抑制作用。

1.2 胆管癌

胆管癌是起源于胆管上皮的异质性恶性肿瘤,约占所有胃肠道癌症的3%,其发病率在不同地区有较显著的差异,亚洲地区的发病率在3.1/10万人~85/10万人,而欧美地区的发病率仅为0.4/10万人~3.4/10万人^[17]。胆管癌的预后很差,其5年总生存率较低,从2%(已发生转移)~25%(可切除)不等^[18]。目前,及时地进行手术和肝移植是有可能治愈胆管癌的,但在晚期胆管癌中,可供选择的有效的全身疗法极为有限^[19]。Vaeteewoottacharn等^[20]利用冷冻组织成功建立了12个胆管癌PDXs模型,成功率为75%,并且这些皮下肿瘤保留了与患者组织相同的组织学结构。Garcia等^[21]建立了1组CCA-PDXs模型,并发现JQ1,一种溴结构域(bromodomain)抑制剂可以有效抑制其中1种PDXs模型小鼠肿瘤的增长。Saha等^[22]通过应用IDH突变的肝内胆管癌PDXs模型,成功验证了他们在高通量筛选中观察到的现象,即达沙替尼对IDH突变的肝内胆管癌细胞表现出惊人的杀伤能力。

1.3 肛管鳞状细胞癌

肛管鳞状细胞癌约占所有胃肠道恶性肿瘤的2.7%,其全球发病率呈逐年上涨的趋势^[23-24]。至少90%的肛管鳞状细胞癌患者与感染人乳头瘤病毒(HPV)有关^[25-26]。10%~20%的肛管鳞状细胞癌患者会发生远处转移,有回顾性研究发现这部分患者的中位无进展生存期在7~16个月^[27]。对于这部分患者和占总数20%~30%的复发患者来说,目前仍缺乏有效的治疗药物^[28]。Morris等^[29]成功利用

肝转移的肛管细胞癌组织构建了PDXs模型并进行药效学相关试验,进而发现西妥昔单抗较未治疗的对照组相比,可明显减小小鼠的肿瘤体积,而磷脂酰肌醇3-激酶(PI3K)抑制剂阿培利司则无明显治疗效果。

1.4 恶性间皮瘤

恶性间皮瘤是一种罕见癌症,起源于肺(胸膜)、心脏、腹膜或睾丸的间皮层,发病率占全部癌症类型中的0.2%,而死亡率0.3%^[30]。因20世纪石棉制品的广泛使用,目前恶性胸膜间皮瘤是欧美国家的主要间皮瘤亚型,约占90%,腹膜间皮瘤约占10%,其余类型的间皮瘤占比极低^[31-32]。尽管间皮瘤发病率低,但是因缺乏有效的治疗手段,患者的预后很差,急需进行相关疾病进程和药物治疗等方面的研究^[33]。Chen等^[34]成功建立了2个恶性胸膜间皮瘤的PDXs模型,进而利用代谢组学分析发现这些PDXs模型中存在着氨基酸、三羧酸循环、糖酵解以及核苷酸等代谢失调的情况。Yang等^[35]则发现阿帕替尼可以有效地抑制肿瘤细胞对恶性胸膜间皮瘤PDXs模型裸鼠膈下和肝脏侵袭。Wu等^[36]选用了50名恶性胸膜间皮瘤患者的肿瘤组织进行PDXs模型的构建,并成功建立了20个PDXs模型,之后对其中的10个进行了顺铂和培美曲塞治疗的药效学试验,对其中的9个进行了基因组的分析,此外还观察到能成功建立PDXs模型的肿瘤组织来源患者预后较差。

1.5 罕见妇科癌症

罕见妇科癌症每年粗发生率约为22.73/10万人,在罕见癌症中的发病率仅次于血液系统恶性肿瘤,严重威胁女性健康,随着HPV疫苗在预防和治疗常见妇科癌症中的应用,罕见妇科癌症开始受到了更多的关注^[10]。子宫浆液性癌是一种罕见的妇科癌症,Xiao等^[37]发现H3K27去甲基化抑制剂GSK-J4治疗后可明显抑制子宫浆液性PDXs模型小鼠肿瘤部位的P16INK4A表达,提示其可能有一定的治疗作用。卵巢成熟囊性畸胎瘤是一种罕见的妇科恶性肿瘤,Tamauchi等^[38]利用取自1名32岁的卵巢成熟囊性畸胎瘤患者的肿瘤组织成功建立了卵巢成熟囊性畸胎瘤PDXs模型。乳腺外佩吉特病是一种罕见的附件肿瘤,Kitamura等^[39]发现CDK4/6抑制剂阿贝西利或哌柏西利能显著抑制乳腺外佩吉特病PDXs模型小鼠的肿瘤生长,提示CDK4/6抑制剂可能是治疗乳腺外佩吉特病的新型有效药物。

1.6 睾丸癌

睾丸癌是年轻男性中最常见的实体肿瘤,好发于欧美国家。尽管其5年生存率高达95%,但是以手术为主、化疗为辅的治疗手段依然会带来一些副作用,比如生育功能丧失及睾酮缺乏等^[40]。因此,依然需要开发新的治疗手段。de Vries等^[41]尝试使用8例患者的肿瘤组织进行睾丸癌PDXs模型的构建,最终成功建立了3种PDXs模型,进一步分析表明,尽管PDXs模型小鼠肿瘤组织存在一定程度上的小鼠细胞浸润,但基本保持了原发肿瘤的免疫组化特征。Rosas-Plaza等^[42]发现将顺铂和哺乳动物雷帕霉素靶蛋白1/2(mTOR1/2)抑制剂联用可以有效抑制化疗敏感或耐受型睾丸癌PDXs模型小鼠肿瘤体积的增长,其机制可能与增强细胞凋亡有关。

1.7 黑色素瘤

皮肤黑色素瘤的发病率近年来上升较快,其不同人种和地区间存在很大差异,澳洲的发病率最高,达到每年31/10万人~42/10万人,其次是西欧(19/10万人)、北美(14/10万人~18/10万人)和北欧(17/10万人~18/10万人),而包括中国在内的大多数亚非国家,皮肤黑色素瘤仍然很罕见,年发病率通常低于1/10万人^[43]。因此,在欧美国家,皮肤黑色素瘤不算是罕见癌症,而在中国,其依然可以视为罕见癌^[44]。发于肢端、葡萄膜和黏膜的黑色素瘤其发病率更低,如葡萄膜黑色素瘤发病率仅为每年0.5/10万人,在世界范围内均归为罕见癌^[45]。随着治疗方法的发展,在欧洲,葡萄膜黑色素瘤的5年生存率达68.9%,黏膜黑色素瘤的生存率也达到了40.6%,尽管如此,依然需要对罕见黑色素瘤的防治进行进一步研究^[46]。Decaudin等^[47]发现采用Bcl-2/XL/W抑制剂ABT263与MDM2抑制剂HDM201联用可提升6种葡萄膜黑色素瘤PDXs模型客观缓解率(ORR),表明不同药物联用可能对葡萄膜黑色素瘤的治疗有一定意义。Xu等^[48]发现80%以上的黏膜黑色素瘤患者存在至少1种CDK相关基因的拷贝数变异,而广谱CDK抑制剂AT7519和特异性CDK4/6抑制剂PD0332991对CDK4信号通路异常的黏膜黑色素瘤PDXs的肿瘤生长抑制作用明显高于CDK4信号通路正常细胞,表明CDK可能成为黏膜黑色素瘤的1个靶点。

1.8 恶性胚胎肿瘤

儿科恶性胚胎肿瘤是由在胎儿和/或产后发育过程中尚未完成终末分化过程的细胞群体引起的。

神经母细胞瘤、视网膜母细胞瘤、肾母细胞瘤和肝母细胞瘤这4类恶性胚胎肿瘤是目前在儿童早期最常见的肿瘤类型,约占儿童癌症的20%^[49]。Brackeveldt等^[50]建立了原位神经母细胞瘤PDXs模型,并对模型进行了核磁共振、生物标志物、全基因组基因分型阵列分析等的研究,发现PDXs模型保留了患者特异性的未分化肿瘤组织学、增殖能力及染色体畸变。Aerts等^[51]利用视网膜母细胞瘤PDXs模型来观察光敏剂对小鼠肿瘤的抑制作用,并发现不同的光敏剂及不同PDXs模型的基因组背景对疗效有较大影响。Monzavi等^[52]发现在连续传代的肾母细胞瘤PDXs模型中发现了移植物抗宿主情况的发生,并讨论了预防方法。Bondoc等^[53]通过免疫组化、RNAseq、单细胞转录图谱等比较了肝母细胞瘤PDXs模型和肝母细胞瘤患者肿瘤组织,发现PDXs模型可以忠实地反映肝母细胞瘤的特征,包括蛋白和基因表达的变化,并发现AXIN2和FANCD2表达上调可能预示肝母细胞瘤PDXs模型的成功建立。

1.9 脊索瘤

脊索瘤是沿轴向骨骼和颅底发生的罕见恶性骨肿瘤,其总发病率约为0.08/10万^[54]。目前关于脊索瘤缺乏高质量的临床试验证据,同时也缺乏有效的化疗药物,急需相关模型进行针对性的研究^[55]。Passeri等^[56]建立了12个脊索瘤的PDXs模型,并发现所有的PDXs模型都与组织来源患者保持了相同的肿瘤组织病理学特征,进而观察到Zeste 增强子同源物2(EZH2)抑制剂Tazemetostat可以有效抑制占模型总数25%的PBRM1纯合缺失型PDXs模型的肿瘤生长,表明了EZH2抑制剂对这一脊索瘤亚型的治疗具有一定前景。Scheipl等^[57]发现表皮生长因子受体(EGFR)抑制剂Sapitinib可以有效抑制脊索瘤PDXs模型SF8894的肿瘤生长。Salle等^[58]发现与肋部接种相比,在靠近腰骶的部位接种,建立脊索瘤PDXs模型的成功率更高,组织学和免疫染色分析还证实PDXs模型重现了所来源的原发性肿瘤的特征,部分PDXs模型的肿瘤还展示出了一定程度的骨侵袭。

1.10 胃肠胰神经内分泌肿瘤

胃肠胰神经内分泌肿瘤(GEP-NENs)与常见的胃肠胰腺癌不同,其特征是上皮管状腺结构的丧失以及神经内分泌标志物的弥漫性表达。GEP-NENs大致分为2种组织病理学亚型:胃肠胰神经内分泌肿瘤(GEP-NETs)和胃肠胰神经内分泌癌(GEP-NECs)^[59]。随着内窥镜筛查的普及,GEP-NENs的

发现率逐年上升,近30年间,美国的GEP-NENs从每10万人中的1.09例增加到5.25例^[60]。尽管对可采用根治性手术切除进行治疗的患者而言,其5年生存率很高,但无法采用根治性切除治疗的患者仍然缺乏有效的治疗手段^[61-62]。Tanaka等^[63]成功建立了2种GEP-NECs的PDXs模型,并观察到PDXs模型中各种激素肽的免疫组化表达水平与原发肿瘤基本相同,同时其血清胰高血糖素和血清素显著高于对照小鼠。Jiang等^[64]发现构建的胃神经内分泌癌PDXs模型具有VEGF高表达和较高的肺转移倾向,而顺铂可以通过抑制化疗敏感性循环肿瘤细胞来抑制这种肺转移倾向和原发肿瘤的生长。

1.11 肾上腺皮质癌

与可能影响到10%人口的肾上腺良性肿瘤相比,肾上腺皮质癌的发病率极低,据估计每年为0.7/100万人~2/100万人,而其5年生存率仅为35%。除手术治疗外,米托坦是唯一被美国食品药品监督管理局(FDA)批准用于治疗肾上腺皮质癌的药物,但综合多项研究结果分析,其响应率只有不到30%,急需开发新的治疗手段^[65]。Kiseljak-Vassiliades等^[66]成功构建了CU-ACC1和CU-ACC2这2个肾上腺皮质癌的PDXs模型,RNA测序和免疫组织化学均证实新建的PDXs与来源的患者肿瘤表达相同的肾上腺皮质标志物。Kar等^[67]用这2种模型进行药物筛选,并发现靶向盘状同源区域(PDZ)连接激酶(PBK)的小分子抑制剂HITOPK032可显著抑制CU-ACC1这种PDXs模型的肿瘤生长。Lang等^[68]则发现帕博利珠单抗可以抑制人源化CU-ACC2-PDXs模型小鼠的肿瘤生长,且原发患者也对帕博利珠单抗表现出一定的响应,表明PDXs模型可以一定程度上模拟原发肿瘤的生物学特征。

1.12 胶质母细胞瘤

胶质母细胞瘤是最常见的原发恶性脑肿瘤,占有所有胶质瘤的57%,占有所有原发性中枢神经系统恶性肿瘤的48%^[69]。胶质母细胞瘤具有较高的异质性,常规疗法会产生抗原阴性肿瘤细胞逃逸,导致治疗效果不理想,Choe等^[70]发现在携带EGFRvIII异质表达的胶质母细胞瘤PDXs模型小鼠中,单次静脉输注采用逻辑门设计的EGFRvIII synNotch CAR-T细胞可以在识别EGFRvIII之后特异性地杀伤EphA2和IL13Rα2阳性的肿瘤细胞,显示出比传统的CAR-T细胞更高的抗肿瘤疗效和持续性,且无瘤外杀伤作用,较好地解决了肿瘤异质性的问题。Vaubel等^[71]则通过构建96种包括IDH

野生型、IDH突变型、H3 K27M突变型在内的胶质母细胞瘤PDXs模型,并对其进行全外显子组测序、RNA测序和全基因组甲基化分析,进而归纳出了胶质母细胞瘤的分子异质性,并概括了显著的遗传和表型特征,为相关的研究打下基础。

1.13 血液系统恶性肿瘤

各类罕见血液系统恶性肿瘤的总发病率为27.73/10万人/年,居罕见癌症各大类之首^[10]。与实体瘤常规采用皮下移植的方式不同,血液系统恶性肿瘤PDXs模型还可以采用尾静脉或骨内注射人源肿瘤细胞的方式建立,在移植前还可对小鼠进行亚致死剂量的辐照以提高成功率。因血液系统恶性肿瘤的分类极为复杂,不同疾病类型的PDXs模型建立时还需进行相关的探索性试验以确定最佳条件。2022年世界卫生组织(WHO)第五版造血与淋巴组织肿瘤分类^[72-73]对血液系统恶性肿瘤按规格级别、细胞谱系等进行了分类更新,主要可分为髓系增殖性疾病和肿瘤、树突细胞/组织细胞肿瘤、B细胞增殖性疾病和肿瘤、T和NK细胞增殖性疾病和肿瘤、淋巴组织间质源性肿瘤和遗传肿瘤综合征。

婴儿(小于1岁)急性淋巴细胞白血病是儿童血液系统恶性肿瘤中最具侵袭性的类型之一,Kerstjens等^[74]发现伊立替康可完全阻断2种*MLL*基因重排婴儿急性淋巴细胞白血病PDXs模型中的肿瘤细胞扩增。Lin等^[75]利用PDXs模型进行体内成簇规律间隔短回文重复序列(CRISPR)筛选,发现肌醇转运蛋白SLC5A3和E3连接酶MARCH5可能是急性髓系白血病中较有转化研究意义的靶点。慢性粒单核细胞白血病是一种以外周血单核细胞增多为特点的罕见白血病,Hunter等^[76]发现从是否获益的角度来讲,慢性粒单核细胞白血病PDXs模型可以较好地反映鲁索替尼治疗的效果。套细胞淋巴瘤是一种罕见的非霍奇金淋巴瘤亚型,Kagiyama等^[77]发现一种新的EZH1/2抑制剂,OR-S1,对伊布替尼耐药的套细胞淋巴瘤患者肿瘤建立的PDXs模型具有抗肿瘤作用。Mundy-Bosse等^[78]发现DNA低甲基化剂,5-氮杂胞苷可能通过使NK细胞发育基因重新表达和调控NK细胞表型分化从而延长了结外NK/T细胞淋巴瘤PDXs模型小鼠的生存期。多发性骨髓瘤是一种克隆浆细胞异常增殖的恶性肿瘤,Yue等^[79]人给予硼替佐米耐药的多发性骨髓瘤PDXs模型小鼠抗CD47抗体,发现肿瘤生长被显著抑制,通过流式细胞术分析,观察到肿瘤相关巨噬细胞从M2型转化为M1样的类型,表明CD47抗

体在多发性骨髓瘤治疗中可能通过影响肿瘤相关巨噬细胞发挥作用。

2 PDXs模型的不足

尽管PDXs模型展现了较好的保真度和适用性,其也存在着一些不足,比如,不同癌症PDXs模型的建立成功率存在较大的差异^[20]。此外,还存在人源淋巴瘤污染的情况,如Kalavaska等^[80]发现睾丸生殖细胞肿瘤(TGCTs)-PDXs模型小鼠的肿瘤组织在免疫组化检测中没有保持与原发性肿瘤相同的特征,进而发现可能是患者异种移植样本中的肿瘤浸润淋巴细胞(TIL)在植入免疫缺陷型小鼠体内后形成了淋巴瘤,造成了PDXs模型建立成功的假象。另外,PDXs模型还无法被用于评估肿瘤免疫疗法^[81]。而大部分罕见肿瘤PDXs模型的构建和研究仅局限于少数实验室,没有得到更广泛的应用和推广也是阻碍PDXs模型在罕见癌症研究中应用的一个原因。

3 结语及展望

最近几年,mini-PDXs模型、人源化小鼠PDXs模型、患者来源的类器官模型等新的手段也开始被应用于越来越多的研究中,更广泛全面的关于PDXs模型的合作也在不断推进中,尽管PDXs模型存在一些问题,但是随着方法的不断完善及机制的深入研究,再结合其他模型和算法,其依然可以为罕见癌症的研究提供大量有用的信息,并为人类健康事业的发展贡献一份力量^[18, 82-84]。

利益冲突 所有作者均声明不存在利益冲突

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