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·述　　评·

异种肝移植的挑战与机遇

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【摘要】器官移植是治疗终末期器官衰竭最有效的方式，但供器官的严重匮乏导致许多患者在等待移植的过程中死亡。随着基础研究的突破、基因编辑技术的发展和新型免疫抑制剂的问世，异种移植被视为解决供器官短缺问题最具潜力的方式。近些年，国内外研究人员在非人灵长类动物（NHPs）、脑死亡患者，终末期心力衰竭、终末期肾病和晚期肝癌患者上陆续开展了多项研究，但免疫排斥反应和凝血功能障碍等诸多问题仍限制着受者的生存，也阻碍着异种移植在临床应用方面取得实质性突破。因此，本文系统地回顾了当前国内外异种移植研究的最新进展，聚焦异种肝移植后免疫排斥反应和凝血功能障碍等问题的解决策略。

【关键词】基因修饰猪；异种移植；异种肝移植；免疫排斥反应；凝血功能障碍；共刺激阻断剂；跨物种感染；生理不兼容

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Challenges and opportunities of liver xenotransplantation

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【**Abstract**】Organ transplantation is the most effective treatment for end-stage organ failure. However, donor shortage leads to many patients dying while waiting for transplants. With breakthroughs in basic research, advancements in gene editing technologies, and developments of new immunosuppressive drugs, xenotransplantation is regarded as the most promising solution to address the organ shortage crisis. In recent years, researchers both domestically and internationally have conducted multiple studies on non-human primates (NHPs), brain-dead donors, and patients with end-stage heart failure, end-stage renal disease, and advanced liver cancer. Nevertheless, challenges such as immune rejection and coagulation dysfunction continue to limit recipient survival, hindering significant breakthroughs in the clinical application of xenotransplantation. This review summarizes the latest developments in xenotransplantation research globally, with a focus on immune rejection and coagulation dysfunction following liver xenotransplantation.

【**Keywords**】Genetically modified pig; Xenotransplantation; Liver xenotransplantation; Immune rejection; Coagulation dysfunction; Co-stimulation blocker; Cross-species infection; Physiologic incompatibility

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0 引言

器官移植是治疗终末期器官衰竭最有效的手段。中国每年新增器官衰竭患者超30万例，只有不足2万例可接受器官移植，许多患者在等待供器官的过程中死亡[1]。异种移植被视为解决供器官短缺最具潜力的方式，并被Science评选为“全球最值得关注的前沿医学问题”。

20世纪初，外科医生多次尝试将野生型（Wild Type，WT）猪、猴等动物器官移植给器官衰竭患者，受者多于术后数日内死亡[2]。后续，得益于硫唑嘌呤、泼尼松和他克莫司等免疫抑制剂问世，并应用于临床异种肾、心、肝移植，受者预后得到改善，生存时间显著延长，提示异种移植物长期有功能存活是有可能实现的[3-6]。

21世纪初，Lai等[7]通过基因编辑技术敲除了猪细胞表面的α-1,3-半乳糖苷酶（α-1,3-Galactosidase，α-Gal），基本避免了猪–灵长类动物异种移植后的超急性排斥反应。随着科学家对猪CD46和CD55等位点基因编辑改造，供器官人源化水平进一步提升。与此同时，新型免疫抑制（共刺激分子阻断剂）也极大地缓解了异种移植后的免疫排斥反应，应用抗CD40单抗的异种心、肝移植受者生存时间分别延长至146 d和29 d[8-9]。

随着基因编辑技术的发展，对猪基因进行多位点（>10基因）改造成为可能。2020年，全球首个13基因编辑猪于中国问世，初步奠定了新一代临床异种移植供体猪的雏形[10]。同年，西京医院窦科峰院士团队[11]也成功实施了上述13基因编辑猪–恒河猴肝心肾多器官联合移植，植入肝脏的受者存活26 d，为该领域的研究提供了强有力的支持。随后，Jayme教授团队[12]将10基因编辑猪肾成功植入脑死亡患者体内，肾脏正常工作74 h，异种肾移植正式迈向临床发展的过渡阶段。更值得关注的是，世界首例猪–人异种心脏移植和异种肾脏移植先后于美国马里兰大学医学中心和麻省总医院完成，开辟了基因编辑猪在异种器官移植领域的新纪元[13-15]。

与心脏、肾脏相比，受限于肝脏复杂的生理功能，异种肝移植的发展较为缓慢。2024年1月，宾夕法尼亚大学医疗团队通过器官灌注系统，首次运用69基因编辑猪肝脏，在体外支持脑死亡患者肝功能达72 h，为肝衰竭患者带来了新的希望[16]。同年3月，窦科峰院士团队[17]将多基因编辑猪肝植入脑死亡患者体内，术中移植肝恢复血流后即刻分泌胆汁，未见超急性排斥反应，且已持续工作10 d，引领中国异种肝移植研究迈向全球前列。随后，安徽医科大学与云南农业大学合作，成功将转基因猪肝植入巨大肝癌患者体内，术后移植物功能良好，患者状态稳定，助推异种肝移植研究走向临床[18]。与此同时，董家鸿院士团队[19]将基因编辑猪肝、肾联合移植入脑死亡患者体内，术后移植物血流良好，胆汁、尿液流出。免疫排斥反应和凝血功能障碍是目前阻碍异种肝移植受者生存最主要的原因，而有效的药物治疗和供体的基因编辑改造是解决上述问题的重要方式。因此，本文系统性回顾了国内外异种移植临床、临床前研究进展（见表1），聚焦异种肝移植后免疫排斥反应和凝血功能障碍等问题的解决策略。

表1 异种移植临床、临床前研究

Table 1 Clinical and preclinical research on xenotransplantation

年份	器官	供体	受者	药物治疗方案	存活时间	参考文献
1966	肝	WT黑猩猩	人	HC	<1 d	[6]
1968	肝	WT猪	狒狒	Aza、Cs	3.5 d	[20]
1970	肝	WT猪	恒河猴	ATG	<1 d	[21]
1970	肝	WT猪	黑猩猩	ATG	<1 d	[22]
1992	肝	WT狒狒	人	FK 506、PDN、PG	70 d	[3]
1994	肝	WT猪	猕猴	α-Gal depletion、WBI、ATG、猪BMTx	3 d	[23]
1998	肝	WT猪	恒河猴	CsA、CTX、Cs	<1 d	[24]
1998	肝	WT猪	狒狒	sCR1	<1 d	[25]

续表

年份	器官	供体	受者	药物治疗方案	存活时间	参考文献
2000	肝	hCD55猪	狒狒	CsA、CyP、Cs	8 d	[26]
2005	肝	hCD55、hCD59、HT猪	狒狒	CyP、Daclizumab、Cs、RTX、CsA、MMF	1 d	[27]
2010	肝	GTKO猪	狒狒	ATG、Tac、MMF、Cs	6 d	[28]
2010	肝	GTKO、hCD46猪	狒狒	CyP、Tac、MMF、Cs	7 d	[28]
2012	肝	GTKO猪	狒狒	ATG、CVF、Tac、Aza、Cs、aCD154 ab、LoCD2b	9 d	[29]
2014	肝	GTKO猪	狒狒	ATG、CVF、Tac、Cs	15 d	[30]
2015	肝	GTKO猪	藏猕猴	ATG、CVF、Cs、Tac、MMF、aCD154 ab	14 d	[31]
2016	肝	GTKO猪	狒狒	ATG、CVF、Tac、Cs、hPCC	7 d	[32]
2016	肝	GTKO猪	狒狒	ATG、CVF、Belatacept、Tac、Cs、hPCC	25 d	[33]
2017	肝	GTKO猪	狒狒	ATG、CVF、Tac、Cs、aCD40 ab、hPCC	29 d	[9]
2020	肝	TKO、PERV-KO、hCD46-KI、hCD55-KI、hCD59-KI、hTHBD-KI、hTFPI-KI、hCD39-KI、hB2M-KI、HLA-E-KI、hCD47-KI猪	恒河猴	ATG、aCD40 ab	26 d	[11]
2021	肾	GTKO猪	脑死亡患者	PDN、MMF	54 h	[34]
2021	肾	TKO、GHR-KO、hCD46-KI、hCD55-KI、hTHBD-KI、hEPCR-KI、hCD47-KI、hHO-1猪	脑死亡患者	PDN、ATG、aCD20 ab	74 h	[12]
2022	心	TKO、GHR-KO、hCD46-KI、hCD55-KI、hTHBD-KI、hEPCR-KI、hCD47-KI、hHO-1猪	终末期心衰患者	RTX、ATG、Berinert、KPL-404、PDN、MMF	60 d	[13]
2022	心	TKO、GHR-KO、hCD46-KI、hCD55-KI、hTHBD-KI、hEPCR-KI、hCD47-KI、hHO-1猪	脑死亡患者	NED、dobutamine	66 h	[35]
2023	肝	TKO、A3GALT2-KO、hCD46-KI、hTHBD-KI猪	食蟹猴	RTX、ATG、CVF、etanercept、aCD154 ab	34 d	[36]
2023	肾	TKO、GHR-KO、hCD46-KI、hCD55-KI、hTHBD-KI、hEPCR-KI、hCD47-KI、hHO-1猪	脑死亡患者	Eculizumab、Solumedrol、ATG、RTX、TAC、MMF、PDN	7 d	[37]
2023	肾	GTKO+胸腺肾	脑死亡患者	/	61 d	[38]
2023	心	TKO、GHR-KO、hCD46-KI、hCD55-KI、hTHBD-KI、hEPCR-KI、hCD47-KI、hHO-1猪	终末期心衰患者	/	42 d	[39]
2024	肝	TKO、hCD46-KI、hCD55-KI、hTHBD-KI猪	脑死亡患者	/	10 d	[17]

续表

年份	器官	供体	受者	药物治疗方案	存活时间	参考文献
2024	肾	TKO、GHR-KO、PERV-KO、hCD46-KI、hCD55-KI、hTHBD-KI、hEPCR-KI、hCD47-KI、hHO-1猪	终末期肾病患者	/	50 d	[40]
2024	肾	GTKO+胸腺肾	终末期肾病患者	/	肾脏存活47 d	[41]
2024	肝	TKO、hCD46-KI、hCD55-KI、hTHBD-KI、hEPCR-KI、hCD47-KI、hCD39-KI、hCD59-KI猪	晚期肝癌患者	/	/	[18]
2024	肝肾联合	TKO、hCD46-KI、hCD55-KI、hCD59-KI、hTHBD-KI、hCD39-KI猪	脑死亡患者	/	7 d	[19]

注：WT：Wild Type, 野生型；HC：hydrocortisone，氢化可的松；Aza：Azathioprine，硫唑嘌呤；Cs：Cyclosporin，环孢素；ATG：Anti-human Thymocyte Globulin，抗胸腺细胞球蛋白；FK506：Tacrolimus，Tac，他克莫司；PDN：Prednisone，泼尼龙；PG：Prostaglandin，前列腺素；WBI：Whole Body Irradiation，全身辐照；BMTx：Bone Marrow Transplantation，骨髓移植；CsA：Cyclosporin A，环孢素A；CTX：Cytoxan，环磷酰胺；sCR1：soluble Complement-Receptor-1，可溶性补体受者1；CyP：Cyclophosphamide，环磷酰胺；HT：H-Transferase，α-1,2-fucosyltransferase，α-1,2-岩藻糖转移酶；Daclizumab：达克珠单抗；RTX：Rituximab，利妥昔单抗；MMF：Mycophenolate Mofetil，吗替麦考酚酯；CVF：Cobra Venom Factor，眼镜蛇毒因子；aCD154 ab：anti-CD154 antibody，抗CD154单抗；LoCD2b：rat anti-primate CD2 IgG2b，鼠抗灵长类动物CD2 lgG2b抗体；hPCC：human Prothrombin Complex Concentrate，人凝血酶原复合物；aCD40 ab：anti-CD40 antibody，抗CD40单抗；TKO：Triple Knock Out，GTKO、CMAH-KO、B4GALNT2-KO；KO：Knock Out，敲除；aCD20 ab：anti-CD20 antibody，抗CD20单抗；Berinert：complement C1 esterase inhibitor，补体C1酯酶抑制剂；KPL-404：人源化aCD40 Ab；NED：Norepinephrine Equivalent Dose，去甲肾上腺素等效剂量；A3GALT2：alpha-1,3-galactosyltransferase 2，α-1,3-半乳糖基转移酶2；dobutamine：多巴酚丁胺； etanercept：依那西普。

1 免疫排斥反应

鉴于人与猪间较大的遗传差异，供、受者间的免疫排斥反应是异种移植的主要障碍。此类反应主要包括超急性免疫排斥反应（Hyperacute Rejection，HAR）、急性血管性排斥反应（Acute Vascular Rejection，AVR）、急性细胞排斥反应（Acute Cellular Rejection，ACR）和慢性排斥反应（Chronic Rejection，CR）。

1.1 超急性免疫排斥反应

HAR常发生于移植后24 h内，主要机制为受者预存抗体结合猪细胞表面的α-Gal，进而介导补体和炎症激活，造成血管内皮细胞（Endothelial Cells，ECs）坏死，最终导致微血栓广泛形成和移植物失功。早在1993年，科学家就已发现由GGTA1编码的α-Gal是导致HAR最主要的抗原，但当时的基因编辑技术无法对其进行敲除[42]。外科医生曾尝试通过术前血浆置换和抗Gal抗体中和等方法清除受者预存抗体，但最终只能一定程度上延缓HAR发生[43-44]。后续，得益于基因编辑技术的进步，α-Gal敲除（α-1,3-galactosidase Knockout，GTKO）猪培育成功，猪–灵长类动物异种移植的HAR基本被克服，异种移植进入发展快车道[7,45-46]。

1.2 急性血管性排斥反应

AVR是目前影响异种移植后受者生存的主要原因，常发生于移植后数天至数周，主要机制为受者抗体与猪非Gal抗原结合，进而介导补体依赖的细胞毒性作用（Complement Dependent Cytotoxicity，CDC），最终导致血管ECs损伤，微血栓广泛形成，移植物失功[47-49]。

由CMAH编码的N-羟乙酰神经氨酸（N-Glycolylneuraminic acid，Neu5Gc）和β4GalNT2编码催化形成的SDa血型抗原广泛存在于猪细胞表面，是最主要的非Gal抗原，可介导严重的CDC[50]。将GGTA1/CMAH/β4GalNT2三基因敲除（Triple Knock Out，TKO）后，猪心脏、肾脏等多个组织器官与人血清IgG、IgM结合能力下降，免疫排斥反应减轻[51]。但在猪–人心脏移植中，尽管已敲除GGTA1/CMAH/β4GalNT2，移植物仍可见广泛的抗体结合和ECs损伤[15]。此外，猪–人肾脏移植样本的Bulk RNA和Single cell RNA-seq（scRNA-seq）提示AVR相关基因在移植早期高表达，且抗体引起的内皮细胞活化是其关键特征[52]。上述结果提示，猪细胞仍存在其他“未知抗原”，

而针对此“未知抗原”的鉴定与敲除或将是异种移植下一阶段的重点。

针对猪补体调节蛋白（Complement Regulatory Proteins，CRPs）的人源化改造对防止CDC的发生也具有重要意义。生理情况下，人体通过CRPs（CD46、CD55、CD59）的补体调节作用，可有效调节补体的异常激活，从而避免CDC。猪虽有相似的CRPs，但对人类补体的调节相对低效，无法有效抑制移植后补体的异常激活[50]。CRISPR/Cas9技术的发展使猪高表达人CRPs成为可能，且在猪–非人灵长类动物（Non-Human Primates，NHPs）肾移植试验中，这些CRPs高表达足以抑制移植后补体的异常激活，进而延缓免疫排斥的时间，防止移植物的广泛损伤[53]。

1.3 急性细胞排斥反应

异种移植中，以T细胞显著增殖为代表的ACR可见于移植后期，常发生于AVR后[54]。T细胞可通过直接途径、半直接途径和间接途径激活。直接途径中，灵长类动物特异性T细胞受体（T Cell Receptor，TCR）能直接识别猪ECs等抗原提呈细胞（Antigen-Presenting Cells，APCs）表面的抗原肽–猪白细胞抗原（Swine Leukocyte Antigen，SLA）复合体，从而引发T细胞介导的对猪ECs的细胞毒作用[55]。Li等[56]发现来源于猪ECs的细胞外囊泡也可直接激活受者T细胞并介导免疫应答。但鉴于SLA与HLA结构的相似性，抑制SLA-TCR结合的抗体也会抑制HLA-TCR结合，从而影响人体正常的生理功能[57]。因此，通过共刺激分子阻断剂（抗CD28单抗、抗CD40单抗或抗CD154单抗）阻断T细胞活化必要的共刺激信号，从而避免ACR是目前行之有效的方法[9,58]。异种移植中，T细胞间接途径激活的研究较为有限，主要涉及T细胞识别提呈了猪抗原肽的受者APCs[59]。然而，考虑到SLA等猪源性蛋白质较强的免疫原性，T细胞间接激活在异种移植中或将扮演更为重要的角色。

1.4 慢性排斥反应

受限于受者存活时间，异种肝移植中尚未有CR的报道。但在异种肾移植中，CR常发生于移植后数月至数年，发生机制尚不清楚，一般认为与长期、低幅度的免疫排斥反应有关，主要病理特征为移植物血管内皮细胞增殖、血管狭窄和间质纤维化[58,60]。

2 凝血功能障碍

相较其他实体器官移植，凝血功能障碍在异种肝移植中尤为突出，主要因素有：（1）血小板减少症；（2）凝血调节分子不相容[61]。

2.1 血小板减少症

2.1.1 血小板消耗过度

抗体结合与补体沉积会诱导猪ECs活化，导致von Willebrand因子（von Willebrand Factor，vWF）表达上调与CD39表达下调[62-63]。vWF是一种关键的血浆糖蛋白，可同时结合ECs下暴露的胶原纤维及血小板膜上的GPIb，从而导致血小板黏附于损伤部位。但值得注意的是，猪vWF与人血小板GPIb的结合能力远强于人vWF，可导致血小板过度消耗[64]。Connolly等[65]通过体外肝脏灌注试验，证实了通过人源化猪vWF可有效降低vWF对人/NHPs血小板的异常结合，从而减少移植后血小板的异常消耗。CD39是ECs的表面酶，可催化ATP和ADP（血小板致聚剂）为AMP（血小板解聚剂），从而降低血小板异常聚集的发生[66]。研究发现，将小鼠胰岛与人血共孵育，CD39转基因小鼠凝血的时间（7.9±0.89 min）较WT小鼠（4.3±0.77 min）显著延长[67]。但在猪–狒狒的异种肾移植研究中，却发现即便转入人CD39，受者的凝血情况和生存时间仍未有明显改善，提示CD39可能并非是大型哺乳动物异种移植后调控凝血过程的关键分子[68]。

2.1.2 血小板破坏过多

生理情况下，肝窦内皮细胞（Liver Sinusoidal Endothelial Cells，LSECs）和肝脏巨噬细胞（Kupffer细胞）表面的SIRPα能够与ECs、血小板表面的CD47相结合，以辨别“自我”和“非我”而调控吞噬作用，但猪SIPRα与人CD47相互作用产生的抑制信号较弱，无法有效抑制巨噬细胞对受者细胞的吞噬[69-71]。人SIPRα与猪CD47间也存在分子不相容，且SIPRα也在循环巨噬细胞上表达，因此若仅将猪SIPRα人源化则可能导致猪自身的凝血和免疫紊乱，但对猪SIPRα和CD47同时进行人源化改造，又将影响猪本身的生存[72-73]。因此，在新一代基因编辑技术没有显著性进步前，开发能够有效阻断猪SIRPα与人CD47相互作用的药物，或将是解决这一问题的有效手段。此外，猪LSECs还可通过去唾液酸糖蛋白受者1（Asialoglycoprotein Receptor-1，ASGR1）识别并结合人血小板的半乳糖β1-4 N-乙酰基葡萄糖胺糖蛋白，从而介导对人血小板的吞噬[74]。Paris等[75]通过体外肝脏灌注试验发现，相较WT猪肝脏，ASGR1敲除猪肝脏对人血小板的异常摄取明显降低，证实了敲除ASGR1是避免血小板破坏过多的有效手段。

2.2 凝血调节分子不兼容

抗体结合与补体沉积常会诱导猪ECs活化，组织因子（Tissue Factor，TF）表达上调，凝血系统异常激活[60]。生理情况下，组织因子途径抑制物（Tissue Factor Pathway Inhibitor，TFPI）可结合TF/Ⅶa复合物并抑制其活性，从而阻断凝血系统异常激活，但猪TFPI却无法有效抑制这一过程，最终导致微血栓广泛形成[31]。微血栓广泛形成是AVR的突出特征，是目前限制实体器官异种移植后受者生存的主要因素[47]。体外研究发现，导入人TFPI的猪骨髓间充质干细胞可有效抑制TF途径的异常凝血[31]。同时，也有报道称猪过表达人TFPI会导致猪自发性出血而死亡[76]。未来，局限于猪血管ECs的TFPI人源化改造或将是解决该问题的新趋势。血栓调节蛋白（Thrombomodulin，TM）和内皮细胞蛋白C受者（Endothelial Protein C Receptor，EPCR）表达于ECs表面，生理情况下可激活蛋白质C（Protein C，PC）来调节凝血过程[77-78]。人凝血酶、PC与人ECs共孵育后可见大量PC活化，而WT猪ECs却未见类似结束，表明猪TM和EPCR与人凝血酶和PC存在分子不相容[53]。同时，在体外实验中，相较WT猪ECs，转入人TM和EPCR的猪ECs可产生约为前者数十倍的活化PC[53]。但在猪–NHPs的移植试验中，异种肝移植的情况较心、肾复杂，即使将上述位点全部进行人源化改造，也依旧难以避免术后异常凝血的发生[11]。过表达导入供体的人凝血调节基因或可缓解异种肝移植后的凝血紊乱，但此举也许又会影响供体本身的生存。因此，探索供体正常生存和供器官与人体相容的“平衡点”将会是未来的重要方向。

3 其他

3.1 跨物种感染

猪内源性反转录病毒（Porcine Endogenous Retroviruses，PERV）是一种以前病毒DNA形式整合入猪基因组中的反转录病毒[79]。在猪–灵长类动物器官移植试验中虽尚未有PERV传播的记录，但有报道称PERV-A和PERV-B可在体外感染人类细胞，并整合入人类基因组，最终可能会导致免疫缺陷和肿瘤发生[80-83]。哈佛大学George Church团队运用CRISPR-Cas9技术灭活猪基因组中25个功能性PERV拷贝，首次在DNA和mRNA水平上实现PERV 100%清除[84]。同时，中国科学家成功筛选出天然PERV基因缺陷的小型猪，有效避免了因敲除PERV而引发的多基因修饰对猪自身生存的影响[85]。此外，无指定病原体（Designated Pathogen Free，DPF）培育环境可基本避免其它细菌（如弯曲杆菌、伤寒沙门氏菌）、病毒（猪细小病毒、猪巨细胞病毒）和寄生虫感染[86]。但遗憾的是，世界首例猪–人心脏移植的受者，虽未见PERV，但却发生了猪巨细胞病毒/猪玫瑰状病毒感染，提示针对跨物种感染的预防、检测和治疗还需进一步探索[13]。

3.2 移植物生理不兼容

肝脏的生理功能相较其他实体器官更为复杂。研究发现，猪肝与人肝产生的蛋白质在氨基酸序列和表达量方面均存在一定差异，例如，猪白蛋白与人白蛋白的氨基酸序列同源性仅为76%，且猪血清白蛋白浓度仅为2.6 g/dL（人类为3.5~5.0 g/dL），这可能导致移植受者出现低白蛋白血症[87-88]。WT猪的凝血酶原时间（Prothrombin Time，PT）较短，且内源性凝血途径启示因子FⅫ水平较高，易造成移植后凝血级联反应失控[89]。此外，在异种肾移植中，也发现猪肾来源的肾素无法有效激活NHPs的肾素–血管紧张素–醛固酮系统[90]。因此，针对猪白蛋白、凝血因子等进一步人源化改造对提升异种肝移植后受者的长期生存具有重大意义。

综合上文中提到的问题，目前在异种移植中常见的基因编辑位点如下（见表2）：

表2 异种移植供体猪常见的基因修饰位点

Table 2 Common genetic modification sites in donor pigs for xenotransplantation

基因修饰	全称	功能	文献
超急性免疫排斥反应			
GTKO	α-1,3-galactosyltransferase knockout	敲除异种抗原α-Gal	[46]
急性血管性排斥反应			
β4GalNT2-KO	β-1,4N-acetylgalactosaminyltransferase 2- knockout	敲除异种抗原Sd^a	[91]

续表

基因修饰	全称	功能	文献
CMAH-KO	Cytidine monophosphate-N-acetylneuraminic acid hydroxylase knockout	敲除异种抗原Neu5Gc（N-glycolylneuraminic acid）	[91]
hCD46	Transgenic human membrane co-factor protein	抑制C3转化酶和C5转化酶形成与活性	[92]
hCD55	Transgenic human decay-accelerating factor		[92]
hCD59	Transgenic human membrane inhibitor of reactive lysis	抑制攻膜复合物形成	[92]
急性细胞排斥反应			
hCTLA4-Ig	Transgenic human cytotoxic T lymphocyte-associated antigen 4-immunoglobulin	与CD28竞争性结合CD80、CD86，抑制T细胞活化	[93]
SLA I-KO	Swine leukocyte antigen class 1-knockout	抑制CD8 T活化	[94]
hCD47	Transgenic human CD47	减少巨噬细胞的激活和吞噬	[95]
HLA-E	Transgenic human leukocyte antigen-E	结合NK细胞杀伤抑制受者，抑制细胞毒作用	[96]
β2M-KO	β-2-microglobulin gene knockout		[97]
炎症反应			
hHO-1	Transgenic human heme oxygenase-1	清除活性氧，抑制炎症反应	[98]
hA20	Transgenic TNFAIP3	降低LPS诱导的NF-κB信号活性，抑制炎症反应	[99]
shTNFRI-Fc	Transgenic soluble human tumor necrosis factor-α receptor inhibitor-Fc	结合TNF-α，抑制炎症反应	[100]
血小板减少症			
hvWF	Transgenic human von Willebrand Factor gene	减少血小板的异常黏附、聚集	[65]
hSIRP α	Transgenic human signal-regulatory proteins	减少猪Kupffer细胞和LSECs对血小板的吞噬	[71]
ASGR1-KO	Asialoglycoprotein receptor 1 knockout	减少猪LSECs对血小板的吞噬	[75]
hCD39	Transgenic human ectonucleoside triphosphate diphosphohydrolase	血小板致聚剂ATP、ADP为血小板解聚剂AMP	[67-68]
凝血调节分子不相容			
hTFPI	Transgenic human tissue factor pathway inhibitor	抑制外源性凝血途径异常激活	[31]
hTHBD	Transgenic human thrombomodulin	抑制凝血酶的异常扩散	[101]
hEPCR	Transgenic human endothelial protein C receptor		[101]
其他			
hALB	Transgenic human albumin	避免移植后低白蛋白血症	[87]
GHR-KO	Growth hormone receptor knockout	避免异种移植物过度生长	[87]
PERV-KO	Porcine endogenous retrovirus knockout	避免跨物种交叉感染	[84]

4 结语

受限于免疫排斥反应及凝血功能障碍等因素，异种肝移植后的受者生存期相对较短（34 d），远低于肾移植（758 d）和心脏移植（195 d），无法满足临床需求[36,53,102]。但随着基因编辑技术的进步，以TKO为核心，人源化CRPs、重要凝血调节分子和敲除“未知抗原”为重点的基因编辑猪将是解决上述问题的发展趋势。此外，鉴于目前异种移植个性化、特异性免疫抑制方案的缺乏，研发新型靶向免疫抑制药物及完善免疫抑制方案评价体系将是下一步亟待解决的问题。随着上述难题的不断解决，相信在不远的将来，异种移植将有望缓解供器官短缺这一重要临床难题。

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