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胰岛素瘤相关研究进展

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摘　要

胰岛素瘤(insulinoma)是一种以低血糖为临床表现的肿瘤。随着近年影像学、核医学等学科发展，胰岛素瘤检出率、确诊率逐渐升高。目前细胞毒性化疗、靶向治疗、肽受体放射性核素治疗(PRRT)等最新治疗手段提高了胰岛素瘤临床治愈率。本文就胰岛素瘤发病机制、诊疗方法等方面最新进展进行综述。

关键词

胰岛素瘤，发病机制，影像学，药物治疗

Research Progress of Insulinoma

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Abstract

Insulinoma is a type of tumor in which hypoglycemia is the clinical manifestation. With the development of imaging, nuclear medicine and other disciplines, the detection rate and diagnosis rate of insulinoma have gradually increased. At present, cytotoxic chemotherapy, targeted therapy and peptide receptor radionuclide therapy (PRRT) have improved the clinical cure rate of insulinoma. This article reviews the latest progress in the pathogenesis, diagnosis and treatment of insulinoma.

Keywords

Insulinoma, Pathogenesis, Imaging, Drug Therapy

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1. 引言

胰岛素瘤(insulinoma)即胰岛β细胞肿瘤，是以β细胞为主的最常见的胰腺内分泌肿瘤(pNETs)。胰腺内分泌肿瘤根据是否分泌激素及产生相应效应，分为非功能性肿瘤(NF-pNETs)及功能性肿瘤(F-pNETs)。胰岛素瘤是发病率最高的 F-pNETs 之一，其年发病率为 1~4/百万[1]，多见于青中年，女性较男性常见，女性发病率约占 60%左右[2]。胰岛素瘤有三个 90%，即 90%为良性、90%为单发、90%肿瘤生长于胰腺内，常见于胰头、体、尾，其发病率均为 33%。因β细胞过度、不适当分泌胰岛素，该病临床常表现为 Whipple 三联征[2]。胰岛素瘤多为散发性，但也可见于各种遗传性疾病，如 MEN1、VHL 等。本文主要探讨散发性胰岛素瘤，从其发病机制、诊断、治疗、预后等方面进行综述。

2. 发病机制

2.1. 胰岛素瘤相关 LOH 改变

杂合缺失(LOH)常与肿瘤抑制基因相关，当一个等位基因异常或缺失时，其相关基因功能缺失，常丧失肿瘤抑制功能，从而导致肿瘤发生。相关研究表明[3] [4] 22q LOH 在胰岛素瘤中最常见。蒋卫君对 40 例胰岛素瘤组织标本(32 例为良性，8 例为恶性)进行 PCR，研究发现 22q13.3 LOH 可能与恶性胰岛素瘤相关[5]。11q LOH、9q 扩增[6]、1q LOH 也与胰岛素瘤发病密不可分。

2.2. MEN1 基因

MEN1 基因位于 11q13 染色体上，是目前公认研究较为详细的与胰岛素瘤发病相关的抑癌基因。Menin 以核蛋白形式与其他蛋白相结合，在细胞周期调节、基因表达、DNA 修复等方面具有多种功能[7]。Bertolino 等[8]发现特异性敲除β细胞 MEN1 基因的小鼠胰岛随月龄增大而增大，第 10 月时，小鼠发生胰岛素瘤概率为 100%。国内在 3 例确诊散发性胰岛素瘤患者瘤体标本外显子测序发现了均有 MEN1 基因突变[9]。蒋卫君[5]在 40 例胰岛素瘤中发现 40%肿瘤发生 MEN1 LOH。以上研究提示胰岛素瘤发生机制可能与 MEN1 基因表达异常密切相关。

2.3. IGF2 基因

IGF2 (insulin-like growth factor 2)即胰岛素样生长因子 2，在细胞增殖分化、凋亡、转化等方面具有重要作用。有关学者[10]对 62 例胰腺或小肠内分泌肿瘤患者分析发现，IGF2 差异甲基化区域(differentiallymethylated region 2, DMR2)高甲基化是胰岛素瘤特异事件，DMR2 高甲基化可导致 IGF2 印记丢失及 IGF2 高表达。研究证实[11]人胰岛素瘤体 IGF2 mRNA 及 IGF2 蛋白表达水平较瘤旁组织高，且发现过表达 IGF2 质粒后可促 Bcl-2 增加及 Bax 减少，从而进一步证实了高表达 IGF2 可能使胰岛素瘤体细胞获得抗凋亡能力。

2.4. DAXX/ATRX 基因

死亡结构域相关蛋白(death-domain-associated protein, DAXX)/ATRX(alpha thalassemia/mental retardation syndrome X-linked)基因复合体突变导致缺陷 DNA 修复过程异常，且导致染色体有丝分裂变异，从而发生细胞异常增殖。DAXX/ATRX 基因突变在胰岛素瘤中频率较低，一例纳入 39 例胰岛素瘤研究[12]中

仅 1 例(2.5%)发生 ATRX 突变，而未检出 DAXX 突变。Hong 等人发现，发生 DAXX/ATRX 突变的胰岛素瘤更容易同步远处转移，但异时性远处转移两者发生率无显著差异[13]。DAXX/ATRX 基因突变也与病程前 2 年高复发风险相关[13]。

2.5. mTOR 信号通路相关基因

哺乳动物雷帕霉素靶蛋白(mTOR)是一类丝/苏氨酸激酶，其可调节多种癌基因、抑癌基因，从而调节细胞生长、凋亡、自噬等。该信号通路可参与胰岛 β 细胞生长、凋亡[14]。YY1 基因为 mTOR 通路靶基因，Cao 等[12]检测 39 例胰岛素瘤发现，30% (34/113)胰岛素瘤有 YY1 基因突变，其中 YY1 T372R 突变为唯一突变，该突变与胰岛素瘤恶变相关。

2.6. F2R 基因

凝血因子 II 凝血酶受体(coagulation factor II receptor, F2R)又称蛋白酶激活受体 1 (protease activated receptor, PAR1)是 G 蛋白偶联受体。众所周知，凝血级联反应与肿瘤之间有着密不可分的关系，血管形成是肿瘤进展不可或缺的步骤。Zhou [15]等在文章中指出，F2R 在胰岛素瘤中过表达，Yin 等[16]指出 F2R 可通过诱导血管内皮生长因子(vascular endothlial growth factor, VEGF)表达，显著增加了肿瘤血管生成及瘤体生长。F2R 还可参与信号转导，引发炎症，导致内皮屏障破坏，均有助于肿瘤发展[17]。Kreutter G [18]等通过实验证明，F2R 表达增加可促进胰岛 β 细胞增殖及胰岛素释放。

2.7. CXCL12 基因

趋化因子 CXC 配体 12 (CXCL12)即基质细胞衍生因子 1 (stromal cell-derived factor-1, SDF-1)，属于 CXC 趋化因子家族，有 SDF-1α 和 SDF-1β 两种亚型[19]。CXCL12 与受体 CXCR4 结合，通过 G 蛋白偶联受体途径发挥生理作用。研究表明，CXCL12 及其受体 CXCR4 参与前列腺癌[20]胰腺癌[21]、卵巢癌[22]、胃癌[23]等恶性肿瘤发生与发展。Aysegul IIhan 等人[24]发现，与正常胰岛细胞相比，CXCL12 在胰岛素瘤细胞及人胰岛素瘤组织中高表达。稳定转染人 CXCL12 的大鼠 Rin-5F 胰岛素瘤细胞可形成细胞集落，且转染型集落大小为假转染型集落大小两倍，提示 CXCL12 基因可能与胰岛素瘤发病相关。

2.8. GATA6 基因

GATA6 (GATA binding protein 6)作为 GATA 锌指转录因子家族成员，与 GATA4、GATA5 共同控制胚胎期内胚层、中胚层细胞分化，参与心、胰腺、肝、胃肠等器官发生[25]。研究表明，GATA6 表达于胰腺内分泌细胞。魏美林等人[26]发现 GATA6 在胰岛素瘤中高表达，通过减少胰岛素瘤细胞内活性氧(ROS)产生，降低 Bax/Bcl-2 比例，使胰岛素瘤细胞抗凋亡能力增加。

2.9. Robo2 基因

Robo2 (roundabout2)蛋白由 Robo2 基因编码而成，为 Robo 受体家族成员。该家族是一类保守的跨膜受体蛋白，由 Robo1、Robo2、Robo3、Robo4 4 种亚型组成。Robo2 在膈肌、心脏、乳腺、肾脏等器官发育中起重要作用[27] [28] [29] [30]。Sophie Escott 等人[31]发现，Robo2 通过调节 Tead 转录因子从而调控胰腺祖细胞。而 Robo 受体是 β 细胞中内分泌细胞分选及胰岛结构成熟必备条件。敲低小鼠胚胎中的 Robo1、Robo2 可使胰腺体积缩小、发育不良[32]。Iacovos P. Michael 发现，miR-137 在高侵入性 pNETs 中高表达，其发挥刺激肿瘤生长及局部侵犯作用，Robo2 即该 miRNA 候选靶基因[33]。Zhou [15]等人对胰岛素瘤上调差异表达基因(differentially expressed genes, DEGs)进行排序，发现 Robo2 基因位于第二位。综上，Robo2 可能通过 miR-137 发挥促胰岛素瘤生长及侵犯作用。

3. 诊断

胰岛素瘤诊断主要有生化定性及影像定位诊断。

3.1. 生化诊断

胰岛素瘤常有 Whipple 三联征，且低血糖发作时体内胰岛素、C 肽同步升高，胰岛素释放指数(IRI/G)常 > 0.3 [34]。目前来说 72 小时饥饿实验为胰岛素瘤诊断金标准[35]。有关研究[36]行 48 小时禁食实验，每 6 小时监测一次患者体内胰岛素及 C 肽含量，确诊阳性率大于 97%，故该实验认为 48 小时禁食实验足以诊断胰岛素瘤。

3.2. 影像学定位

常规影像学方法包括经腹超声、CT、MRI 等。其中经腹超声受医生水平、肥胖、肠气等影响，平均灵敏度 32.6% [37]。计算机断层扫描可监测出 70%~80%瘤体。MRI 敏感性为 35%~63% [38]。增强 CT、MRI 为临床术前手术定位及明确肿瘤有无转移常用手段，且 MRI 在明确有无肝转移方面较 CT 敏感。当术前非侵入性检查定位失败时，可考虑选择性动脉钙刺激静脉采血(ASVS)，其敏感性为 62.5%~100% [37]。超声内镜(EUS)灵敏度较高，为 82%~93% [39]，且 EUS 联合细针穿刺活检有助于确诊、定位隐匿病变。

近来，核医学技术发展迅速，许多新兴分子成像技术应用于临床诊断。生长抑素受体显像(SRS)利用生长抑素受体高亲和力结合生长抑素合成类似物，常用于 pNET 定位。但胰岛素瘤中仅 40%~50%表达生长抑素受体 2 (somatostatin receptor 2, SSTR2)，因此 SRS 敏感性仅有 25% [40]。90%以上胰岛素瘤均表达 GLP-1 受体，受体密度为正常胰岛 β 细胞 6~12 倍[41]。基于上述理论基础，^{68}Ga-Exendin-4 PET/CT 用于检测胰岛素瘤，其灵敏度为 97.7% [42]。但因恶性胰岛素瘤 GLP-1R 表达率仅 36% [43]，故 10%胰岛素瘤中恶性肿瘤患者应用此检查手段准确性会降低。

4. 治疗

手术切除仍是目前治愈该病唯一有效手段，治愈率 > 95% [44]。保留器官功能的胰腺部分切除术是胰岛素瘤标准术式，且不需清扫淋巴结[45]。对于恶性或难治复发性胰岛素瘤应积极采取手术切除，可联合化学栓塞(TACE)、放射栓塞(SIRT)、射频消融(RFA)、高强度聚焦超声(HIFU)、全身药物治疗等以提高患者生存率[46]。

用 177-Lutetium 标记生长抑素类似物(somatostatin analogues, SSAs)进行肽受体放射性核素疗法(PRRT)可缓解 SSTR2 阳性的难治性胰岛素瘤患者临床症状[47]。

全身药物治疗常用于术前血糖控制及手术无法治愈患者。

二氮嗪为 K-ATP 通道开放剂，可刺激 α-肾上腺素能受体从而直接抑制 β 细胞释放胰岛素；它还可能通过抑制 cAMP，使其浓度升高及增强糖原分解。该类药物常作为胰岛素瘤一线用药[48]，在良性胰岛素瘤中有效率为 50%~60% [49]。但二氮嗪可致水钠潴留、恶心、多毛等，可能需要与利尿剂结合使用，使用时应注意上述不良反应。

患者二氮嗪不耐受时，生长抑素类似物也可用于胰岛素瘤治疗。其可特异性结合 SSTR2 从而抑制胰岛素异常分泌从而达到缓解症状的目的。但因其也可抑制胰高血糖素、生长激素等升糖激素分泌，故有时可引发严重低血糖[50]。胰岛素瘤 SSTR2 表达较低，故此类药物仅对 40%~60%患者有效[51]。一项研究表明，与奥曲肽相比，兰曲肽能更好地控制低血糖[52]。我国胰腺神经内分泌肿瘤诊疗指南认为，对于 G1 级和 Ki67 < 10%的 pNETs，若其 SRI 阳性，SSAs 可作为一线诊疗方案[53]。SSAs 常见不良反应主要有腹痛、腹泻、胆石症、胃肠胀气等。

糖皮质激素通过糖异生及增加体内胰岛素抵抗，可一定程度缓解低血糖症状[54]。胰高血糖素可提高体内血糖水平，但同时也可刺激胰岛素分泌，故需权衡利弊使用此药[55]。

链脲佐菌素(STZ)、5-氟尿嘧啶(5-FU)、阿霉素等细胞毒性药物可运用于晚期转移性胰岛素瘤。全身化疗适应症包括胰岛素瘤 Ki67 值 > 10%、使用 SSAs 治疗期间病情进展、症状恶化等。ENETS 指南指出标准化疗方案阿霉素联合 STZ 可致 60%以上患者肿瘤减小，低血糖症状缓解时间延长至 1.5 年[46]。在两项随机对照研究中，STZ、阿霉素联合使用时疾病缓解率约在 22%~33% [56]。50%使用 5-FU 联合 STZ 治疗患者出现了 3~4 级细胞毒性，甚至 5%病例出现中毒死亡[57]。ECOG 进行的一项前瞻性随机 2 期临床试验中对比单独使用替莫唑胺和替莫唑胺联合卡培他滨疗效，发现卡培他滨联合替莫唑胺可显著改善无进展生存时间(progression free survival, PFS)和总生存期(overall survival, OS)，且副作用较 5-FU 联合 STZ 小[58]。

目前靶向治疗也应用于胰岛素瘤治疗中。雷帕霉素(mTOR)抑制剂依维莫司可抑制肿瘤血管生成、细胞增殖。国外随机对照临床试验中表明，依维莫司显著延长了晚期进展性 pNETs 患者 PFS [59]。酪氨酸激酶抑制剂舒尼替尼可抑制血管内皮生长因子受体(VEFGR)及血小板衍生生长因子受体(PDGFR)，从而抑制肿瘤生长。一项随机、双盲第 3 阶段临床试验表明，舒尼替尼不仅显著延长恶性胰岛素瘤患者无进展生存期，还提高了总体生存期[60]。上述两种药物均可用于晚期转移性胰岛素瘤治疗。

5. 预后

87.5%的患者手术切除后低血糖症状消失，10 年生存率为 88% [2] [61]。研究表明，恶性胰岛素瘤 10 年生存率为 29%，且初次手术复发概率高[2]。所有胰岛素瘤均有恶性潜能，故患者均应随访。随访内容主要包括血糖、血清胰岛素、血清 C 肽、腹部 B 超、腹部 MR 等指标。

6. 结论

随着 ^{68}Ga-Exendin-4 PET/CT、ASVS 等检查手段发展，人们对胰岛素瘤认识得越来越充分，该病也由既往的罕见病转变为少见病。对于恶性胰岛素瘤和难治性复发性胰岛素瘤，可以使用依莫司维、舒尼替尼等靶向药物，一定程度上可延长患者生存期。目前胰岛素瘤发病机制尚不完全明确，故仍需进一步研究，便于更好地诊断治疗该病。

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