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常染色体显性多囊肾病的分子靶向药物治疗研究进展

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摘要:常染色体显性多囊肾病(ADPKD)是一种单基因遗传性肾脏疾病,其特征是囊肿进行性形成,导致肾脏体积增加和肾功能下降,最后进展为终末期肾病。既往临床上对ADPKD的治疗以对症支持治疗为主,无法延缓多囊肾病的病情进展,临床上亟需针对ADPKD的有效治疗方案。近年来,随着人们对ADPKD病理生理机制研究的不断深入,针对ADPKD致病靶点和相关信号通路的分子靶向药物研发不断取得进展突破,目前已有多种ADPKD的分子靶向药物进入临床试验阶段。本文就ADPKD分子靶向药物研究进展进行综述,以期对该病治疗及新药研发有所裨益。

关键词:常染色体显性遗传多囊肾病; 信号通路; 分子靶向药物; 致病基因

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Research Progress of Molecular Targeted Drugs in Autosomal Dominant Polycystic Kidney Disease

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Abstract Autosomal dominant polycystic kidney disease (ADPKD) is a single-gene inherited kidney disease characterized by the progressive formation of cysts, leading to increased kidney volume and decreased kidney function, and resulting in end-stage renal disease. The previous clinical treatment of ADPKD is mainly symptomatic supportive treatment, which cannot delay the progression of polycystic kidney disease. Therefore, an effective treatment plan for ADPKD is urgently needed clinically. In recent years, with the continuous in-depth research on the pathophysiological mechanism of ADPKD, the research and development of molecular targeting drugs for the pathogenic targets of ADPKD and related signaling pathways have made continuous breakthroughs. Currently, a variety of molecular targeting drugs for ADPKD have entered the stage of clinical trials. In this paper, the research progress of molecular targeting drugs of ADPKD was reviewed, in order to be helpful for the treatment of ADPKD and the development of new drugs.

Keywords autosomal dominant polycystic kidney disease (ADPKD); signaling pathways; molecular targeted therapy; pathogenetic gene

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常染色体显性遗传多囊肾病 (autosomal dominant polycystic kidney disease, ADPKD) 是常见的单基因遗传性肾脏疾病, 多见于中年起病, 发病率较高, 为 1/1 000 到 1/2 500, 全球约半数 ADPKD 患者最终进展为终末期肾病^[1]。长期以来, 由于缺乏对 ADPKD 的病理生理机制的认识, 临床上对 ADPKD 的患者仅限于对症支持治疗, 但这却并不能延缓 ADPKD 的进展。近年来, 随着 ADPKD 病理生理机制研究的不断深入, 越来越多的靶点受体以及信号通路被发现, 例如: 哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR)、酪氨酸激酶 (scr tyrosine kinase, Src)、葡萄糖神经酰胺合成酶 (glucose-ceramide synthetase, GCS) 和腺苷酸活化蛋白激酶 (AMP-activated protein kinase, AMPK) 等靶点受体以及 Kelch 样 ECH 相关蛋白 1 (Kelch-like ECH-associated protein 1, Keap1)/ 核转录因子 E2 相关因子 2 (nuclear factor erythroid 2 related factor 2, Nrf2) 及丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 等通路^[2-3]。目前, 针对相应受体及信号通路的靶向药物也逐渐被证实可有效延缓 ADPKD 的进展速度^[3-4]。本文就 ADPKD 药物作用的靶点及治疗的机制进行阐述, 以期对该病的治疗提供新思路。

1 治疗 ADPKD 的靶向药物

1.1 以 V₂ 受体为靶点的药物

V₂ 受体主要位于集合管和髓袢升支粗段, 具有抗利尿作用。精氨酸加压素 (arginine vasopressin, AVP) 是一种维持体内液体平衡的激素, AVP 与集合管和 V₂ 受体结合后通过激活水孔蛋白和上皮钠通道增加水渗透性和钠的重吸收。托伐普坦 (Tolvaptan) 是一种 V₂ 受体拮抗剂, 其作用机制是拮抗 AVP 与 V₂ 型受体结合, 抑制尿液浓缩, 刺激球管反馈, 抑制钠盐重吸收, 并通过抑制 AVP 诱导环磷酸腺苷 (cyclic adenosine monophosphate, cAMP) 的产生来抑制囊肿生长并延迟终末期肾病的发生^[5-6]。

Tolvaptan 是美国食品和药物管理局批准的第一种治疗成人 ADPKD 快速进展期的药物^[7]。两项关于 Tolvaptan 治疗 ADPKD 的大型临床随机试验^[8-9]结果表明, Tolvaptan 减缓了 ADPKD 患者的肾小球滤过率 (estimate glomerular filtration rate, eGFR) 下降速度。最新的欧洲肾脏指南指出, Tolvaptan 适用于特定类型的 ADPKD 患者, 需要注意使用 Tolvaptan 可能会出现口渴、多尿、夜尿及肝功能受损

等不良反应^[10], 故 Tolvaptan 作为目前批准可投入市场的新型靶向药, 在肯定疗效的基础上需警惕其不良反应。

1.2 以 Src 受体为靶点的药物

Src 是多囊肾中表皮生长因子途径激活和扩增的关键介质, ADPKD 中 Src 过度激活导致细胞增殖、凋亡和基质粘附; 抑制 Src 激活能抑制其下游通路, 从而抑制 cAMP 介导的促细胞增殖作用^[11]。

融合基因 (breakpoint cluster region-abelson, Bcr-Abl) 在人体内表达的蛋白质是一种异常的酪氨酸激酶, 而伯舒替尼 (Bosutinib) 是一种口服的 Src/Bcr-Abl 酪氨酸激酶抑制剂, 可以同时抑制 Bcr-Abl 和 Src 激酶的活性^[12]。一项临床试验^[11]将疗程 ≤ 24 个月、基线 eGFR ≥ 60 mL/(min · 1.73 m²)、肾脏总体积 (total kidney volume, TKV) ≥ 750 mL 的 169 位 ADPKD 患者按 1 : 1 : 1 随机分配至 Bosutinib 200 mg/d、Bosutinib 400 mg/d 与安慰剂治疗组, 结果显示, Bosutinib 可降低肾脏生长速率, 但可能会出现腹泻和肝细胞毒性等不良反应。

1.3 以 SST 受体为靶点的药物

生长抑素 (somatostatin, SST) 是一种参与多种细胞过程的激素, 抑制细胞内 cAMP 产生。细胞内高水平的 cAMP 参与细胞增殖和体液分泌, cAMP 水平升高可导致肾小管上皮细胞异常增殖和氯化物驱动的肾脏液体分泌, 进而形成囊肿, 然而, 因其在体内可被迅速消除, SST 的治疗潜力有限^[13]。

目前, 已经合成了具有更长半衰期的类似物, 例如奥曲肽 (octreotide)、兰瑞肽和帕瑞肽。一项多中心随机双盲临床试验研究发现^[14], octreotide 联合 Tolvaptan 治疗 ADPKD 患者 1 周后, eGFR 降低 10 mL/(min · 1.73 m²), 总肾脏体积降低 41 mL。另外, SST 类似物可延缓 TKV 下降速度, 抑制慢性肾脏疾病进展为终末期肾病, 其在减少 ADPKD 患者的 TKV 中具有独特优势^[15]。

1.4 以 HMG-CoA 为靶点的药物

一氧化氮 (nitric oxide, NO) 水平降低、不对称二甲基精氨酸水平升高和氧化应激增加是 ADPKD 患者内皮功能障碍的主要原因, 内皮功能障碍反过来会损害肾血流量 (renal blood flow, RBF)。他汀类药物能抑制羟甲基戊二酰辅酶 A (hydroxy methylglutaryl coenzyme A, HMG-CoA), 通过提高 NO 生物利用度和减少氧化应激来改善脂质代谢和 RBF, 将有助于减缓 ADPKD 的进展并改善肾功能^[16]。

HMG-CoA 抑制剂具有抗增殖、抗炎和抗氧化作用^[17]。20 年前, Gile 等^[18]研究发现, 洛伐他汀可显

著降低杂合雄性大鼠的囊肾大小、囊体积密度和血清尿素氮水平。近些年来 Cadnapaphornchai 等^[19]开展了普伐他汀类药物治疗 ADPKD 患者的临床试验,与随机接受安慰剂治疗的患者相比,接受普伐他汀治疗的患者表现出高度校正的总肾脏体积显著增加,同时研究强调了在 ADPKD 患者发生严重结构性疾病之前进行早期干预的重要性。

1.5 以 mTOR 为靶点的药物

mTOR 是一种丝氨酸/苏氨酸蛋白激酶,它与细胞生长、增殖、蛋白质合成、细胞代谢调控和转录调控密切相关^[20]。mTOR 的典型调节机制是通过激活经典的磷脂酰肌醇 3-激酶 (phosphatidylinositol-3-kinase, PI3K)/蛋白激酶 B (protein kinase B, Akt) 信号通路,导致上皮细胞增殖,而 mTOR 抑制剂 (雷帕霉素及其类似物)上调了 PI3K-Akt 和 PI3K-细胞外信号调节激酶 (extracellular regulated protein kinases, ERK) 信号,并通过阻断增殖和纤维化使肾脏形态和功能正常化^[21]。

西罗莫司或雷帕霉素都是 mTOR 抑制剂,可导致肾脏体积显著持久减少并改善肾功能^[22]。研究发现^[23],含有西罗莫司的免疫抑制方案可有效延缓 ADPKD 患者多囊肾体积的下降。p53 是一种重要的抑癌基因,可以调控细胞周期、DNA 修复及细胞凋亡等关键生物过程,而 E3 泛素连接酶 (mouse double minute 2, MDM2) 是 p53 的主要负调控因子,能够与 p53 结合并促使其降解,从而限制 p53 的活性,p53-MDM2 相互作用,对于细胞的正常生长和发育至关重要^[24]。为克服 mTOR 抑制引起的自噬激活,p53-MDM2 选择性抑制剂可有效防止 17 号染色体的基因降解并增加 p21 基因表达,从而减少细胞增殖并促进细胞凋亡^[25]。

2 潜在的 ADPKD 新靶向药物

2.1 促进钙释放的靶向药物

Ca²⁺/cAMP 信号在 ADPKD 病理生理学机制中起核心作用。在 ADPKD 患者中,因细胞内钙含量降低导致 cAMP 活性增高,使钙敏感的 cAMP 降解酶 (磷酸二酯酶) 活性降低,这两者都会导致细胞内 cAMP 水平升高;相反,细胞内 cAMP 含量增高使肾小管上皮细胞异常增殖和氯化物驱动的肾脏液体排除,导致囊肿形成^[13]。

雷公藤甲素是从传统中药雷公藤中分离出来的天然产物,雷公藤甲素增加了细胞内 Ca²⁺ 浓度,增加细胞凋亡并减少囊性负荷^[26],因此雷公藤甲素具有

发展为 ADPKD 的治疗药物的潜力。

2.2 以 GCS 为靶点的药物

糖鞘脂 (glycosphingolipid, GSL) 是脂质分子,通过增加 GCS 活性和增加神经酰胺从头合成而在 ADPKD 细胞中积累,GSL 积累会破坏纤毛信号传导,导致囊肿形成^[27]。Venglustat 是一种有效的 GCS 抑制剂,阶段性多囊肾分期统计模型表明^[28],Venglustat 治疗快速进展的 ADPKD 患者,可使 TKV 增长率降低 50%,因此 GCS 抑制剂 Venglustat 可能具有减弱 GSL 产生和减缓囊肿形成的潜力。

2.3 以 AMPK 为靶点的药物

AMPK 是能量代谢的传感器和调节器,对囊性纤维化跨膜电导调节剂 (cystic fibrosis transmembrane conductance regulator, CFTR) 和 mTOR 通路有负性调节作用^[29]。ADPKD 囊腔的液体分泌依赖于活跃的电解质转运,其中 CFTR 氯通道起着重要作用^[30]。在这个过程中 AMPK 可直接抑制 CFTR 的功能,而对 mTOR 的抑制则是通过其磷酸化实现,这与 Akt 介导的失活磷酸化是相反的^[31]。

二甲双胍可通过激活 AMPK 来抑制 CFTR 和 mTOR 途径,从而减少囊肿形成与液体分泌^[3,32]。研究发现^[33],二甲双胍可延缓 ADPKD 患者 eGFR 的下降速度,但未达到显著程度。因此,未来需要更大样本量的随机对照试验来进一步明确二甲双胍对 ADPKD 患者的获益程度。

2.4 以 Keap1-Nrf2 通路为靶点的药物

氧化应激已成为 ADPKD 疾病进展的重要因素之一^[34]。Nrf2 是调节氧化应激防御反应的重要转录因子,Keap1 在细胞内以二聚体形式存在,它与 Cullin3 蛋白/Ring-box1 蛋白的泛素-蛋白质连接酶形成复合物 (Kelch-like ECH-associated protein 1-Cullin 3-Ring-box 1, Keap1-CUL3-RBX1),而氧化应激诱导 Keap1 分子的构象变化,从 Keap1-CUL3-RBX1 复合物中释放 Nrf2 并使其易位至细胞核^[35]。此外,Nrf2 与抗氧化反应元件结合以诱导众多靶基因的转录,从而减少氧化应激^[36]。在 ADPKD 小鼠模型中,Nrf2 基因的缺失增加了活性氧的产生并促进了囊肿的生长^[34]。

甲基巴多索隆 (Bardoxolone),具有较强的促凋亡和抗炎活性,同时还是有效的 Nrf2 激活剂。目前 Bardoxolone 治疗 ADPKD 患者的 3 期临床试验已完成 (clinical trials: NCT03918447),目前结果暂未发布,具体临床效果有待进一步探索。

2.5 以 MAPK 通路 B-Raf 抑制剂为靶点的药物

大鼠肉瘤 (rat sarcoma, Ras) 是一种重要的鸟苷

三磷酸酯酶(guanosine triphosphatase, GTPase)蛋白,可以在细胞内传递信号并参与多种生物学过程,包括细胞增殖、分化、存活和细胞周期调控等^[37], B-Raf 原癌基因,丝氨酸/苏氨酸激酶(B-Raf proto-oncogene, serine/threonine kinase)属于 MAP3K (RAF 蛋白)家族的一员^[38]。Ras 蛋白活化后可以与 B-Raf 相互作用,促进 B-Raf 的激活,并进一步传递信号至 MAPK 通路的下游^[39]。在野生型肾上皮细胞中,cAMP 依赖型蛋白激酶(cAMP-dependent protein kinase, PKA)通过磷酸化来抑制 Raf1 和 MAPK 信号传导,然而,在 ADPKD 细胞中或者在钙剥夺条件下(即降低细胞外钙浓度或使用钙通道阻滞剂),PKA 以非 Raf-1 抑制的方式增加 Ras 和 Src 依赖性通路,并增加 B-Raf 的表达和活性^[40]。这表明 MAPK 信号通路在 ADPKD 中可能发挥重要作用。

索拉菲尼作为 B-Raf 蛋白激酶抑制剂,具有抗血管内皮生长因子受体和血小板衍生生长因子受体激酶的活性,可抑制 B-Raf/丝裂原细胞外信号调节激酶/ERK 信号通路,进而达到抑制细胞增殖和体外囊泡生长的效果^[41]。但也有研究表明^[42],Raf 抑制剂虽然可以延缓 ADPKD 大鼠肾脏囊肿的增大速度,但可能由于肾纤维化程度增加而没有改善肾功能,未来仍需要进一步深入探索 Raf 抑制剂在 ADPKD 治疗中的疗效。

2.6 靶向 miRNA 治疗

微小核糖核酸(MicroRNA, miRNA)是小分子非编码 RNA,作为基因表达的序列特异性抑制剂,miRNA 与目标 mRNA 结合导致翻译抑制,并最终导致目标 mRNA 序列的降解^[43]。miRNA 已成为 ADPKD 疾病进展的潜在调节剂,特别是 miR-17-92 和 miR-21^[44]。

c-Myc 原癌基因可激活 miR-17-92 簇,影响囊肿上皮代谢以增强囊肿增殖,而 cAMP 反应元件结合蛋白通路激活 miR-21,通过抑制促凋亡基因使囊肿细胞存活^[45]。当用抗 miR-17 治疗多囊肾病 1 基因(polycystic kidney disease 1, Pkd1)敲除小鼠时,囊肿生长被有效抑制^[46-47]。因此 miR-17 家族是治疗 ADPKD 的一个很有前景的药物靶点。

2.7 CFTR 抑制剂

CFTR 通道介导氯离子与液体分泌到囊内并促使囊肿体积扩大^[48]。CFTR 抑制剂 VX-809 可改善 Pkd1fl/fl、Pax8rtTA、Teto-Cre 和 Pkd1RC/RCADP-KD 小鼠的囊肿体积扩大^[49]。VX-809 降低腺苷环化酶同工酶 3 和 cAMP 的水平,诱导 CFTR 定位于基底膜,增加钠氢交换蛋白和上皮钠离子通道蛋白在顶

膜的表达,从而逆转囊性上皮细胞由分泌型向吸收型的转变^[50]。

3 展望

综上所述,随着 ADPKD 病理生理机制研究的不断完善,ADPKD 致病靶点和相关信号通路的分子靶向药物不断取得进展突破,部分靶向用药对 ADPKD 的治疗已获得初步的成果,例如以 V₂ 受体、Src、SST、HMG-CoA 等为靶点的药物,可延缓 ADPKD 进展并改善患者生活质量。目前还有很多新靶向药物处于临床初步研究阶段,ADPKD 患者如何选择合适药物,以及如何避免或处理药物带来的不良反应等问题仍是需要解决的重点。未来单一疗法不太可能对所有 ADPKD 患者有效,多元化治疗仍是一项艰巨的挑战,相信在未来 ADPKD 的治疗必将得到解决,从而进入一个全新的时代。

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