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SMARCAL1在维持复制叉、端粒稳定性中的作用及Schimke免疫骨性发育不良的研究进展

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摘　要

SMARCAL1也称为HARP，是一种ATP依赖退火解旋酶，可在DNA损伤期间稳定复制叉。该基因中的突变是造成Schimke免疫性骨发育不良(SIOD)的原因，SIOD是一种常染色体隐性遗传疾病，以生长功能障碍、肾脏损害、T细胞免疫缺陷为表征。我们总结了SMARCAL1在应对DNA复制应激过程中对DNA修复，维持端粒和复制叉稳定上的主要作用、SMARCAL1基因突变导致的疾病表型、癌症预测、SIOD的诊疗进展等方面进行总结。

关键词

DNA复制，稳定性，SMARCAL1，端粒，SIOD

The Role of SMARCAL1 in Maintaining Replication Fork and Telomere Stability and the Research Progress of SIOD

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Abstract

SMARCAL1, called HARP, is an ATP-dependent annealing helicase that stably replicates forks during DNA damage. Mutations in this gene are responsible for immune bone dysplasia (SIOD), SIOD is an autosomal recessive inherited disease characterized by growth dysfunction, kidney damage, and T cell immunodeficiency. We summarized the main role of SMARCAL1 in DNA repair and telomere and replication fork stability in response to DNA replication stress, disease phenotypes caused by SMARCAL1 gene mutations, cancer prediction, and diagnosis and treatment progress of SIOD.

Keywords

DNA Replication, Stability, SMARCAL1, Telomere, SIOD

1. 引言

SNF2 (非发酵蔗糖 2)是一种存在于从酵母到人类的 ATP 依赖染色质重塑酶家族。这个家族的成员参与基因转录、DNA 重组、细胞周期调控、DNA 甲基化和 DNA 损伤修复等各种过程。SNF2 家族蛋白包含一种由 7 个保守序列构成的类解旋酶 ATP 酶结构域，和在许多 DNA 和 RNA 解旋酶中发现的序列有相似性[1]。1986 年首次从小牛胸腺中分离出 SMARCAL1 [2]。从线虫到人类，不同物种中都有 SMARCAL1 的存在。在人和小鼠的所有组织中均见 Smarcal1 基因表达，如在人免疫系统中，Smarcal1 在单核细胞中表达量为 1.25‰、B 淋巴细胞表达量为 1.58‰、CD4 + T 细胞表达量为 1.25‰、CD8 + T 细胞表达量为 1.99‰、NK 细胞中的表达量为 0.1‰；在内分泌系统的胰腺细胞中表达量为 0.1‰、前列腺细胞中表达量约为 0.02‰；在睾丸细胞中表达量则为 0.16‰ [3]-[10]。Smarcal1 基因突变与 Schimke 免疫骨性发育不良(Schimke immuno-osseous dysplasia, SIOD)这个综合征密切相关[11] [12]。所以说 SIOD 是一种罕见的累及多系统、进行性加重的常染色体遗传病，主要表现为骨骼发育不良造成的生长迟缓、局灶节段性肾小球硬化(FSGS)最终发展为肾衰竭、T 细胞免疫缺陷、脑发育受损等[6] [13] [14] [15] [16]。除此之外，部分 SIOD 患者还表现有角膜混浊、动脉粥样硬化、中风、偏头痛、甲状腺功能减退、骨髓衰竭等症状[6] [13] [16]。

很多研究结果显示，SMARCAL1 在维持基因组稳定性和停滞的 DNA 复制叉的活化中起到作用[17] [18] [19]。

本文将从 SMARCAL1 的结构与功能、SMARCAL1 在 DNA 损伤部位应答中所起的作用，以及在端粒的完整性维护过程中的作用、SMARCAL1 活性调节与基因组稳定性的关系、SMARCAL1 基因突变引起的疾病及基因－表型相关性、SMARCAL1 相关的癌症预测、等方面进行总结。

2. SMARCAL1 的结构与功能

人 Smarcal1 基因位于 2q34-q36，含有 17 个外显子，编码由 954 个氨基酸残基组成的蛋白质[20]。

SMARCAL1 N末端包括一个RPA (复制蛋白A)相互作用的序列，之后是2个串联的HARP结构域[13] [21] [22]；其中解旋酶结构域位于它的C端，具有ATP酶的活性，并被115个氨基酸的长序列连接成两个RecA类的结构域。与RPA作用的序列位于N-末端；与“退火解旋活性”有关的结构域位于239-307与331-4002区间的“HARP”结构域[23]。C-末端是解旋酶的结构域，有ATP酶催化活性(由115个氨基酸残基组成的“RecA”结构域)和SWI/SNF“核小体重塑蛋白”结构[6]。SMARCAL1的ATP依赖DNA退火解旋酶含有2个HARP结构域组成的ATPase [17] [24] [25]。在停滞的复制叉重塑、端粒DNA完整性维护、S期细胞周期关卡通路的激活、利用NHEJ机制修复DNA双链断裂损伤等过程中，当DNA出现损伤时，与单链DNA结合的单链DNA结合蛋白RPA32识别SMARCAL1 N端的RPA作用结构域，同时招募SMARCAL1到dsDNA-ssDNA的单链DNA一侧[3] [6] [17] [26] [27] [28] [29]。

3. SMARCAL1在DNA损伤应答中的作用

3.1. SMARCAL1通过与RPA的相互作用被招募至DNA损伤部位

RPA是由RPA1、RPA2和RPA3形成的异三聚体复合物，在复制、重组和修复过程中结合ssDNA从而防止DNA二级结构的形成[30]。当存在或不存在DNA损伤的情况下，RPA都可以覆盖并保护ssDNA。RPA作为一种用于招募DNA修复酶的支架蛋白被募集到DNA损伤部位。SMARCAL1与RPA在DNA损伤部位共同定位，且SMARCAL1与RPA有直接的相互作用[31] [32] [33] [34]。SMARCAL1的RPA结合序列与其他DNA修复蛋白中的序列非常相似，其中包括复制叉保护复合物成员TIPIN和复制应激反应的重要参与者RAD52 [35]-[40]。SMARCAL1在其N端区域有一个RPA2相互作用的序列。该序列与一个可以结合RPA2的α螺旋相对应[35]。SMARCAL1和RPA间相互作用的破坏造成无法正常的把SMARCAL1招募到DNA的损伤部位。

3.2. SMARCAL1参与DNA损伤应答

SMARCAL1在ATR、ATM和DNA-PK检测点的激酶磷酸化，在参与DNA损伤应答中被活化。有研究表明了SMARCAL1在DNA双链断裂(DSB)位点的作用。在接受辐照的U2OS细胞中，在DNA损伤部位，SMARCAL1被招募后识别DNA末端，并且与γH2AX和RAD51病灶共同定位[41]。具体步骤是使用线性化的质粒结合在链亲和素珠包被的珠子上，可以提取出结合在DNA上的蛋白质，然后通过质谱比色法鉴定这些蛋白质。仅在一端生物素化的线性DNA分子结合链亲和素珠后，呈现出一个类似于DNA双链断裂的游离DNA末端。相反，如果DNA的两端均被生物素化，则两端均被珠覆盖。将这种技术与非洲爪蟾卵提取物一起使用，研究发现，只有一个DNA末端被生物素化时，SMARCAL1才被有效招募到DNA上，而当两个末端都被生物素化时，则SMARCAL1则未被被招募[31] [41]。表明了进行加工了的游离DNA末端，以形成单链DNA (ssDNA)，才具备招募SMARCAL1的条件。在直接结合试验中，也与以上的结果一致，SMARCAL1对没有加工的的DNA末端不具有高亲和力[32]。

3.3. SMARCAL1应对DNA复制应激的应答

有研究表明，敲除SMARCAL1的细胞对诱导复制应激的药物(例如羟基脲(HU)、蚜虫碱或喜树碱)表现出超敏性[35]。在凝胶迁移试验中，与ssDNA或双链DNA相比，SMARCAL1对分叉DNA结构的亲和力更高。当蛋白与分叉的DNA结合时，激发了SMARCAL1的ATP酶活性。但在使用部分双链DNA作为底物的解旋酶测定中，SMARCAL1无法显示出解链活性。与之相反，在部分解链的质粒DNA用作底物的退火解旋酶测定中，在RPA和ATP存在的情况下，SMARCAL1能够重绕ssDNA链。这些结果

表明 SMARCAL1 是 ATP 驱动的退火解旋酶，它可以退火互补的 RPA 结合 ssDNA [42]。

3.4. SMARCAL1 对新生的 DNA 链进行退火调节停滞的复制叉的回退

SMARCAL1 除了上述两个功能外还可以通过对新生的 DNA 链进行退火来调节停滞的复制叉的回退[43]。RecG 是一种具有 3’至 5’极性的 DNA 解旋酶，可回退停滞的复制叉并完成霍利迪中间体(Holliday intermediates)的分支迁移。RecG 与 SSB (单链 DNA 结合蛋白)相互作用，这种相互作用可在 DNA 上稳定 RecG 并促进 RecG 的复制叉的回退[44]。回退的 DNA 复制叉是一种类似于霍利迪(Holliday)连接体的四向 DNA 结构。这些 DNA 结构可以通过切割产生单端 DNA，然后可以用于启动 DNA 的重组修复机制[45]。回退的 DNA 复制叉的切割是通过一种与 SLX4 突变蛋白相互作用的内切酶 MUS81 的调解[46] [47]。MUS81 的耗竭对正常细胞没有影响，但却会阻止缺乏 SMARCAL1 的细胞中 γH2AX 的聚集[32]。从而证实，SMARCAL1 可保护停滞的复制叉避免核酸酶异常加工，因为核酸酶异常加工可能导致基因组不稳定，所以 SMARCAL1 在维持基因组稳定性方面有着很重要的作用。

3.5. SMARCAL1 在复制叉重启中起特定作用，而不是经典的同源重组过程

质谱实验证实 WRN 解旋酶是一种 SMARCAL1 相互作用蛋白[48]。WRN 是一种解旋酶/核酸外切酶，它在 DNA 修复中有多种功能，可以保持基因组脆弱部位的稳定性[49]。RPAS 作为一种支架蛋白，调解 MARCAL1 和 WRN 的相互作用，而 SMARCAL1 和 WRN 在复制叉修复中均具有重叠作用，又各自独立，有区别[48]。研究报告指出，在 MMC 引起的复制叉停滞后，WRN 与 RAD52 共同定位，而 WRN 的活性受 RAD52 调节[50]。总而言之，这些数据表明 SMARCAL1、WRN 和 RAD52 可以保护和修复受损的复制叉，但是这些蛋白质的确切的底物和调解方式尚无实验明确。SMARCAL1 还可以在体外催化分支迁移。此外，基因转换报告(HDR-GFP)分析检测到，有效的基因转化并不需要 SMARCAL1 [13]。这些数据表明 SMARCAL1 在复制叉重启中起特定作用，而不是经典的同源重组过程。

4. SMARCAL1 在端粒完整性维护过程的作用

端粒在 S 期的异常结构会干扰 DNA 在这些部位的复制[51]。因为有富含 G 序列的存在，才有可能形成 G-四链体结构。这些结构阻碍了复制叉前进，造成复制叉停滞和/或复制叉崩溃[52]。此外，端粒由双链六聚体重复序列 TTAGGG 组成，TTAGG 可分解成阻碍 DNA 复制的 T 环。在某些细胞中，除了常见的 TTAGGG 重复序列外，端粒还包含其他类型的六聚体重复序列，例如 TCAGGG 或 TTCGGG [53] [54] [55] [56]。在缺乏端粒酶的情况下，酵母和哺乳动物细胞均依靠一种同源重组通路(BIR)调解端粒的维持，促进端粒表型的的延伸(ALT)。聚合酶 δ 是来调节 ALT 和 BIR 参与保守的 DNA 复制合成[57] [58] [59]。延伸的端粒细胞有长而异构的端粒。这些细胞的另一个特征是 C 环的存在，即端粒 DNA 的额外染色体环，它可以是一部分单链结构，并且可以作为 ALT 活性的标记物[43] [60]。

造成端粒激活和维持的确切机制尚不明确。推测可能是因为 SMARCAL1 在停滞的复制叉处重塑了染色质，延伸的端粒中富含 SMARCAL1，所以它对端粒起着重要作用。有研究证实，缺少 SMARCAL1 会加大端粒 DNA 损伤以及 C 环的增加，C 环的丰度与 SMARCAL1 的缺失程度有关[61]。另一项研究表明，延伸的端粒中富含 SMARCAL1，而缺少 SMARCAL1 会影响端粒长度[62]。还有研究显示，SMARCAL1 在端粒中的作用与其他应答 DNA 复制应激的解旋酶无关[23] [61] [63]。

5. SMARCAL1 活性调节与基因组稳定性的关系

不同类型的 DNA 损伤会触发激活不同的 DNA 修复蛋白。DNA 损伤应答的主要调解剂是激酶 ATR、

ATM 和 DNA-PK，它们让各种下游 DNA 修复酶磷酸化。SMARCAL1 会导致依赖 HU、IR 或 UV 以 ATR，ATM 和 DNA-PK 方式诱导的 DNA 损伤后磷酸化。目前已经确定了包括 S173、S652 和 S919 在内的多个磷酸化部位。SMARCAL1 被招募到 DNA 损伤部位，这与这些部位的磷酸化无关。然而，仿磷酸化的 S652D 突变在体外损伤了其 DNA 依赖 ATP 酶和分支迁移活性[64]。因此，该部位的磷酸化主要是由 ATR 诱导，它限制了 SMARCAL1 对停滞复制叉的异常处理，防止复制叉崩溃。相反，在 S889 磷酸化未应激细胞中也很明显，它激活了 DNA 依赖 ATP 酶和 SMARCAL1 的分支迁移活性。因此，调解 SMARCAL1 的正常水平对于确保基因组稳定性也很重要，因为 SMARCAL1 的耗竭或过表达都会加大 DNA 损伤[65]。

6. SMARCAL1 基因突变引起的疾病及基因-表型相关性的研究

SMARCAL1 基因的突变会引起常染色体隐性遗传疾病，即(SIOD) [66]，世界范围内 SIOD 的发病率约为 1/300 万~1/100 万[13]。SMARCAL1 表达于全身多个组织及器官，包括骨骼、肾脏、胸腺、甲状腺、神经及血液等。因此 SMARCAL1 基因变异可导致全身多脏器系统功能异常，主要表型为骨骼、肾脏和免疫系统受损[44]。

6.1. 脊柱发育不良

几乎所有的 SIOD 患者都有身材矮小的表型，主要表现为短躯干矮小，颈短，腰椎前凸、腹部突出[67] [68]。研究统计 SIOD 男性患者成人身高约为 135-156cm，女患者成人身高约 97.5~142.5 cm [67]。

SMARCALl 是目前已知的唯一能导致 SIOD 的基因，然而并不是所以的患儿都可以检测到 SMARCALl 的突变[68]。Hunter [68]等人研究了 33 名 SIOD 患者的 SMARCAL1 基因发现有 66%的患者是 SMARCAL1 基因突变，剩下 34%的患者未检测到此突变。分析这 33 名患者的骨骼 X 线片基因有问题的患者脊柱发育不良(SEDT)基本上仅局限于骨盆、脊柱、股骨骺[29]。还发现少部分的成人患者年轻时患有骨质疏松症和髋关节病[68]。在没有可检测到 SMARCAL1 突变的患者中，大部分患者 SEDT 放射学表现与突变患者无明显区别。因此，脊柱发育不良不能用来判断具有 SEDT 的 SIOD 患者是否具有 SMARCAL1 突变。

所有的患者都具有正常的生长激素水平。迄今为止，未见 SIOD 患者垂体前叶功能缺失的文献报道[8]。具有 SMARCAL1 突变的 SIOD 患者的特征性骨骼特征[68]是：可能存在的宽蝶鞍；椎骨的扁平化及髋部的异常逐年恶化；横向移位的股骨头骨骺，小的，发育不全的基底髂骨，向上倾斜的髋臼；没有分割缺陷的扁平椎体；髋关节病和椎骨骨质减少(儿童期，青春期和成年早期)。

6.2. 肾脏疾病

SMARCAL1 在肾脏发育期间的所有细胞中均有表达，在成熟人肾中肾小管上皮细胞及集合管细胞中表达[69]。大量蛋白尿是 SIOD 患者的最早期表现，SIOD 肾病最常见的病理结果为局灶性节段性肾小球硬化(FSGS)，大多对治疗的药物包括糖皮质激素、环磷酰胺、他克莫司、环孢菌素 A 等免疫抑制剂治疗无反应，最终发展为肾衰(ESRD)，在未成年时死于肾衰竭[67] [70]。研究表明 SIOD 的 FSGS 与肾小球中 NOTCH 受体、配体的表达的明显增加密切相关[7]。增加的 NOTCH 信号传导是 FSGS 的已知明确致病机制[71] [72]。

Morimoto [73]等人发现 SIOD 病人肾脏中的 Wnt 和 Notch 信号通路的组分和标志物的表达增加，SIOD 病人肾小球中未磷酸化的 β-连环蛋白和 Notch1 细胞内结构域的表达水平增加。研究发现增加的 Wnt 和 Notch 活性增加是由 SMARCAL1 缺乏引起的，并且为肾脏病理 FSGS 的致病原因，导致大多数 SIOD 患者起初的大量蛋白尿为表型的肾病[73]。对其他以大量蛋白尿为表型的肾小球病的研究发现，Wnt [74] [75]

[76] [77]和 Notch 信号传导的增加[71] [72] [78] [79]导致足细胞功能障碍。Wnt 和 Notch 信号传导对于肾脏发育至关重要，但是在出生后肾脏的肾小球中却无法检测到[79] [80] [81]。

6.3. T 细胞免疫缺乏

原发性免疫缺陷病是由免疫系统内在缺陷引起的异质性疾病组，常表现为反复病毒、细菌或真菌感染[82]。在正常的人 T 细胞发育中，T 细胞谱系的祖细胞来自骨髓，胸腺中分化产生不成熟的 CD4 和 CD8 细胞。然后离开胸腺并进入外周成熟。在胸腺内 T 细胞完成克隆多样性，如果 SIOD 患者的外周的 T 细胞是单克隆或寡克隆[83]，提示 T 细胞发育缺陷。T 细胞缺乏导致约 80% SIOD 的患者淋巴细胞的减少，存在的 T 细胞主要是记忆 T 细胞，与胸腺对 T 细胞的产生减少一致[29]。B 细胞计数通常是正常或略升高。T 细胞缺乏的发生与 SIOD 患者 T 细胞中白细胞介素 7 受体 α 的缺乏有关[29] [84]。IL-7 及其受体系统在早期 T 细胞发育中起着重要作用。在淋巴细胞发育过程中，编码免疫球蛋白和 T 细胞受体抗原结合域的功能基因需要经过与 NHEJ 类似的 V(D)J 重组才能形成[85] [86]。与 NHEJ 类似，V(D)J 重排也需产生 DNA 双链断裂，并由 NHEJ 机制完成断链末端的连接[85] [86]。而 SMARCAL1 的突变常影响 NHEJ 在 V(D)J 重排重组的连接效率，这可能是 SIOD 患者常见 T 细胞免疫缺陷的原因之一[83] [87]。

T 细胞免疫缺陷增加机会性感染的风险，如卡氏肺孢子虫的感染，大部分的 SIOD 患者反复感染各种病毒(包括水痘－带状疱疹病毒、单纯疱疹病毒、巨细胞病毒)、细菌和真菌[13] [20]。T 细胞缺乏而导致的反复感染是 SIOD 死亡的主要原因。5.4 其他系统异常也有部分 SIOD 患者会合并中枢神经系统(CNS)的症状，伴有高血压和动脉粥样硬化。会出现短暂性神经系统发作、偏头痛样头痛或短暂性脑缺血发作[57]。短暂性脑缺血发作的源头可能是加重的动脉粥样硬化并伴有严重的高血压[1] [13]。大多数患者的智力是正常，少数患者出现精神运动发育迟缓。少数 SIOD 患者出现角膜混浊、牙齿畸形和毛发稀疏[88]。Kilic [57]等人也提出血管炎症和血管反应的发生与 SMARCAL1 突变导致免疫的紊乱有关。有研究证明 SIOD 患者中 ELN 的表达明显降低[89]，ELN 基因编码的是弹性蛋白前体，弹性蛋白前体对维持动脉壁的完整性有非常重要的作用。三个 SIOD 患者的死后动脉组织病理学分析显示弹性蛋白纤维的分裂和碎裂[8] [89]。弹性蛋白减少导致动脉壁平滑肌细胞的增殖从而导致内膜的增生[90]。SIOD 主动脉中弹性蛋白表达的减少可能与 ELN 转录减少以及转录后 ELN mRNA 衰变增加有关[90]。Haffner [91]等报道了一名严重 SIOD 的 6 岁男孩，表现为波动性偏瘫和癫痫发作、剧烈的偏头痛、暂时性脑缺血发作；发作初始、期间血管造影、磁共振成像均正常；发作后可见灌注和动脉狭窄减少，多个可逆限制扩散区域。这一系列症状和影像学表现提示患儿为可逆性的脑血管收缩综合征。

6.4. SIOD 患者基因型与表型的相关性

根据人类基因突变数据库(HGMD)报道，目前已发现 60 多种 SMARCAL1 基因突变。突变类型包括错义突变、无义突变、剪切突变、微小插入或缺失、交叉缺失等，其中错义和无义突变最多，达 30 多种[23]。早期研究表明 SIOD 影响的个体中存在基因-表型相关性：严重 SIOD 患者表现出两个无义、移码或剪接突变，而轻度受影响的个体具有错义突变[20]。缺失、无义和移码突变通常导致 SMARCAL1 的 mRNA 和蛋白质的表达缺失，而错义突变可能改变亚细胞定位、酶活性及蛋白质水平。导致 SIOD 发生的 Smarcal1 基因突变多为双等位基因功能缺失、错义突变、插入/缺失(insertion and deletion, Ins/Del)、大片段缺失以及 SMAR-CAL1 mRNA 拼接错误[14] [92]。上述基因改变常出现在 SMARCAL1 的 RecA 样结构域 I 中，由于突变影响了 SMARCAL1 的 ATP 酶活性，故常见疾病的严重程度与突变体 SMARCAL1 所表现出的 ATP 酶活性成反比[93]。SMARCAL1 的突变与 SIOD 患者的染色体不稳定相关，这表明该表型可能是该

疾病的重要特征[94]。在另一篇最新论文中，染色质变化也与 SIOD 相关。SMARCAL1 还可能结合染色质而直接影响基因表达。果蝇的 SMARCAL1 直系同源物 Marcal1 与 trxG 和 PcG 相互作用，而 Marcal1 缺陷影响着染色质的结构和基因表达[95]。SMARCAL1 等位基因缺失、无义或移码突变常见于重症患者。重症 SIOD 患者的症状在孕期外显，表现为胎儿生长迟缓、甲状腺功能减退症、骨髓衰竭、短暂性脑缺血发作、中风和肾衰竭等，一般死于 5 岁前。SMARCAL1 等位基因错义突变患者症状较轻，多数发病较晚，常见 8~13 岁以后发病，数年后进展至肾衰[23] [96]。Lipska [95]等人通过分析来自 28 个家族的 34 名 SIOD 患者的肾脏相关基因型-表型，未发现肾病病程的基因型-表型相关性，但发现肾组织对基因组不稳定性的累积效应具有高度敏感性。研究表明 SIOD 疾病的严重程度与 SMARCAL1 的活性成反比[97]。然而，除了基因变异可以影响基因表达及临床表现外，许多其他遗传因素或环境因素也可以影响基因表达，改变临床表型[89]。

7. SMARCAL1 基因突变与癌症易感性

虽然报道过几例 SIOD 患者伴随非霍奇金淋巴瘤[98]，但 SIOD 患者的癌症易感性并不高，这可能是因为 SIOD 患者的免疫缺陷与 T 细胞功能缺陷有关[99]。在小鼠实验中，SMARCAL1 的失活导致对 DNA 损伤因子如伊立替康(CPT-11)的超敏反应[107]。在另一项研究中，去除 SMARCAL1 基因的小鼠无法表达 RPA 结合结构域(第一个 HARP 域和第二个 HARP 域的一部分[100])，从而对癌症的发展形成阻力。因此，当接触低剂量的 IR 时，野生型小鼠因为 T 细胞祖细胞中 DNA 突变的积累而发展为 T 细胞淋巴瘤，而缺少 SMARCAL1 N 末端结构域的小鼠则表现出肿瘤形成的延迟，这可能是因为缺少 SMARCAL1，增加了 T 细胞祖细胞对 DNA 损伤的易感性并诱导祖细胞凋亡[100]。

8. SIOD 的诊疗进展

SIOD 的诊断是在依靠先证者的临床特征和放射学表现中建立起来的[7]。如果通过基因明确 SMARCAL1 的双等位基因存在致病变异，即使临床特征轻微或不典型，也可诊断 SIOD [4]。对于具有以下特征的个体，应怀疑 SIOD：1) 身材矮小(99%)，表现为短躯干、短颈、腰椎前凸；2) 脊柱发育不良(75%)，同前叙述；3) 肾病，几乎所有的 SIOD 患者都会出现蛋白尿且逐渐演变成终末肾衰，83%的患者肾脏病理为 FSGS；4) T 细胞缺乏(76%)，CD4 和 CD8 细胞都减少，比例正常[7]。

Saraiva 等[23]依据疾病出现的时间和疾病的严重程度将 SIOD 分为早发严重型和迟发缓和型两种类型。若 SIOD 患者在胎儿期就出现宫内发育迟缓，生后生长迟缓则归为早发严重型，其余为迟发缓和型。两种类型的临床表现没有明显差异，但早发严重型的肾病最终全部发展为终末期肾病。迟发缓和型的肾病经过合理的替代治疗可存活到成人期[23]。Boerkoel 等[5]发现 SIOD 患者中孕 33 周前的早产儿的存活年龄明显下降；约 2/3 的患儿在 2 岁前即出现生长发育延迟；一半以上患者在 15 岁前死亡。

SIOD 治疗目前无特异治疗，主要是针对合并症及并发症的对症处理及预防，对于慢性肾衰竭可行腹膜透析或者血液透析或肾移植，对于免疫缺陷可行骨髓移植，或联合移植来提高患者存活率[5]。T 细胞免疫缺陷，若发生反复口腔疱疹感染或带状疱疹，可预防性使用抗病毒药物；进行疫苗接种以预防肺孢子菌肺炎。对自身免疫紊乱者进行免疫调节治疗。粒细胞集落刺激因子治疗中性粒细胞减少症。改善血流量或降低凝血能力药物以治疗短暂性脑缺血发作或中风。定期监测骨骼疾病的发展，每年检测肾脏功能、免疫和血液学状况。SIOD 预后差，多数患者 15 岁前死亡，部分死于肾衰竭、各种感染及脑栓塞，只有少数患者可存活至成年[100]。

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