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# 可变剪接在卵巢癌中的作用研究进展

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## 摘　要

**卵巢癌(ovarian cancer, OC)是发生在卵巢的恶性肿瘤性疾病。卵巢癌大多发病隐匿，进展迅速，加之缺乏高效的早期诊断措施，许多病人初次诊断时已属晚期。在诊断和治疗方面已取得了一定的进展，但其五年生存率仍然低，所以迫切需要研究OC的发生和发展机制。中心法则中RNA是由DNA转录而来的，作为一个转录本来源的DNA转录区域却不一定是由某个连续DNA片段提供的，甚至可能有间隔DNA转录区的交叉，不同区域不同顺序的转录产物共同组成一个转录本，极大增加了DNA产生RNA的复杂度。人类基因组中多数基因都会发生RNA的可变剪接(alternative splicing, AS)，AS可实现相同的前信使RNA生成多个mRNA剪接异构体和下游蛋白质亚型。一个基因的不同编码区可以以不同的方式剪接，导致该基因的多种转录状态，最终的蛋白产物可能具有不同的或相互拮抗的功能和结构特征。这在很大程度上扩大了人类基因的复杂性和多样性，影响着肿瘤细胞表型和信号通路，从而影响肿瘤的发生、发展。OC中也发现可变剪接事件，笔者就AS在OC中的作用作综述。**

## 关键词

**可变剪接，卵巢癌，耐药，精准治疗**

# Research Progress on the Role of Variable Splicing in Ovarian Cancer

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## Abstract

**Ovarian cancer (OC) is a malignant tumor disease that occurs in the ovaries. The incidence of ova-**

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**rian cancer is mostly hidden, rapid progress, coupled with the lack of efficient early diagnosis measures, many patients are in the late stage when they are diagnosed for the first time. Some progress has been made in diagnosis and treatment, but the five-year survival rate is still low. Therefore, there is an urgent need to study the occurrence and development mechanism of OC. In the central rule, RNA is transcribed from DNA, but the DNA transcriptional region as a transcript source is not necessarily provided by a continuous DNA fragment, and there may even be intersecting DNA transcripts. Transcripts from different regions and different sequences form a transcript, which greatly increases the complexity of DNA to produce RNA. However, RNA alternative splicing (alternative splicing, AS) occurs in most genes in the human genome, and AS can achieve the same pre-messenger that enables RNA to produce multiple mRNA splicing isomers and downstream protein subtypes. Different coding regions of a gene can be spliced in different ways, resulting in a variety of transcriptional states of the gene, and the final protein products may have different or mutually antagonistic functional and structural characteristics. This greatly expands the complexity and diversity of human genes and affects the phenotype and signal pathway of tumor cells, thus affecting the occurrence and development of tumors. Alternative splicing events are also found in OC. The author summarizes the role of AS in OC.**

## Keywords

**Alternative Splicing, Ovarian Cancer, Drug Resistance, Precision Medicine**



## 1. 引言

可变剪接(alternative splicing, AS)是指一个 mRNA 前体通过不同的剪接方式产生不同的 mRNA 剪接异构体的过程，可变剪接增加了 mRNA 和蛋白质的多样性[1]。一个基因可以发生多次可变剪接事件，可变剪接事件的发生频率高，数量多[2]。很多的研究结果表明，可变剪接在癌症的发展和进展中起主导作用，因为在癌症中，AS 是高度失调的，参与了肿瘤细胞的几乎所有特征[3]，并且剪接变体的调控生产对于几乎所有生物过程的重要功能都是必需[4]。癌细胞经常利用 AS 灵活性来产生促进生长和生存的蛋白质。以这种方式产生的许多同种异构体受到发育调节，并在肿瘤中优先重新表达[5]。在可变剪接 7 种剪接类型中最常见的是外显子的跳跃[6]。在肿瘤治疗中 DNA 或 RNA 的分析有重要意义[7]。可变剪接是一个动态的过程，与细胞生命活动密不可分[8]。可使蛋白质组多样化以便执行复杂的生物学功能来适应外部和内部环境变化[9]。可变剪接的过程是很复杂繁琐的，我们对其过程有一定了解。可变剪接的机制之一就是剪接因子与沉默子或增强子的调节位点之间的 RNA-蛋白质相互作用[10]。越来越多的证据表明，异常选择性剪接(AS)事件与癌症的发病机制有关，AS 与卵巢癌发展密切相关，在 10,582 个基因中鉴定出 48,049 个 AS 事件，包含 7 种可变剪接类型[11]。

卵巢癌(ovarian cancer, OC)是致死率最高的妇科恶性肿瘤[12]，早期症状不典型，晚期预后不可控，易复发易耐药，为临床诊疗带来巨大的负担。OC 的 5 年生存率约为 47%，而死亡原因是复发和化疗耐药[13]。2021 年美国新发卵巢癌发病率很高[14]，中国每年新发卵巢癌 52,971 例，并呈现出上升趋势，每年约 30,886 例女性患者因 OC 而死亡[15]。Yao 等探索了丰富的与 OC 预后相关的 RNA 剪接网络和调控模式，AS 为 OV 的治疗提供了大量的生物标志物和潜在靶点，并且在 OC 综合治疗中，干扰 AS 的潜

在的意义[16]。

## 2. 可变剪接与卵巢癌的分子分型

卵巢癌的分型一直在完善，目前无统一的结论，但为今后建立成熟的卵巢癌的分子分型体系奠定了坚实基础和重大参考价值。目前最新的是 2020 年对约 6000 例非卵巢癌患者的输卵管上皮细胞进行单细胞 RNA 测序，发现 4 分泌细胞亚型，在 TCGA 等多个数据库中对每个癌组织中五种细胞亚型的占比进行分析，发现 EMT 亚型占比高的肿瘤患者预后差[17]。上皮型卵巢癌通常出现在晚期，是妇科癌症死亡的最常见原因，治疗需要专家的多学科护理[18]。上皮剪接调节蛋白(Epithelial Splicing Regulatory Protein, ESRPs)是上皮细胞特异性 RNA 结合蛋白，可调节上皮细胞的可变剪接，从而参与上皮-间质转化。在 OC 细胞中，DNA 低甲基化与 ESRP1 或 ESRP2 过表达相关，ESRP1 的过表达调节了 EMT 标记和癌症相关基因的可变剪接，从而导致从间质表型向上皮表型的转换[19]。卵巢癌与可变剪接有密切关系，但相关研究比较少。卵巢癌不仅存在着不同的分子亚型，同一分子亚型也存在着异质性，对卵巢癌异质性的深入探索有利于进行精准治疗、并改善患者的预后和生存质量。

## 3. 可变剪接与卵巢癌发生、发展

可变剪接主要是从以下三个经典层面进行调控：RNA 层面、转录层面、表观遗传学层面。

近年来研究证据表明，剪接因子肿瘤的发生和发展中发挥着重要作用[20] [21]。SF3B4 是经典剪接因子家族 SF3B 的一个亚基[22]。体外和体内实验表明，SF3B4 的过表达促进 OC 细胞增殖和迁移，下调 SF3B4 则会相反。其中非编码小分子 RNA 509 3p (micro RNA 509 3p, miR-509-3p)直接与 SF3B4 的 3'-UTR 结合降低 SF3B4 mRNA 的表达，因为其发生可变剪接：第 8 内含子的保留和过早终止密码子的产生，而 SF3B4 的低表达会导致 RAD52 的低表达。此外，RAD52 的表达降低还抵消了 SF3B4 过表达的促瘤作用，也就是说 miR-509-3p 负调控 SF3B4，调控 RAD52 的可变剪接而促进了 OC 的进展[23]。剪接因子的异常表达在肿瘤的发生发展中起着重要作用。在所有的剪接因子突变中，剪接因子 SF3B1、U2AF1、SRSF2、ZRSR2 的主要杂合点突变是促进疾病进展的驱动突变因素[24]。RNA 测序研究进一步揭示，所有这些突变都改变了剪接体的功能，从而导致了许多序列特异性的错误剪接事件[25] [26] [27] [28]。剪接因子 BUD31 的调控的是卵巢癌细胞生长和卵巢癌进展的关键因素，剪接因子 BUD31 促进 BCL2 家族成员 BCL2L12 第三外显子的包含从而产生全长 BCL2L12，全长的 BCL2L12 抗凋亡的并促进卵巢癌的进展，相反敲低 BUD31 促进第三外显子跳跃，从而导致 BCL2L12 的截断异构体经历无义介导的 mRNA 衰变，卵巢癌细胞随后发生凋亡[29]。

RNA 结合蛋白(RBPs)影响肿瘤的发生和发展，可以作为癌症治疗的新的潜在靶点。MEX-3 RNA 结合家族成员 A (mex-3 RNA binding family member A, MEX3A)一种包含环指结构域和 RNA 结合域的双功能蛋白，在卵巢癌中是一个重要的致癌因子，促进了的卵巢癌细胞生长，影响着肿瘤发生[30]，MEX3A 基因敲除导致 timeless circadian regulator (TIMELESS) mRNA 的第 23 内含子的保留，并且由于无义介导的 RNA 衰变的刺激，TIMELESS mRNA 减少，抑制卵巢癌细胞的生长和侵袭[31]。小核核糖核蛋白多肽 B (small nuclear ribonucleoprotein polypeptides B and B1, SNRPB)是剪接体的核心成分，调控着 Pre-mRNA 的可变剪接。然而，其在卵巢癌中的作用和潜在机制仍不清楚。Li 等研究通过对 TCGA 和 CPTAC 数据库的分析，确定 SNRPB 是卵巢癌的关键驱动因素与正常输卵管相比，新鲜冷冻卵巢癌组织中 SNRPB 的表达显著增加。免疫组织化学显示，在福尔马林固定、石蜡包埋的卵巢癌切片中 SNRPB 的表达增加，且与卵巢癌的不良预后呈正相关。在功能上，SNRPB 基因敲除抑制了卵巢癌细胞的增殖和侵袭，而过表达则起到相反的作用。且在顺铂处理后 SNRPB 表达增加。根据 RNA-seq，几乎所有与 DNA 复制和同源重组相关的差异表达基因在 SNRPB 被敲除后下调。BRCA2 是肿瘤抑制基因，其突变型易患乳腺癌和卵巢

癌。深入的研究表明，BRCA 蛋白参与了许多关键的细胞过程[32]。外显子 3 跳跃导致 DEGS DNA 聚合酶 $\alpha$1POLA1 提前终止密码子，导致无意义介导的 RNA 衰退；第三外显子跳跃导致 BRCA2 同源重组所必需的 PALB2 结合域丢失，并增加卵巢癌细胞对顺铂的敏感性。POLA1 或 BRCA2 基因敲除可部分抑制 SNRPB 过表达的卵巢癌细胞恶性程度的增加，总而言之，SNRPB 是一个重要的致癌驱动因素，抑制了 POLA1 和 BRCA2 的第三外显子跳跃来促进卵巢癌的进展。因此，SNRPB 是卵巢癌潜在的治疗靶点和预后标志物[33]。

有诸多与卵巢癌相关的可变剪接事件，如剪接因子 USP39 通过靶向高迁移率族 AT Hook 蛋白 2 (high mobility group AT-hook 2, HMGA2)促进 OC 进展[34]。胰岛素样生长因子 2-MRNA 结合蛋白 3 (insulin like growth factor 2 mRNA binding protein 3, IGF2BP3)和 lin-28 homolog B, Lin28B 与 OC 患者耐药有关[35]。富含脯氨酸和谷氨酰胺的剪接因子(splicing factor proline and glutamine rich, SFPQ)通过调节 OC 中富含丝氨酸和精氨酸的剪接因子 2 (serine and arginine rich splicing factor 2, SRSF2)的活性来调节铂的反应[36]。SORBS2 抑制 OC 的免疫逃避[37]。可见 AS 影响着 OC 的关系极密切，影响着 OC 的生物学行为，AS 让我们从多个维度全面了解 OC，从而为 OC 治疗提供思路。

## 4. 可变剪接与卵巢癌预后、治疗

Zhang 等单因素 COX 回归分析结果显示：在 OC 中的 15,278 个基因中，有 31,286 个基因与 AS 事件相关，其中 1524 个 AS 事件与 OS 显著相关[38]。耐药正是治疗肿瘤面临的一大挑战，可变剪接改变了靶 mRNA 3'UTR 结合位点，而这种改变会影响产生的蛋白质，以及影响靶蛋白的药物亲和力，最终导致耐药性[39]，细胞外基质蛋白-1a (extracellular matrix protein 1a, ECM1a)是 ECM1 的一种分泌型亚型，分泌型 ECM1a 亚型通过 GPR 基序结合整合素 $\alpha X\beta 2$ 和激活 AKT/FAK/Rho/细胞骨架信号而诱导肿瘤发生。ATP 结合盒亚家族 G 成员 1 (ATP binding cassette subfamily G member 1, ABCG1)转导 ECM1a 整合素 $\alpha X\beta 2$ 的相互作用信号，促 AKT/FAK/Rho/细胞骨架分子的磷酸化，并通过上调 CD326 介导的细胞干细胞来增强癌细胞对顺铂的耐药性。相反，非分泌型 ECM1b 亚型结合肌球蛋白并阻断其磷酸化，损害细胞骨架介导的信号传导和肿瘤发生。此外，ECM1a 诱导异种核核糖核蛋白 L 样(heterogeneous nuclear ribonucleoprotein L like, hnRNPLL)蛋白的表达，从而有利于发生 ECM1a 的 mRNA 可变剪接。ECM1a、$\alpha X\beta 2$、ABCG1 和 hnRNPLL 高表达与生存率低相关，而 ECM1b 高表达与生存率高相关。异构体通过与肌球蛋白结合来抑制肌球蛋白的磷酸化，阻止细胞骨架诱导的肿瘤发生。ECM1b 增加 hnRNPLL 剪接因子的表达，这导致 ECM1 的剪接增加，从而产生多种异构体[40]，影响 OC 的治疗效果。

综上所述，国内外对可变剪接在卵巢癌的研究尚处于起步阶段，可变剪接异常参与 OC 的全程，包括分型、发生、进展和化疗耐药，所以可能为其诊断提供新的标志物，为其治疗提供新的靶点，也可为其预后提供新的标志物。但仍有很多需要深入细化探索的知识。而目前对于可变剪接抗肿瘤药物开发正在进行中，继续探索可变剪接在卵巢癌的发生发展的机制，很可能是改善卵巢癌早期诊断和治疗的新思路。2023 年 3 月 22 日，国家癌症中心在《中华肿瘤杂志》发布了最新的全国癌症统计数据[41]，公布 2016 年中国恶性肿瘤流行数据，卵巢癌在全国的发病例数位居第 18 位，在贵州居于第 15 位。笔者希望可以通对可变剪接在卵巢癌中的作用的研究进一步了解卵巢癌基因表达调控的机制，并为下一步卵巢癌精准医疗奠定基础。

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