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# 宫颈癌放射治疗中DNA损伤修复相关基因

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## 摘　要

**宫颈癌是全世界女性最常见的恶性肿瘤之一，也是女性癌症死亡的第二大常见原因。放射治疗可在宫颈癌患者的所有阶段进行。辐射抗性是肿瘤放射治疗中的关键问题。因此，研究宫颈癌放射治疗过程中DNA损伤修复相关基因，有利于寻找新的治疗靶点以进一步提高宫颈癌放疗疗效。**

## 关键词

**宫颈癌，放射治疗，DNA损伤修复，*GS*，*LINP1*，*VRK1*，*HOTAIR***

# DNA Damage Repair Related Genes in Cervical Cancer Radiotherapy

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## Abstract

**Cervical cancer is one of the most common malignant tumors in women around the world, and it is also the second most common cause of cancer death in women. Radiation therapy can be performed at all stages of cervical cancer patients. Radiation resistance is a key issue in tumor radiotherapy. Therefore, the study of genes related to DNA damage and repair in the course of cervical cancer radiotherapy is helpful to find new therapeutic targets to improve further cervical cancer radiotherapy efficacy.**

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**Keywords**

**Cervical Cancer, Radiation Therapy, DNA Damage and Repair, *GS*, *LINP1*, *VRK1*, *HOTAIR***



## 1. 前言

宫颈癌是全世界女性最常见的恶性肿瘤之一[1]。虽然现在已经有了人类乳头状瘤病毒(HPV)疫苗，并且已经建立了有效的筛查方法来降低其发病率和死亡率，但宫颈癌仍然是发展中国家女性中第二常见的癌症和第三主要的癌症死亡原因[2]。2016 年根据国家癌症综合网络(National Comprehensive Cancer Network, NCCN)指南指出，放射治疗可在宫颈癌患者的所有阶段进行，包括：作为无法手术的早期患者的治疗；在较大的早期和晚期肿瘤中联合化疗或作为术后的辅助治疗；作为姑息治疗，可缓解癌症引起的症状并改善晚期患者的生活质量。但是，有些患者对放射治疗的反应较差，复发和治疗失败的发生率较高[3] [4] [5]。

放射抗性是肿瘤放射治疗中的关键问题。放疗引起 DNA 损伤进而杀死肿瘤细胞，特别是 DNA 双链断裂(DSBs)。DNA 双链断裂本身通常不是致命的，但它使细胞无法修复 DNA 双链断裂最终导致细胞死亡[6]。因此，DNA 损伤修复能力是影响细胞放射反应的重要因素之一[7]。因此，关于哪些因素是宫颈癌的抗放射性和不良预后的原因，还有待于更多研究。

真核生物中两种主要的 DNA 损伤修复途径是同源重组(HR)和非同源末端连接(NHEJ) [8]。这些修复系统在亚致死性损伤和产生剂量率效应中起重要作用，如果损伤得以完整和精确的修复，细胞的放射敏感性就会发生改变；如果损伤不能被修复，则会诱导细胞凋亡[9]。本文将对宫颈癌放射治疗 DNA 损伤修复相关基因进行综述。

## 2. 谷氨酰胺合成酶(*GS*)

谷氨酰胺合成酶(*GS*)是一种代谢酶，它催化谷氨酸和氨的连接形成谷氨酰胺[10]。肿瘤细胞利用谷氨酰胺作为必需的代谢原料，以满足肿瘤细胞快速增殖的能量需求[11] [12] [13]。耐辐射细胞具有高谷氨酰胺合成代谢。因此，谷氨酰胺及其代谢底物可为 DNA 损伤修复提供调控机制[14]。*GS* 的下调可延迟 DNA 修复，减弱核苷酸代谢，增强体内外的辐射敏感性；*GS* 的高表达促使肿瘤细胞在放射时仍能生长。Fu S. 等人[6]研究在辐射诱导应激下，谷氨酰胺代谢对肿瘤放射治疗反应的影响。他们发现抗辐射细胞具有较高的谷氨酰胺合成代谢。该研究在体外实验中发现 *GS* 基因敲除可延迟 DNA 修复，减弱核苷酸代谢，增强放射敏感性。最终结果显示谷氨酰胺合成酶通过促进核苷酸合成和加速 DNA 修复，将谷氨酰胺代谢与放疗反应联系起来。也有研究证实谷氨酰胺合成酶与胰腺癌、前列腺癌、胃癌、肺癌等肿瘤辐射抗性有关[15] [16] [17] [18]，需要更进一步研究谷氨酰胺合成酶与宫颈癌辐射抗性的关系。

## 3. 非同源末端连接途径 1 (*LINP1*)

非同源末端连接被认为是哺乳动物细胞 DSB 修复的主要途径。此种途径的修复过程是在不需要 DNA 末端之间广泛的同源性连接实现的[19]。研究显示 *LINP1* 促进非同源末端连接介导的 DNA 损伤修复活性[20] [21]，其表达可能受 EGFR 途径调控[22]。Liang 等[23]人研究表明非同源末端连接途径 1 (*LINP1*)与乳腺癌细胞的增殖、转移和化学抗性有关。Li 等[24]人通过 qRT-PCR 和 Western blot 方法检测，探讨 *LINP1*

在卵巢癌中的作用机制，结果发现卵巢癌组织中 *LINP1* 的表达明显高于癌旁组织，并证实 *LINP1* 通过下调 *KLF6* 促进肿瘤细胞的转移和增殖。Wang X.等[25]人使用 γ-H2AX 聚焦形成实验观察放疗前后宫颈癌 Hela S3 细胞的凋亡情况，发现 *LINP1* 通过 NHEJ 途径提高 DNA 损伤修复效率，参与宫颈癌的抗辐射性。虽然 *LINP1* 的表达水平与宫颈癌患者放疗后肿瘤反应的关系尚未完全阐明，但他们的研究表明 *LINP1* 可能是宫颈癌的一个重要的预后指标和一个新的治疗靶点。

## 4. *VRK1*

越来越多的证据表明，长链非编码 RNA (*lncRNAs*)在妇科肿瘤的凋亡、转移、侵袭、迁移和细胞增殖中起着重要的生理作用[26]，*VRK1* 是其中一种。*VRK1* [25] [27]是一种丝氨酸激酶，与细胞增殖[28]和 DNA 损伤反应有关[29] [30] [31]。Li 等人[32]用 qPCR 检测乳腺癌细胞中 *VRK1* 的表达情况，发现 *VRK1* 在乳腺癌组织中表达下调，抑制细胞增殖，促进细胞凋亡，与肿瘤分期降低、生存期延长有关。*VRK1* 在细胞增殖和 DNA 修复过程中起着至关重要的作用，如果被抑制，可以导致肿瘤生长减缓，基因不稳定性增加，也可能使肿瘤更具免疫原性，可用于治疗[33]。*VRK1* 在宫颈癌细胞 DNA 放射损伤修复中的作用机制需进一步研究探讨。

## 5. *HOTAIR*(长非编码核糖核酸 HOX 转录反义 RNA)

HOX 转录反义 RNA (*HOTAIR*)是一个 2158 核苷酸长的 lncRNA，从染色体 12q13.13 上的 HOXC 位点表达，它被发现能够沉默肿瘤抑制因子，激活癌基因和关键信号通路[34] [35] [36] [37] [38]。体内实验还发现，*HOTAIR* 在宫颈癌组织中高表达，并与临床分期、肿瘤大小和淋巴结转移相关[39] [40]。Guo X.等[41]人研究发现 *HOTAIR* 的功能被抑制可以通过抑制宫颈癌 HeLa 细胞的 Wnt 信号通路，减少自噬和逆转上皮－间充质转化，从而提高对放疗的敏感性。也有研究表明 *HOTAIR* 的敲除可通过抑制 *Wnt/β-catenin* 途径抑制细胞增殖并在 G1 期阻滞[42]。此外，Jing L.等人[43]的研究证明 *HOTAIR* 的敲除上调了 *p21* 的表达，从而提高了宫颈癌细胞的放射敏感性。持续稳定的 *HOTAIR* 基因敲除显著抑制肿瘤生长，并使宫颈癌对体内放疗敏感。他们的研究提供了新的证据，说明 *HOTAIR* 可以促进宫颈癌的增殖、侵袭和转移。这些发现表明，靶向 *HOTAIR* 治疗宫颈癌是一种有效的治疗策略。

## 6. 研究展望

恶性肿瘤治疗的一个主要方法是在肿瘤细胞中产生灾难性的 DNA 损伤，目前放射治疗是恶性肿瘤治疗的常用方法，其能直接损伤肿瘤细胞 DNA。放射治疗可在宫颈癌治疗的所有阶段进行，如根治性放疗、术前或术后辅助放疗及晚期或复发放疗。尽管宫颈癌放疗已取得显著效果，现在也使用铂类等放疗增敏剂，但仍存在一些放疗效果不佳或复发病例。在放射治疗过程中，DNA 双链断裂未及时得到修复，即可引起肿瘤细胞凋亡。肿瘤细胞的抗辐射性一直是限制宫颈癌治疗效果和导致其复发的主要障碍。目前关于宫颈癌放射性损伤 DNA 修复相关基因的研究是热点，如 *GS*、*LINP1*、*VRK1*、*HOTAIR* 等。因此需要更多试验去研究宫颈癌放射治疗过程中 DNA 损伤修复相关基因及其机制，从而发现一些新的治疗策略以提高宫颈癌放疗疗效。

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