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·综述·

## LOXL2——具有潜在临床应用价值的新标志物

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**【摘要】** 赖氨酰氧化酶样蛋白 2 (Lysyl oxidase-like 2, LOXL2) 是赖氨酰氧化酶家族成员之一, 其在细胞外主要参与基质胶原蛋白和弹性蛋白的交联产物的形成, 在细胞内主要通过 Snail 途径调节上皮细胞-间叶样细胞转化 (Epithelial-mesenchymal transition, EMT) 过程, LOXL2 正在作为一种新的治疗方法的靶点研究。但是在不同肿瘤中或不同肿瘤亚型中的表达情况差异明显, 需要进一步研究。

**【关键词】** 赖氨酰氧化酶样蛋白 2; 侵袭; 转移

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赖氨酰氧化酶样蛋白 2 是近年来逐渐受到重视的一种胺氧化酶。它与组织纤维化和肿瘤的侵袭、转移都有密切的关系, 但是在不同类型的肿瘤中, 发挥的作用是不同的, 甚至是矛盾的。需要我们进一步的深入研究, 以了解其中的分子生物学机制, 为临床治疗或预测提供一种新的途径或指标。

### 1 赖氨酰氧化酶家族

赖氨酰氧化酶样蛋白 2 (Lysyl oxidase-like 2, LOXL2) 是赖氨酰氧化酶家族成员之一, 这个家族具有代表性成员, 分别是 LOX、LOXL1、LOXL2、LOXL3、LOXL4。它们的-COOH 端具有高度保守的序列, 这决定了它们的同源性和相似性<sup>[1]</sup>。然而, LOX 家族各亚型的 N-端具有更大的差异性, 这可能决定了这一组同工酶各自不同的功能角色和组织分布<sup>[2]</sup>。赖氨酸-酪氨酸辅酶因子和四组氨酸铜结合域是赖氨酰氧化酶家族成员独有的<sup>[3-4]</sup>, 也是 LOX、LOXL2、LOXL4 发挥胺氧化酶活性的必要结构<sup>[5-8]</sup>。赖氨酰氧化酶家族中最具代表性的 LOX 和 LOXL 一直被看做是与基质胶原蛋白和弹性蛋白的交联产物形成密切相关的细胞核外酶<sup>[4, 9]</sup>。然而, Hayashi 等<sup>[9]</sup> 和 Csiszar 等<sup>[10]</sup> 的研究发现, 在正常壮年小鼠的各种组织的不同区域细胞的核内和核外都有 LOX 和 LOXL 存在, 发挥各种对肿瘤的发生和进展密切相关的生物学功能, 包括: 细胞生长调控<sup>[11]</sup>、粘附、细胞运动和侵袭<sup>[3, 12]</sup>。

### 2 LOXL2 与肿瘤

1997 年, Saito 等<sup>[13]</sup> 首次研究发现, 相对于粘附性肿瘤细胞株, 在各种非粘附肿瘤细胞株中 LOXL2 表达均下调。在 RAS 转化小鼠的纤维母细胞中 LOXL2 mRNA 的表达减少近 60%<sup>[14]</sup>。还有报道, 在

头颈部鳞状细胞癌 (HNSCC) 和浆液性卵巢癌中发现 LOXL2 表达的下调<sup>[15-17]</sup>。Saux 等<sup>[18]</sup> 在 1998 年将 LOXL2 基因定位于 8p21.2-p21.3, 这个区域的染色体丢失现象在多种恶性肿瘤中被发现, 包括卵巢癌<sup>[19]</sup>、头颈部鳞状细胞癌<sup>[20]</sup>、肠癌<sup>[21-22]</sup>、食管癌<sup>[23-24]</sup> 和乳腺癌<sup>[25-26]</sup>。

但是, 在新近的研究中却发现 LOXL2 的高表达和肿瘤的侵袭行为有关。首先在高致瘤性、转移性鼠鳞状细胞癌和梭状细胞癌中发现 LOXL2 mRNA 的表达, 而同时在无致瘤性的角质细胞株中未发现 LOXL2 mRNA 的表达<sup>[27]</sup>。而且同样的情况也出现在高侵袭性、转移性乳腺癌细胞株与低侵袭性、转移性乳腺癌细胞株的对比研究中<sup>[3]</sup>。有关 LOXL2 的表达与乳腺癌的临床肿瘤分级的研究资料也支持上述结果<sup>[29]</sup>。而且进一步研究发现, 原本无侵袭性的 MCF-7 乳腺癌细胞株被转染了 LOXL2 基因后即出现了侵袭性<sup>[29]</sup>, 支持了 LOXL2 是一种致癌基因的观点。随后, 有多家分别报道在乳腺癌、肠癌、食管癌、胆管癌、胰腺癌和胃癌细胞和组织中 LOXL2 的表达升高, 而且这种高表达与更差的分化、更高的 N 分期和临床 TNM 分期以及较差的生存期有关<sup>[29-33]</sup>。

在 RAS 转化小鼠的纤维母细胞、头颈部鳞状细胞癌、肺腺癌和浆液性卵巢癌中发现 LOXL2 表达的下调。但是, 在乳腺癌、肠癌、食管癌、胆管癌、胰腺癌和胃癌中 LOXL2 的表达上调, 这说明了 LOXL2 在肿瘤发展过程中的角色是复杂的。而且在 Zhan 等<sup>[34]</sup> 的报道中, 在 NSCLC 中 LOXL2 表达的显著下调, 而且和更高的 N 分期和临床 TNM 分期有密切联系, 但这种现象仅仅出现在肺腺癌患者, 而在肺鳞癌患者中却没有观察到这种联系。这更进一步说明了 LOXL2 的复杂性。

### 3 LOXL2与EMT

进一步研究发现,在上皮细胞-间叶样细胞转化(Epithelial-mesenchymal transition, EMT)过程中LOXL2的表达上调,其中包括上皮表型的丢失和间叶细胞的活动性表型的获得<sup>[35]</sup>。SNAIL是EMT过程中至关重要的一种转录因子<sup>[27]</sup>。Fong等<sup>[29]</sup>研究显示LOXL2能够与SNAIL相互作用并提高SNAIL蛋白的稳定性,诱导EMT。当SNAIL表达的转移性癌细胞中LOXL2下调,引起E-cadherin的合成,减少了间叶细胞转化和促血管生成物质的生成,减低了侵袭性。虽然目前还不确定LOXL2是否通过抑制SNAIL活性的促进侵袭、转移,但重要的是发现了在EMT过程中LOXL2与NAIL相互作用的重要性,这对于肿瘤的进展,特别是侵袭性和远处转移非常重要<sup>[29]</sup>。LOXL2抗体可以明显抑制肿瘤的生长和转移<sup>[32]</sup>。在上皮细胞株T47D、MCF-7、HCT-116、HCT-15和DLD-1中,LOXL2的表达缺失,而在高侵袭性和转移性的乳腺癌细胞株MDAMB-231和Hs578T中表达<sup>[29]</sup>,MDAMB-231和Hs578T具有间叶细胞表型<sup>[3]</sup>,这与前面的结果是一致的。在一些组织中,例如乳腺和卵巢,早期可能出现LOXL2的表达缺失,但在肿瘤的演化过程中出现LOXL2的再表达,这种现象可能与微环境的变化诱因有关。事实上,MCF-7细胞与纤维母细胞在特定的培养基中共同培养,能够被促发LOXL2的表达<sup>[2]</sup>。这和家族中的另一个成员LOX是相近的。LOX已经被证明,根据细胞类型和转化状态的不同,可以表现出肿瘤抑制或促肿瘤两种截然不同的功能<sup>[3,36-37]</sup>。此外,Peng等<sup>[32]</sup>研究显示分泌的LOXL2能够同时激活Snail/E-cadherin and Src kinase/Focal adhesion kinase (Src/FAK)途径。然而,LOXL2诱导胃癌细胞侵袭和远处转移仅仅通过Src/FAK途径。

### 4 LOXL2的调节

Kaneda等<sup>[38]</sup>提出,是否象LOX一样,LOXL2表达调节存在一种外在转录调节机制。Fong等<sup>[29]</sup>用脱甲基因子处理肠癌细胞株,结果发现LOXL2表达的增加。Lind等<sup>[39]</sup>报道,在肠癌细胞株与原位癌细胞中,LOXL2表达和甲基化率是相同的。然而,但在随后的肠癌细胞的进展演化中,随着启动子的去甲基化,获得了LOXL2的表达。表达的调控也可能通过肿瘤演化和EMT过程中的转录因子完成,如AP1、NFjB和WT1<sup>[40-42]</sup>。这意味着遗传和外在环境因素都可能参与了癌症进展过程中LOXL2基因表达的调节。

综上所述,LOXL2可能会成为一种预测肿瘤侵袭性和远处转移风险的指标,或者成为一种新的治疗方法的靶点,但仍需要进一步的研究来证明在体内肿瘤转移过程中LOXL2的功能作用,探索如何把LOXL2阻断发展成为一个新的、具有发展潜力的治疗策略。

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