综　述

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SENP1在肺癌病理生物学中的作用★

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摘要： SENP1是一种参与去SUMO化的蛋白质，是肿瘤发生和复发、转移的一个危险因素，与多种肿瘤的发生、侵袭、转移及耐药相关，其在肿瘤组织中的表达具有十分重要的意义。SENP1通过与多种分子、靶蛋白相互作用调控细胞周期、促进肿瘤血管生成、参与细胞铁死亡等，导致肺癌的复发和转移，是肺癌患者预后不良的影响因素。本文对SENP1及其靶蛋白在肿瘤发生发展中的作用机制、对肺癌耐药和预后的影响进行总结。

关键词： SENP1；肺癌；靶向治疗；耐药；预后
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The role of SENP1 in lung cancer pathobiology★

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Abstract: SENP1, a protein involved in de-SUMOylation, is a risk factor for tumor occurrence, recurrence and metastasis. It is associated with the occurrence, invasion, metastasis and drug resistance of a variety of tumors. Its expression in tumor tissues is of great significance. SENP1 contributes to the recurrence and metastasis of lung cancer by interacting with a variety of molecules and target proteins to regulate the cell cycle, promote the tumor angiogenesis, and participate in cellular iron death, etc. SENP1 is an affecting factor for the poor prognosis of lung cancer. In this paper, we reviewed the mechanism of SENP1 and its targeting proteins in tumor development, and their effects on drug resistance and prognosis of lung cancer.

Keywords: SENP1; Lung cancer; Targeted therapy; Drug resistance; Prognosis

0　前言

据统计，我国肺癌发病率和死亡率分别占全球的37.0%和39.8%[1]。肺癌的治疗方式有多种，例如手术、化学治疗及靶向和免疫疗法等[2]。进一步研究肺癌发生发展的分子机制，探索新的治疗靶点和治疗模式是肺癌治疗的重要发展方向[3]。肺癌的发生、发展与遗传因素及环境因素密切相关，各种内外因素导致的驱动基因突变和信号通路异常激活是肺癌发生及靶向治疗耐药的关键因素[4]。目前，多种异常激活的基因已经成为肺癌精准诊断和治疗的重要靶点，包括EGFR、ALK、ROS1、BRAF、KRAS、NTRK、PD-L1等[5]。探索肺癌中的分子机制可以为肺癌靶向治疗提供新的诊断和治疗靶标。众多研究表明，SUMO特异性蛋白酶（sentrin-specific protease，SENP）在多种肿瘤中表达异常，提示其与肿瘤的发生、发展及耐药密切相关[6]。

1　SENP1在肺癌中的作用机制

SENP1是一种参与去SUMO化的蛋白质，几乎

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在所有癌症中过表达[6]。蛋白SUMO化失衡导致肿瘤的发生和发展，包括血管生成、转移及耐药特性改变[7]，SENP负责SUMO前体的成熟及SUMO修饰的底物解耦合，SUMO化参与了许多重要的细胞生物学过程，而SENP1表达与肿瘤的侵袭性和复发直接相关[8]。因此，调控蛋白SUMO化修饰并维持其平衡的重要分子SENP成为肿瘤治疗的靶点[9]。

1.1 SENP1/HIF-1α信号通路

低氧诱导因子-1α（hypoxia-inducible factor-1α，HIF-1α）是肿瘤进展和靶向治疗的关键转录因子，过表达的HIF-1α通过各种机制调控肿瘤进展，包括血管生成、细胞增殖和存活、细胞侵袭和转移、代谢重编程、肿瘤干细胞维持、诱导遗传不稳定和治疗耐药性[10]。醛酮还原酶家族1成员C1（aldo-keto reductase family 1 member C1，AKR1C1）可增强HIF-1α的表达，推动肿瘤代谢重编程，进而促进非小细胞肺癌（non-small cell lung cancer，NSCLC）细胞增殖[11]。成纤维细胞中的HIF-1α可激活NF-κB信号通路，增强CC类趋化因子配体5（CC chemokine ligand 5，CCL5）的后续分泌，从而促进肺癌细胞生长[12]，并通过上调NRP1表达诱导肺腺癌细胞转移和血管生成拟态（vasculogenic mimicry，VM）形成[13]。在体外实验中，下调HIF-1α表达可诱导细胞凋亡，抑制肺腺癌A549细胞生长[14]。SENP1参与了HIF-1α的低氧反应和稳定化的激活。在缺氧导致的实体瘤中，SENP1表达上调并促进肿瘤增殖，通过去SUMO化保持HIF-1α的稳定性和转录活性[15]，而HIF-1α可激活血管内皮生长因子（vascular endothelial growth factor，VEGF）[16]。miR-199a可通过靶向下调HIF-1α/VEGF信号通路来阻止NSCLC细胞增殖[17]。SENP1和HIF-1α存在正反馈效应[18-19]，可改善缺氧环境，促进肿瘤生长和转移，在肿瘤血管生成中起重要作用[20]。另外，SENP1可通过与雄激素受体、HIF-1α、C-JUN和Cyclin D1等结合来介导细胞活动，并在通过SUMO化机制改善靶蛋白稳定性方面起着关键作用[21]。SENP1在缺氧环境下可积极调节HIF-1α表达，表明SENP1/HIF-1α轴可作为潜在靶向治疗方向[22]。

1.2 SENP1与铁死亡在肺癌中的作用机制

铁死亡与传统的细胞凋亡和坏死概念不完全相同，其与铁代谢和氧化损伤密切相关，标志是活性氧显著增加、线粒体体积缩小及膜密度增大，与肿瘤的发生、发展和治疗密切相关[23]。铁死亡通过肿瘤微环境中多种信号分子的释放来抑制或促进肿瘤进展[24]，并且其相关基因可预测肺腺癌患者的总生存期（overall survival，OS）[25]。细胞铁死亡调控蛋白也受SUMO化修饰的调控[26]，而过表达SENP1可使肺癌细胞免受顺铂诱导的铁死亡，表明SENP1可能与顺铂耐药相关。A20是一种有效抗炎分子，其抗炎特性常归因于其作为泛素编辑酶抑制炎症性NF-κB信号转导的能力[27]。研究发现，SENP1过表达小鼠中A20和ACSL4表达上调，而GPX4和SLC7A11的表达受到抑制，表明SENP1可通过上调与ACSL4和SLC7A11具有相互作用的炎症信号分子A20的表达，调节肺癌细胞中铁死亡相关基因的表达[28]。

1.3 SENP1促进肺癌转移

肿瘤细胞向周围迁移仍然是癌症相关死亡的主要原因[29]。对NSCLC患者的研究发现，NSCLC组织中SENP1的表达水平明显高于正常肺组织，SENP1表达上调与肿瘤直径>5 cm（P=0.045）、淋巴结转移（P=0.003）、TNM晚期（P=0.012）显著相关[30]。肺癌术后化疗患者中，SENP1高表达组复发率和转移率较低表达组高37.1%，OS率较低表达组低16.8%[31]。尽管化疗是许多转移性癌症患者的标准治疗方法，但对肿瘤侵袭和转移的分子机制的完全理解仍然是一个重大挑战[32]。类似相关研究还发现，SENP1可通过HIF-1α信号通路调节两种关键骨重塑蛋白——基质金属蛋白酶2（matrix metalloproteinase 2，MMP2）和MMP9的表达，促进前列腺癌转移[33]。三阴性乳腺癌（triple negative breast cancer，TNBC）组织中SENP1的高表达促进了肿瘤的发展，并导致患者预后不良。SENP1调节GATA结合蛋白1（GATA binding protein 1，GATA1）的SUMO化，进一步调节COP9信号转导复合体5（COP9 signalosome complex subunit 5，CSN5）转录，减弱锌指E盒结合的同源盒蛋白1（zinc finger E-box binding homeobox 1，ZEB1）泛素化，这是TNBC中上皮间质转化（epithelial-mesenchymal transition，EMT）的关键，并导致肿瘤的侵袭和转移[34]。

2 SENP1在肿瘤中的其他作用途径

SENP1在多种肿瘤中高表达，并通过多种途径促进肿瘤的侵袭及转移。P53是一种关键的肿瘤抑制因子，其功能的丧失往往是肿瘤发生的先决条件[35]。在肿瘤进展过程中，P53的功能与多种转录

和非转录活动有关，这些活动导致了机体对细胞增殖、衰老、死亡和DNA修复的严格控制[36]。SENP1是重要的P53去SUMO化酶，SENP1缺失协同DNA损伤诱导剂依托泊苷诱导P53活化和P21表达，抑制肿瘤细胞生长[37]。SENP1-Sirt3信号转导在代谢应激期间调节Sirt3激活和线粒体代谢，参与免疫反应和免疫细胞活性的稳态调控[38]。此外，转化生长因子β（transforming growth factor-β，TGF-β）在晚期肿瘤中具有前转移作用，其生物活性主要由SMAD蛋白家族介导，SMAD4是TGF-β通路的中心信号转导和转录因子[39]，本身不会导致肿瘤形成，而是促使其他基因引发肿瘤进展[40]。SENP1通过靶向SMAD4去SUMO化在多种肿瘤中起到重要作用[41]。SENP1可抑制SMAD4的SUMO化，并参与TGF-β1下游的EMT[42]。在前列腺癌中，SENP1通过上调E-钙黏蛋白（E-cadherin）表达使SMAD4去SUMO化，促进EMT，是晚期前列腺癌的潜在治疗靶点[43]。鼻咽癌组织中SENP1和STAT蛋白水平显著升高，SENP1可抑制STAT1的SUMO化，诱导STAT1蛋白表达和核易位，促进鼻咽癌的增殖和侵袭[44]。MYC癌基因参与多种人类肿瘤的发生[45]，在绝大多数肿瘤中通过肿瘤细胞内在机制、宿主免疫反应和肿瘤微环境（tumor microenvironment，TME）依赖机制启动和维持肿瘤生长[46]。lncRNA MNX1-AS1可驱动IGF2BP1的相分离，促进c-MYC和E2F1信号转导，并激活细胞周期进程，促进NSCLC细胞增殖[47]。一种新的致癌lncRNA——肺癌相关转录本3（lung cancer associated transcript 3，LCAT3）将远端上游元件结合蛋白1（far upstream element binding protein 1，FUBP1）募集到MYC远端上游元件（far upstream element，FUSE）序列中，激活MYC转录，促进肺癌细胞增殖、存活、侵袭和迁移[48]。SENP1在细胞增殖、肿瘤形成和细胞周期进程中起重要作用[49]，通过SUMO化调节许多细胞进程，包括蛋白质降解、蛋白质相互作用、转录、蛋白质定位、细胞周期进程、DNA复制和修复及RNA代谢等[50]。SENP1是一种重要的c-MYC去SUMO化酶，可正向调节c-MYC的稳定性和活性[51]，还可以通过对c-MYC的去SUMO化修饰抑制c-MYC蛋白酶体途径的降解，促进肿瘤进展[52]（图1）。

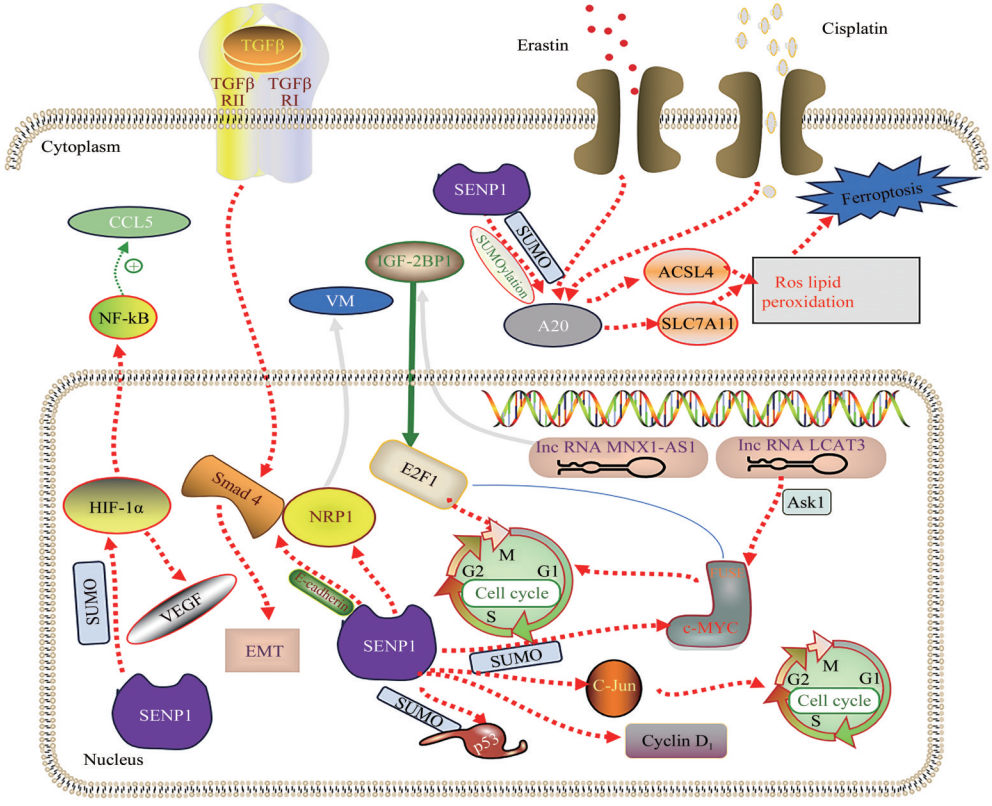

图1　SENP1相关作用机制

Fig. 1　SENP1-related mechanisms

3 SENP1 对肺癌治疗敏感性和耐药的影响

目前，放疗耐受仍然是肺癌治疗中的一个障碍。抑制 SENP1 可增强肺癌细胞的放射敏感性，因此，SENP1 可能成为放射增敏有希望的靶点[53]。SENP1 在肺癌组织中过表达，调控其表达水平被证明能明显影响肺癌细胞的增殖。使用小干扰 RNA（small interfering RNA，siRNA）沉默 SENP1 可使肺癌细胞对辐射敏感，SENP1 的耗竭明显增强了电离辐射（ionizing radiation，IR）诱导的细胞周期停滞、γ-H2AX 表达和细胞凋亡[54]，表明部分小分子 SENP1 抑制剂可作为放射增敏剂[53]。抑制 SENP1 的活性已被证明可以抑制肿瘤细胞的生存、增殖、侵袭和迁移，并增加其化学和辐射敏感性[55]，对新的肿瘤治疗方案的开发具有指导意义[55-56]。此外，SENP1 与跨肿瘤细胞系之间对抗肿瘤药物和药物靶向基因的敏感性和耐药性高度相关[6]。有研究使用 Mc 天然化合物类似物的集合进行药物协同筛选，以确定有效的 SENP1 抑制剂，筛选出的熊果酸和三苯氧胺可通过靶向 SENP1/JAK2/Stat 信号通路克服卵巢癌铂耐药，以治疗铂耐药卵巢癌和 SENP1 依赖性肿瘤[57]。

4 SENP1 影响肺癌的预后

肿瘤患者的预后判断仍是医学上面临的巨大挑战。临床研究发现，SENP1 可能是 NSCLC 中肿瘤特征和预后的指标，在接受辅助化疗的 NSCLC 手术患者中，SENP1 过表达与肿瘤体积较大、淋巴结转移、TNM 分期较晚及无病生存期（disease-free survival，DFS）和 OS 较短相关[31]。在总体生存分析中发现，与 SENP1 低表达患者相比，SENP1 高表达患者生存时间缩短 51.1%。SENP1 过表达与 NSCLC 的放化疗抵抗有关，并可作为 NSCLC 预后不良的风险因素[58]。

目前，针对 SENP1 的作用机制研究揭示了其通过靶蛋白调控肿瘤的部分机制，并且 SENP1 已经表现出作为肿瘤治疗靶点的潜力。进一步阐明 SENP1 及其靶点在肿瘤发生发展中的相互作用，将为肺癌早期诊断、治疗、预后提供新策略，从而提高 SENP1 抑制剂作为肺癌和其他恶性肿瘤治疗新方法的安全性和治疗效果。

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