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自噬介导下的胃癌化疗耐药性

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摘　要

胃癌是消化系统中常见恶性肿瘤之一，铂类药物是标准的一线治疗，在治疗过程中胃癌细胞会以一种适应性方式生存产生多药耐药性细胞株，即化疗耐药性，疾病进展。自噬作为一种高度保守的体内平衡途径，主要受长链非编码RNA (LncRNA)、miRNA等不同因子的调控，在胃癌的化学抗性中起着双重作用。因此，近年来小分子抑制剂或激活剂作为靶向自噬过程中的关键调控点为胃癌的治疗提供了新的策略。在这篇综述中，我们提供了系统总结，着重于自噬与胃癌化疗抗药性之间的关系。我们全面讨论了长链非编码LncRNA和miRNA等不同因子在自噬途径和胃癌化学耐药性调控中的作用和分子机制。

关键词

胃癌，自噬，化学抗性，ncRNA

Autophagy-Mediated Chemotherapy Resistance of Gastric Cancer

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Abstract

Objective: Gastric cancer is one of the common malignant tumors in the digestive system. Platinum drugs are the standard first-line treatment. During the treatment, gastric cancer cells will survive in an adaptive way to produce multidrug resistant cell lines, that is, chemotherapy resistance and disease progression. As a highly conserved homeostasis pathway, autophagy is mainly regulated by different factors such as long non-coding RNA (LncRNA) and miRNA, and plays a dual role in the chemoresistance of gastric cancer. In recent years, small molecule inhibitors or activators have provided new strategies for the treatment of gastric cancer as key regulatory points in the process

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of targeted autophagy. In this review, we provide a systematic summary focusing on the relationship between autophagy and chemotherapy resistance in gastric cancer. We comprehensively discussed the roles and molecular mechanisms of different factors such as long-chain non-coding LncRNA and miRNA in the autophagy pathway and the regulation of gastric cancer chemoresistance.

Keywords

Gastric Cancer, Autophagy, Chemoresistance, ncRNA

1. 前言

胃癌是消化系统中常见恶性肿瘤之一[1]，好发年龄在 50 岁以上，男女发病率比率为 2:1。流行病学显示，胃癌在全球癌症中发病率排名第五，死亡率位居第三[2]。发展中国家发病率及死亡率均排第三[3]。胃癌在中国发病率具有显著的空间差异性，即农村地区胃癌发生率几乎是市区的两倍[4]。其发病原因尚不明确，研究证明，多为个人生活习惯(吸烟、饮酒、工作压力等)、病毒、幽门螺杆菌感染和遗传家族史等多种因素共同作用的结果[5] [6]。胃癌早期一般无特殊症状，具有三高三低的特点，即发病率高、转移率高、死亡率高、早期诊断率低、切除率低、五年生存率低。

胃镜 + 活检是确诊胃癌的主要手段，但由于其是侵入性检查，普及性在临床上受到很大限制，综合胃癌临床特点大多数胃癌患者被确诊已属于中晚期，失去最佳的手术治疗。因此化疗和最佳支持治疗是必不可少的治疗手段。临床上目前将化学治疗作为晚期胃癌的一线标准治疗方法，但化疗药物，无论是常用的细胞毒性药物还是小分子靶向药物，都可能由于肿瘤细胞产生抵抗力形成耐药性的发展遇到治疗障碍，这也是大多数肿瘤复发和转移的常见原因[7]。目前，化疗药物的耐药性已成了亟待解决的主要难题。

2. 胃癌与耐药

胃癌确诊后的初次治疗首选根治性手术切除术，大部分患者会出现术后复发及转移灶[8]。全身性化疗能够有效的控制肿瘤的生长，延长患者生存期并改善晚期患者的生活质量。各种医学指南极力推荐含铂双药联合成为一线化疗方案，长期原方案的化疗就会产生耐药性，以致启动二线甚至三线治疗，但在此过程中胃癌细胞会以一种适应性方式生存产生多药耐药性细胞株，即化疗耐药性，疾病进展[9]。化疗耐药性可分为两类，即固有性耐药和获得性耐药。一方面，固有性耐药被定义为即使不进行任何药物治疗也发生的肿瘤抗药性，通常是由基因突变引起的。另一方面，获得性耐药是指癌细胞在长期的化疗药物的使用期间形成的适应性生存能力。这些方法都涉及到的治疗靶蛋白的高表达和代偿性信号转导途径的活化[10] [11] [12]。但无论是固有性还是获得性，胃癌化学抗性的产生涉及多种复杂因素[13]，包括药物排出增加有效成分可利用度减低[14]，药物在经过酶和非酶转化的过程中发生结构的改变导致药物靶点发生变化[15]，细胞凋亡信号通路的失调[16]，肿瘤细胞所处微环境的潜在作用，比如缺氧、细胞外基质的改变、细胞因子和生长因子[13]，上皮－间质转化诱导化学抗性基因的过表达[17]。

3. 胃癌与自噬

自噬，即“自食”，细胞的一种自我消化现象，在真核生物中是一种高度保守的多步骤的分解代谢过程，是一种适应性生存机制，可在营养不足，氧化应激，缺氧或感染等细胞应激下，为细胞提供了可持续的生物分子和能量来源，维持体内平衡[18] [19]。自噬在癌症中是发挥抑制肿瘤作用还是促进肿瘤生长取决于自噬途径上下调的相互作用[20]。

一方面，自噬通过溶酶体降解肿瘤相关蛋白突变体(P53、P62、BCR-ABL1 等)保持基因的稳定性、调节细胞周期，抑制肿瘤细胞生长和发育[21] [22]；MiR-155 能激活缺氧诱导因子(hypoxia inducible factor, HIF)的活性，激发低氧，反过来，低氧可诱导 miR-155 表达上调，以此形成正反馈，通过靶向作用于 mTOR 信号通路中的 RHEB，RICTOR 和 RPS6KB2 等来诱导自噬的发生，调节细胞周期，使细胞停滞于 G1/S 期，抑制细胞的增殖[23]。另一方面，自噬主要以 PI_3K-AKT-mTOR 途径调节癌细胞有氧糖酵解为癌细胞提供能量和营养，形成细胞内再循环促进已建立的癌症中的肿瘤生长[24]。PI_3K/AKT/mTOR 信号转导途径作为自噬经典途径在胃癌细胞增殖，生长，代谢以及存活起着至关重要的作用。如 Pectolinarigenin 通过 PI_3K/AKT/mTOR 自噬信号通路诱导胃癌细胞的细胞周期停滞在 G2/M 期，抑制细胞生长[22]。并且，胃癌的 EMT 侵袭行为亦是在 PI_3K/mTOR 途径的推动下发生远处转移[24] [25]。Yan 等[26]人，在研究 Yes 相关蛋白(Yap)通过 SIRT1/Mfn2/有丝分裂调节胃癌的生存和迁移的试验中，证实减少线粒体自噬相关因子 caspase-9，可影响细胞凋亡，影响胃癌细胞的存活和迁移。因此，基于自噬的治疗在胃癌症中的干预是非常重要的。

4. 自噬在胃癌的耐药性中的作用

在癌症治疗过程中，化疗药物和自噬相互影响，使癌细胞对药物的敏感性发生双向变化，长此以往，肿瘤细胞进入不可控的增殖状态，导致疾病恶化，发生原发病灶增大及远处转移征象。目前铂类药物是化疗药物的基础用药，其是一种非特异性抑制细胞周期化疗药物，主要促进肿瘤细胞的坏死和程序性死亡[27]。铂类药物广泛用于所有类型的癌症治疗，且是晚期胃癌化疗的一线用药。令人担忧的是长期的化疗过程使癌细胞产生耐药性，疾病进展。越来越多的研究表明，自噬可充当双刃剑并在诱导恶性肿瘤的化疗药物的耐药性的过程中起重要的作用[28] [29]，并取得了一定的成果。自噬的启动涉及多种自噬相关基因，并在 LncRNAs 的调节下干扰自噬通量，参与肿瘤的发生[29] [30]。如胃癌[31]。P62/SQSTM1 作为 RNA 结合蛋白可以直接将 ARHGAP5-AS1 转运到自噬体中进行降解，并逆转多药耐药性胃癌细胞的抗药性[32]。

长非编码 RNA (lncRNA)是通常由 200 多个核苷酸组成的 RNA 分子，没有蛋白质编码能力，并参与各种重要的细胞过程，例如细胞增殖，凋亡，分化和肿瘤细胞侵袭[33] [34] [35]。最近，有大量研究相继提出，lncRNAs 在自噬介导下参与不同类型癌症的化疗耐药性，如结直肠癌[36] [37]、肝癌[38]、肺癌[39]、前列腺癌[40]。并且 LncRNA 表现为竞争性内源性 RNA (ceRNA)，用于调节自噬相关的 microRNA (miRNA) [41] [42] [43] [44]。LncRNA 在自噬调节中具有非常重要的意义。因此，改善肿瘤的治疗敏感性可以通过利用 lncRNA 及 miRNA 表达的调节来实现，逆转抗药性。

更重要的是，大量研究证实 LncRNA 可通过多种机制参与胃癌化学耐药性，如铂类、5 氟尿嘧啶、多西他赛、长春新碱[45]。林等[46]人，发现 lncRNA HULC (长链非编码 RNA 肝癌高表达转录本)与 FoxM1 存在相互作用，且其在 LV-METase (携带蛋氨酸的慢病毒载体)转染的耐药胃癌细胞中具有低表达状态。并进一步证实了 LncRNA HUL 在介导自噬调节 FoxM1 逆转耐药胃癌细胞的 CDDP 的敏感性。宋等人[47]的研究证实 LINC01572 在 DDP 耐药的胃癌患者中表现出高表达水平，miR-497-5p 的低表达状态介导自

噬相关基因 ATG14 和 LC3-II 表达增加，LC-3I 呈现高表达状态，故下调 LINC01572 可诱导细胞自噬逆转 DDP 耐药性。MALAT1 通过促进 AGS/CDDP 和 HGC-27/CDDP 细胞的自噬增强了 CDDP 的抗性[48]。进一步的研究表明，在 AGS/CDDP 和 HGC-27/CDDP 细胞中，MALAT1 通过调节 miR-30b/ATG5 轴，介导与自噬相关的 CDDP 耐药性[49]。

许多研究发现许多 miRNA 亦在自噬相关基因的介导下调节自噬，干扰肿瘤化疗药物的对癌细胞的敏感性[50]。如 miR-212 过表达通过抑制自噬增加结直肠癌细胞对 L-OHP 的敏感性，逆转其对奥沙利铂的耐药性[51]; miR-193b 过表达显著增加食管癌细胞系 KYSE450 对 5-FU 的化学敏感性[52]。同样，miRNA 在胃癌铂类耐药细胞中具有相同的作用。赵等[53]人发现，miR-181a 过表达负性调节自噬途径，增加了癌细胞对顺铂的敏感性，逆转 GC 细胞对顺铂的耐药性。MiR-155 在结肠癌细胞[54]和骨肉瘤细胞[55]中均具有高表达，调节自噬水平升高，导致化疗耐药。先前文献提出 miR-155 在胃癌中异常表达，介导自噬诱导细胞调亡[23]，成为胃癌一线化疗药物抗性中的重要靶点。有研究发现过表达 miR-361-5p 通过 PI3K/Akt/mTOR 途径靶向 FOXM1 抑制了胃癌细胞中 LC3+数量下降、Beclin-1 的表达降低和 LC3 II/I 的比率以及 p62 的表达增加等特点，诱导胃癌多西他赛化学耐药性，为胃癌的机制研究和治疗奠定了基础[56]。黄等人[57]证明 miR-874 过表达通过靶向 ATG16L1 抑制自噬，逆转了胃癌耐药细胞耐药性，为临床预后和化学抗性方面提供了新思路。傅等[58]人提出 miR-148a-3p 调节 RAB12 来显著减少 GC 细胞自噬通量和自噬体的形成来促进 CDDP 诱导的细胞凋亡，增强 CDDP 的对肿瘤细胞的敏感性。更有研究明确了 GC 细胞中的 DDP 耐药性是 miR-21 靶向 PI3K/Akt/mTOR 途径抑制自噬来实现的[59]。华等[60]人，发现 Eras 可以激活 AKT/mTOR 信号通路，由此阻断了 BGC-823 和 AGS GC 细胞中的自噬通量减弱了 GC 细胞中顺铂耐药性。

此外，Guo 等人[61]，还发现，CD13 (一种具有金属蛋白酶活性的跨蛋膜糖白)表达与 GC 细胞中 CDDP 耐药性呈正相关。其主要机制是 CD13 抑制剂 Ubenimex 通过抑制自噬和上皮间质转化(EMT)来抑制 CD13 /EMP3/PI3K/AKT/NF-κB 途径的活化，从而克服 GC 细胞中的 CDDP 耐药性。因此，CD13 是 CDDP 耐药性形成的潜在指标，Ubenimex 可以作为逆转 GC 中 CDDP 耐药性的有效候选者。陆和其同事等人[62]，证实 CD133 作为肿瘤干细胞的标记物之一，在顺铂耐药的胃癌细胞中起着至关重要的作用。下调 CD133 使自噬活性受到抑制，改善了胃癌顺铂耐药细胞系 Cis-KATO-III 中对顺铂灵敏度，为细胞自噬和顺铂耐药性激活提供了新见解。冯等[63]人，证实 Trim14 在 5-FU 和 L-OHP GC 耐药的 GC 组织中表现出高表达水平，调节 AMPK/mTOR 通路促进 GC 细胞的化疗耐药性。研究表明，黄芩素作为一种天然的药用植物，具有抗肿瘤活性。且在 Akt/mTOR 和 Nrf2/Keap 1 信号传导途径的调节下，诱导细胞凋亡，实现了逆转 SGC-7901/DDP 胃癌细胞耐药细胞对 DDP 耐药性[64]。CuB 通过激活由 CIP2A 抑制介导的蛋白磷酸酶 2A(PP2A)抑制了 mTORC1 激活自噬，抑制增殖，诱导 SGC7901/DDP 细胞由 caspase 依赖性凋亡和自噬，以此改善对肿瘤细胞 DDP 的敏感性[65]。聂等[66]发现，WASF3 (Wiskott-Aldrich 综合征蛋白家族成员 3)敲低通过极大地影响了对 Atg12 介导的自噬的抑制，增强胃癌细胞对奥沙利铂的敏感性。

5. 结论

胃癌仍然是消化系统恶性肿瘤中死亡率最高的癌症，标准治疗是 D2 手术切除结合化学疗法。但是对于大部分人群是不可能的，因为确诊时已归属为中晚期，无法行治愈手术。随着医学的发展尽管胃癌的抗肿瘤治疗有所进展，但由于化疗抗性的出现，近年来胃癌患者的总体存活率仍然不容乐观[64]。耐药性是癌症治疗中的主要问题。肿瘤中耐药性的发展抵消了药物治疗的效果，导致肿瘤侵略性的复发，使癌症患者的预后更差，生存质量明显下降。在过去的几十年中，已经投入了大量的努力来研究癌细胞的抗性机制和逆转这种抗性的方法。此外，许多非编码 RNA，包括 microRNA 和 lncRNA 在癌细胞耐药中

起关键作用[65] [66]，其中一些已被用于制定患者的治疗策略。

近年来自噬，作为新兴领域主导癌症治疗的方向，其在癌症的进展和治疗中起着重要的角色。总的来说，，该综述提供了自噬在胃癌化学耐药中令人信服的证据。lncRNAs 和 microRNA 通过诱导自噬调节蛋白的表达以及对自噬信号通路的干扰，成为克服耐药性的新的治疗机点，并为人类癌症的治疗方便带来新的希望。在胃癌铂类耐药性和自噬领域，研究人员集中于 PI3K/AKT 和 MAPK 途径，随着技术和时间的推移将会涉及更多自噬相关途径(p53，MAPK 或 PTEN 途径)进行研究。因此，通过靶向多种信号通路并诱导细胞周期阻滞和凋亡，在调节自噬介导的胃癌化学耐药性中作用的研究，将有助于开发有前途的针对复发/转移性胃癌治疗的药物。

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