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自噬在转铁蛋白受体调节妇科肿瘤中的研究进展

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摘　要

自噬是一种进化上保守的自我降解过程，在维持细胞代谢和稳态上发挥至关重要的作用。在不同条件下，自噬在肿瘤进展中发挥着抑制或促进作用。铁是细胞生长的必需营养物质，通过转铁蛋白受体(TFRC)摄取铁是细胞吸收铁的最重要方式。自噬可以调节细胞铁稳态，自噬及铁代谢失衡均可以导致疾病和肿瘤的发生。在这篇综述中，我们讨论了自噬联合转铁蛋白在妇科肿瘤中的研究进展。

关键词

自噬，转铁蛋白受体，妇科肿瘤

Research Progress of Autophagy in Transferrin Receptor Regulation of Gynecologic Tumors

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Abstract

Autophagy is an evolutionarily conserved self-degradation that plays a crucial role in maintaining cellular metabolism and homeostasis. Autophagy plays an inhibitory or promotional role in tumor

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progression under different conditions. Iron uptake by transferrin receptor is the most important way for cells to absorb iron. Autophagy regulates intracellular iron homeostasis, and the deregulation of autophagy and iron metabolism can lead to disease and tumors. In this review, we discuss the progress of autophagy combined with transferrin receptor in gynecologic tumors.

Keywords

Autophagy, Transferrin Receptor, Gynecological Tumors

1. 引言

自噬(autophagy)是一种促进生存的途径，它捕获、降解和回收溶酶体中细胞内受损的蛋白质和细胞器，来维持细胞的代谢和稳态[1]。自噬可以保护细胞器的功能，防止有毒物质积累，并在饥饿条件下提供代谢底物[2]。自噬功能障碍可以导致许多疾病的发生，包括感染、癌症、神经退行性疾病、自身免疫系统疾病、衰老和心脏疾病[3]。已在许多肿瘤类型中观察到自噬相关蛋白表达升高，表明自噬的增强可以促进肿瘤发生[4]。

铁是一种必需的营养物质，是许多细胞功能的关键组成部分，参与了细胞的生长增值、氧气运输及DNA 的合成等过程[5]。转铁蛋白受体(TFRC)是调节细胞铁稳态的关键因子，TFRC 通过与转铁蛋白复合物结合以促进铁离子进入细胞[6]。铁代谢失衡可以促使肿瘤的发生，促进肿瘤的增长[5]。其原因可能是肿瘤细胞在增殖过程中对代谢和生物合成的需求增加。在许多情况下，癌症细胞通过增加铁的吸收和储存，减少铁的输出改变细胞内铁代谢[2] [7]。自噬通过铁蛋白的吞噬回收铁蛋白复合物来调节铁的生物利用率[8]。本综述主要从自噬的功能、在疾病和肿瘤中的作用、自噬调节铁代谢等方面探讨自噬在 TFRC 调节的妇科肿瘤中的研究进展。

2. 自噬概述

2.1. 自噬简介及功能

自噬是一种保守的分解代谢途径，对生存、分化、发育和稳态至关重要[3]。必需自噬基因 ATG5 的缺失导致酵母菌株在氮缺乏条件下存活率极低，在自噬缺陷的人类神经元细胞表现为细胞死亡增加[9]。同样，ATG5 的诱导性敲除加剧了小鼠神经变性，并导致中枢神经系统稳态丧失[10]。通过自噬，可以清除有害物质和老化或受损的细胞器，同时释放出分解产物作为细胞生长和能量代谢的物质来源。根据细胞物质运到溶酶体内的途径不同，自噬分为以下几种类型：宏观自噬、微观自噬和伴侣介导的自噬，所有这些都促进溶酶体胞质成分的蛋白水解降解。宏观自噬通过双膜结合囊泡(称为自噬体)的中介将细胞质货物输送到溶酶体，该囊泡与溶酶体融合形成自溶体[11]。这一过程使得使生物能量成分得以循环。

自噬在几乎所有细胞中都以低基础水平发生，以执行稳态功能，如控制蛋白质和细胞器的质量和数量[12]。自噬作为一种适应性分解代谢过程，在应对各种代谢压力时被激活。其最重要的生理作用是调动细胞内能量资源，来满足细胞和生物体对代谢底物的需求，并消除有缺陷或受损的蛋白质和细胞器，防止异常蛋白质聚集物积聚，以及清除细胞内病原体[3]。自噬主要发挥适应性作用，保护生物体免受各种

疾病的侵害。

2.2. 自噬相关蛋白

在自噬的发生过程中，有多种自噬相关蛋白(autophagy-related protein, ATG)可调节和控制自噬形成的不同阶段。在哺乳动物细胞中，自噬体的形成是由大约 20 种核心自噬相关蛋白介导的，这些蛋白在自噬过程中协同介导复杂的膜动力学[13]。在下文中，我们将简单介绍几种自噬相关蛋白的功能。ULK1 是一种丝氨酸/苏氨酸蛋白激酶，是酵母 ATG1 的哺乳动物直系同源物。ULK1 被认为参与常规的自噬信号传导。而由 ULK1，FIP200，ATG13 和 ATG101 组成的 ULK1 复合物调节自噬体形成的开始，启动自噬[14] [15]。LC3 (微管相关蛋白 1 轻链 3)，是酵母 ATG8 的哺乳动物同源蛋白，参与自噬体的形成，是自噬的标志物[16]。LC3 位于成熟的双膜自噬小泡的胞质和管腔表面，调节自噬小囊的生长和货物募集，其募集的蛋白质包括 P62，Nbr1 和 NIX 等在内货物衔接蛋白质[17]。P62，在人类中也称为螯合体 1 (SQSTM1)，是一种自噬受体，也选择性自噬的最佳特征底物之一[18]。P62 在选择性自噬中与多泛素化蛋白相结合，作为自噬的成核位点[19]。Beclin-1，是酵母 ATG6 的哺乳动物直系同源物，可以与多种蛋白质相互作用调控自噬[20]。并且 Beclin-1 可以干预从自噬体形成到自噬体成熟的每一个主要步骤[21]。Bcl-2 与 Beclin-1 相互作用，调控下游信号 VPS34 复合物，促进自噬开始，形成自噬体结构。而 UVRAG、Ambra1 (Beclin-1 调节自噬中的激活分子)和 Rubicon 相互作用则调控自噬体成熟过程。UVRAG 与 beclin-1 的 CCD 结构域结合介导自噬体成熟，Rubicon 与 Beclin-UVRAG 复合物的结合抑制自噬体成熟[22] [23]。

2.3. 自噬在疾病发展中的作用

自噬除了在正常生理过程中发挥作用外，还在癌症等病理过程中发挥作用[24]。Fimia GM 等人的研究表明，Ambra1 (Beclin-1 依赖性自噬程序的阳性调节因子)调节自噬，并在胚胎发生中发挥关键作用。小鼠胚胎中的 Ambra1 功能缺陷会导致严重的神经管缺陷[25]。近期研究表明，组蛋白去乙酰化酶 6 (histone deacetylase, HDAC6)，通过乙酰化和去乙酰转录因子 EB (transcription factor EB, TFEB)和叉头盒转录因子 O1 (Forkhead box transcription factor O1 FOXO1)调节自噬－溶酶体途径的活性和脱乙酰化 P65 上调 NOD 样受体热蛋白结构域相关蛋白(NOD-like receptor thermal protein domain associated protein 3, NLRP33)炎症小体，进而影响宿主防御和炎症[26]。Yang Z 等人提出，在免疫系统中，自噬调节抗原摄取和呈递、病原体清除、短期和长期免疫细胞的存活以及细胞因子依赖性炎症等过程来参与宿主保护[27]。因此，自噬缺陷可能会引起炎症，并引发或加剧自身免疫性疾病。Bravo-San Pedro JM 等人提出，在心血管疾病动物模型中，自噬或线粒体自噬基因缺陷的小鼠更易发展特定心血管疾病，自噬的药理学或遗传学抑制会加速疾病进展，并使多种疾病的结果恶化[28]。

2.4. 自噬在肿瘤发展中的作用

在肿瘤发展过程中，自噬既可以抑制肿瘤发生，又能促进肿瘤生长。在肿瘤发生的早期，自噬作为一种生存途径和质量控制机制，可以阻止肿瘤的发生和抑制肿瘤的发展[4]。ATG6/Beclin-1 作为一种自噬和单倍体不足的肿瘤抑制蛋白，在大多数的乳腺癌和卵巢癌中单等位基因缺失。多种研究方法表明 Beclin-1 和其他自噬蛋白的缺失促进乳腺和卵巢上皮肿瘤细胞生长[2] [29] [30]。但是否与肿瘤中基因突变或受其他机制影响仍有待确定。在大多数情况下，自噬促进肿瘤发生。自噬作为一种动态的降解和循环系统，一旦肿瘤发展到晚期，并在环境胁迫下建立，就有助于肿瘤的生存和生长，并通过促进肿瘤的转移促进肿瘤的侵袭性[4]。Yang 等人研究结果证实，在胰腺导管腺癌细胞系和原发肿瘤中，自噬被高度激活，在体外使用自噬抑制剂后，减少了胰腺肿瘤细胞生长[31]。表明了胰腺导管腺癌细胞系依赖于自噬来

持续生长和肿瘤发生。在 KRAS 激活的非小细胞肺癌及 PTEN 缺乏所致的前列腺癌中，ATG7 缺乏抑制肿瘤生长[12]。此外，恶性黑色素瘤细胞中也显示出高水平的自噬[32]。对于这些不同影响的一种解释是，自噬的稳态功能通过清除细胞的致癌成分来阻止肿瘤的发生，而应激诱导的自噬在面对癌症相关应激时促进肿瘤进展[33]。

3. 自噬在 TFRC 调节妇科肿瘤中的相关研究

3.1. 自噬与 TFRC

细胞摄取铁的主要机制是通过转铁蛋白－转铁蛋白受体(TF-TFR)系统。TFRC 是一种 II 型跨膜糖蛋白，几乎存在于所有哺乳动物细胞上，主要功能是通过与转铁蛋白结合，其复合物通过网格蛋白依赖性的内吞作用内化来摄取铁，随后进行胞吞作用[34]。TFRC 正常情况下以低水平表达，而在增殖能力强和代谢旺盛的细胞膜表面呈高表达[35] [36]。而自噬在维持细胞铁稳态方面也发挥着关键作用，铁蛋白通过自噬进入溶酶体来释放铁[37]。Hou 等人在血管性痴呆症模型的大鼠中发现，铁含量增加通过 AMPK 通路正向调节大鼠海马体神经元自噬[38]。Park E 验证了活性氧(reactive oxygen species, ROS)诱导 LC3B 转化并激活自噬，调节铁蛋白降解和 TFRC 表达[39]。

3.2. 自噬联合 TFRC 在妇科肿瘤中的研究

自噬既可以作为肿瘤抑制因子，也可以作为肿瘤启动因子。其走向取决于癌症的类型和阶段、基因突变和肿瘤微环境[40]。已有研究表明，在胰腺癌[41]、肺癌[42]、卵巢癌[43]、宫颈癌[44]、甲状腺癌[45]、结肠癌[46]等在内的许多癌症中，TFRC 的表达明显增高，且与预后不良有关。宫颈癌是最常见的妇科恶性肿瘤。在 Yang 等人的研究中表明，新型 MIR-G1 的过表达增强了宫颈癌 Hela 细胞的恶性生物学行为，促进了核自噬，并促进了体内肿瘤生长[47]。而李沫等人的研究则表明，过表达 CCAT1 促进宫颈癌细胞增长，抑制细胞自噬囊泡聚集，抑制宫颈癌 HeLa 细胞自噬[48]。同样，在卵巢癌和子宫内膜癌中，在不同条件下，自噬对于肿瘤的作用不同[40] [49] [50]。

4. 结论

综上所述，相对于正常细胞而言，肿瘤细胞摄取吸收更多的铁来促进其生存和生长，肿瘤细胞也利用自噬的生存功能来防止细胞损伤和促进肿瘤的发生。包括宫颈癌和卵巢癌在内的妇科肿瘤中，TFRC 呈现高表达。铁蓄积和自噬都可以促进肿瘤增长，自噬激活可以调控 TFRC 的表达。因此，靶向 TFRC 联合自噬可以作为治疗肿瘤的新方向，但二者相互之间的作用仍不明确。所以未来我们需要对其机制进行更进一步的研究。

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