



溶酶体在肿瘤发生及转移中的作用研究进展

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摘要 溶酶体作为细胞内主要代谢活动的中心通信枢纽, 其功能紊乱与多种疾病发生密切相关, 但溶酶体与肿瘤发生的关系仍需进一步探索. 肿瘤转移是一个多步骤的过程, 包括从原发肿瘤部位逃逸、局部侵袭、体内浸润、在体循环中存活、外渗到远处器官, 最后在继发肿瘤部位成功定植和生长, 超过90%的癌症患者死于肿瘤远处靶器官转移. 已有研究表明, 溶酶体在肿瘤转移中发挥重要作用, 但其具体机制并不明确. 本文综述了溶酶体在肿瘤发生及转移中的作用及机制, 为未来开发针对溶酶体的靶向药物, 从而预防和治疗肿瘤, 提供了借鉴和参考.

关键词 溶酶体, 组织蛋白酶, 溶酶体相关膜蛋白, 肿瘤发生, 肿瘤转移

肿瘤是目前对人类健康威胁最大的疾病之一, 全面认识肿瘤发生、转移的相关机制, 将有助于建立早期预防干预的临床策略, 并开发针对性的检测治疗方案. 在精准医疗时代, 靶向胞内细胞器为肿瘤干预及治疗带来了希望. 鉴于溶酶体是细胞内主要代谢活动的中心通信枢纽及其在肿瘤发生发展和抗药性中的调节作用, 溶酶体被认为是肿瘤治疗的重要靶点. 本文将从溶酶体水解酶和溶酶体相关膜蛋白两个方面对溶酶体在肿瘤发生及转移中的作用机制进行综述.

1 溶酶体及其功能

溶酶体是降解和回收细胞废物的动态细胞器, 1955年由比利时列日大学的生物化学家Christian de Duve发现. 在研究胰岛素的作用机制时, de Duve发现

了一个对蛋白质和脂质具有丰富水解活性的生化部分并将其命名为溶酶体^[1]. 溶酶体含有两类必需的蛋白质: 水解酶和整合膜蛋白, 它们对溶酶体功能至关重要. 溶酶体膜包裹的管腔内存在60多种溶酶体水解酶, 它们能清除不同的底物, 例如细胞中完成使命的生物大分子、错误折叠的蛋白质、受损的细胞器以及入侵的病原体等, 这些物质通过包括内吞、吞噬和自噬等途径运输至溶酶体腔内被降解. 棕榈酰蛋白硫酯酶 1 (Palmitoyl protein thiolipase 1, PTT1)使V型-三磷酸腺苷酶(V-ATPase)正确定位^[2]并在Cl⁻, Na⁺, K⁺和其他离子的反通量作用下建立溶酶体腔内的酸性环境(pH范围在4.5~5.5之间), 为溶酶体水解酶活性提供所需要的pH条件, 从而实现溶酶体的清除功能. 溶酶体降解产物或通过扩散和特定的运输通道循环回到胞内再利用, 或通过胞吐作用释放到胞外, 由此可见溶酶体正常

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的清除功能对维持细胞稳态至关重要。溶酶体功能紊乱将增加阿尔茨海默病(Alzheimer's disease, AD)和帕金森病(Parkinson's disease, PD)等神经退行性疾病^[3]、溶酶体贮积症(Lysosomal storage disorders, LSDs)^[4]、动脉粥样硬化^[5]等疾病的患病风险。除腔内水解酶外,溶酶体还含有特定的整合膜蛋白,如利用高度糖基化结构保护溶酶体膜完整性的溶酶体相关膜蛋白(Lysosomal-associated membrane protein, LAMP)^[6],以及多种维持离子稳态的转运蛋白和离子通道^[7],如参与胆固醇等脂质转运的尼曼-匹克C1型蛋白(NPC intracellular cholesterol transporter 1, NPC1)和介导溶酶体中 Ca^{2+} 释放的瞬时受体电位黏脂蛋白1(Transient receptor potential mucolipin 1, TRPML1)等。值得注意的是,溶酶体不是相对封闭的动态细胞器,溶酶体与多种细胞器存在互作,并作为胞内的信号中枢通过释放 Ca^{2+} 对溶酶体生物发生、胞外分泌、自噬体与溶酶体融合等重要功能进行调节^[8]。此外,溶酶体介导的 Ca^{2+} 释放对维持其他细胞器的正常功能也至关重要,例如线粒体相关的TCA循环、脂肪酸代谢、氨基酸代谢以及内质网(endoplasmic reticulum, ER)和高尔基体(Golgi apparatus, GA)中蛋白质的修饰加工等^[2]。研究表明,溶酶体除维持细胞稳态和参与信号转导外,还参与细胞适应、营养感知^[9]、自噬调节^[10-12]、耐药^[13,14]、免疫反应^[15]和细胞死亡^[16]等生理过程。由此可见,溶酶体对生物体健康非常重要,溶酶体变化或功能障碍可能扰乱细胞和组织原有的动态平衡进而引发炎症、细胞凋亡和细胞间错误信号传导,从而可能导致或加剧癌症在内的人类疾病的发生和发展^[17]。

2 溶酶体与肿瘤发生及转移

研究表明,癌症属代谢紊乱疾病^[18,19],许多癌症是由溶酶体功能障碍所引起^[20,21],这表明,溶酶体功能的异常可能是导致癌症代谢紊乱的一个重要因素,从而影响癌症的发生和发展过程,可见溶酶体在癌症生物学中起着重要作用。Appelqvist^[22], Tu^[23]等人研究表明,癌细胞强烈依赖于溶酶体的功能,对溶酶体介导的细胞死亡非常敏感。快速分裂的癌细胞在肿瘤进展过程中依赖于有效的溶酶体功能进行应激反应和营养利用。已有研究表明,自噬-溶酶体活性对于肿瘤的进展起关键作用^[24]。自噬是一个高度保守的细胞分解代谢

的过程,作为一种主要的细胞内降解系统,其降解能力来源于溶酶体,诱导癌症祖细胞的异常增殖^[25-27],促进肿瘤进展^[28,29]。自噬主要有三种形式:巨噬、分子伴侣介导的自噬(Companion mediated autophagy, CMA)和微自噬。在肿瘤发展前期,自噬通过限制染色体的不稳定性抑制肿瘤的增殖进而抑制肿瘤的发生,但同时自噬将干扰细胞的正常衰老,诱导癌症祖细胞的异常增殖^[25-27],促进肿瘤进展^[28,29]。因此,自噬在肿瘤发生和转移过程中的作用复杂且具有双重性。它既可能促进肿瘤的形成和进展,也可能抑制肿瘤的生长和扩散,具体取决于肿瘤类型、病理状态以及细胞环境等因素。Goh等人^[30]研究表明,溶酶体通过调控生长因子信号和提供营养物质调控肿瘤增殖。自噬的激活常见于肿瘤的缺氧区域,该区域还缺乏营养供应。自噬-溶酶体途径可为大分子合成提供前体,为癌细胞提供所需的营养和能量^[31,32],使癌细胞能够在恶劣条件下生存。在应激条件下,雷帕霉素靶蛋白(mechanistic target of rapamycin, mTOR)被抑制^[33],转录因子TFEB入核促进溶酶体、自噬体的生物发生和溶酶体的融合来增加自噬通量,从而有效降解复杂分子,以满足癌细胞对大量营养物质的需求^[34],促进肿瘤发展。

肿瘤发生是一个涉及多阶段反应和突变积累的渐进过程,同样肿瘤转移也涉及多个连续步骤,包括从原发肿瘤部位逃逸^[35]、局部侵袭、体内浸润、在体循环中存活、外渗到远处器官,最后在继发肿瘤部位成功定植和生长^[36,37]。在肿瘤发展过程中,一方面癌细胞的快速增殖依赖于DNA、RNA、新蛋白质等大分子的高合成率,另一方面初始肿瘤与血管相互作用、新生血管的生成,以及肿瘤细胞与微环境之间的相互作用也影响癌症进展。因此,当肿瘤的发生发展缺乏旺盛生长所必需的条件,例如激活血管生成时,可能经历肿瘤休眠或微转移阶段^[38]。不同研究表明,在癌症进展过程中,溶酶体数量、体积、定位及溶酶体相关蛋白酶组成的改变也将影响肿瘤的发生发展^[39-41]。由于溶酶体具有高度动态性和异质性,其大小、数量、定位等随着环境因素以及细胞和生物体的需要而变化^[42]。癌细胞通过调节溶酶体数量、组成和活性来上调新陈代谢,使溶酶体生物合成增加,增强自噬通路以满足癌细胞生长和增殖的需要。与此同时,溶酶体体积也会增大,这解释了与正常细胞相比,癌细胞具有更活跃、更大及相对脆弱的溶酶体^[43]。近年来研究

表明, 溶酶体功能和异质性取决于它们在细胞内的定位. 而在肿瘤细胞中, 溶酶体的定位和异常分泌决定了肿瘤的恶性表型, 促进了肿瘤的侵袭和转移. 在极化细胞, 如神经元中, 溶酶体分布于整个细胞质中, 靠近质膜, 主要参与溶酶体胞吐和质膜修复^[44], 控制mTORC1的激活^[45]; 而在非极化癌细胞中, 溶酶体的定位变化更为动态, 在低氧、低pH的TME条件刺激下, 癌细胞营养缺乏, 诱导大部分溶酶体定位于靠近微管组织中心(microtubule-organizing center, MTOC)核周簇中^[45,46]刺激自噬体-溶酶体融合, 增加自噬通量和营养可利用性^[47]. 而在肿瘤中, ErbB2过表达或K-Ras突变等恶性改变可导致溶酶体向细胞外周重新定位^[48], 特别是在肿瘤侵袭前沿的质膜上. 这种重新定位和随后的胞吐促使溶酶体组织蛋白酶释放, 并促进分泌物的释放, 共同推动了侵袭性表型, 有利于肿瘤的转移^[49]. 其中, 溶酶体向癌细胞外周运动的倾向性是由于Rab7水平的下调, 在这一过程中, 其他Rab蛋白的表达水平变化也会刺激溶酶体向细胞周围运动, 使癌细胞更具侵袭性^[50].

2.1 溶酶体水解酶对肿瘤发生和转移的影响及相关机制

值得注意的是, 溶酶体水解酶在肿瘤的发生和转移中有很大的影响, 尤其是组织蛋白酶对于肿瘤进展有关键作用. 在肿瘤中, 溶酶体水解酶通过增加其向细胞外环境释放强度、调节其活性水平以及重新定位至细胞表面等方式, 影响肿瘤微环境和细胞-细胞相互作用, 促进肿瘤细胞的侵袭和转移. 蛋白酶根据其活性位点的氨基酸, 可分为丝氨酸(组织蛋白酶A和G)、半胱氨酸(组织蛋白酶B, C, F, H, K, L, O, S, V, W和X)和天冬氨酸(组织蛋白酶D和E)蛋白酶. 组织蛋白酶家族作为溶酶体中的主要蛋白酶^[51], 其表达变化在肿瘤中普遍存在^[52], 且与正常组织相比表达量通常增加^[53]. 如表1所示, 组织蛋白酶的上调促进肿瘤增殖和转移, 其高表达往往预示着肿瘤患者较低存活率和不良预后. 然而, 不同癌症对溶酶体的影响各异, 故在不同肿瘤中存在不同的组织蛋白酶表现, 也就是说单个蛋白酶在肿瘤生长、侵袭、迁移和血管生成中可能具有截然相反的作用. 例如Vasiljeva等人^[54]研究表明, 组织蛋白酶B在大多数癌症中存在高表达且对患者不利, 然而Kuester等人^[51]则发现, 高水平的组织蛋白酶B却提

高了甲状腺癌患者的生存率, 其机制可能涉及多个方面, 包括调节其他凋亡相关蛋白的活性或参与细胞凋亡信号通路, 抑制肿瘤细胞增殖和侵袭、促进细胞凋亡、调节肿瘤微环境、抗氧化作用以及免疫调节作用等. 这些机制可能相互作用, 共同影响甲状腺癌的发展和预后. 需要进一步研究揭示组织蛋白酶B在甲状腺癌中的具体作用机制, 以及其在治疗中的潜在应用价值.

组织蛋白酶定位于溶酶体腔室, 除了在溶酶体酸性环境参与蛋白降解外^[140], 组织蛋白酶在某些病理^[141]及生理^[142]过程也表现出特定功能, 在人类高酸性肿瘤微环境(Tumor microenvironment, TME)中^[131,143]还可以通过外分泌起作用^[144], 从而影响肿瘤的发生和转移. 癌细胞通过增加溶酶体的体积和数量, 以及溶酶体V-ATPase的表达和活性, 增强质子储存能力, 抵消Warburg效应导致的细胞质酸化以维持细胞内pH稳态, 随后肿瘤微环境的酸化可进一步刺激溶酶体向细胞外周迁移, 促进质子释放^[43], 从而增强细胞外释放的水解酶的蛋白水解活性. 释放到肿瘤细胞外的组织蛋白酶使肿瘤周围拥有蛋白水解活性环境, 促进了基底膜和细胞外基质(Extracellular matrix, ECM)组分, 如层黏连蛋白、胶原蛋白等的降解, 并通过蛋白水解级联协同作用进一步重塑ECM以促进肿瘤细胞的侵袭和转移^[145]. 组织蛋白酶在降解ECM促进肿瘤转移过程中, 其降解产物同时满足了肿瘤快速增殖的营养需求. 研究表明, 组织蛋白酶还可作为脱落酶使特定的膜蛋白脱落, 这些蛋白大多是已知的癌症进展介质, 并参与细胞黏附和信号传导的调节^[146-148], 促进上皮-间充质转化(Epithelial mesenchymal transition, EMT), 驱动和调控肿瘤血管生成^[149, 105-139, 54, 140-148, 150, 151], 以促进肿瘤组织生长和转移^[152-155], 此时TME中更低的pH将刺激癌细胞调节肿瘤免疫反应, 从而使癌症扩散, 同时减少胞质内的质子负荷导致胞质碱化, 通过减少对生长因子的依赖、促进增殖并降低细胞凋亡易感性来推动肿瘤的发生^[156]. 组织蛋白酶还能破坏细胞与细胞间的连接, 从而促进癌细胞分离获得高侵袭表型^[157]. 值得注意的是, 炎症和TME对于肿瘤的发展至关重要. 炎症反应不仅诱导肿瘤的发生, 并且促进肿瘤的发展及转移, 大量炎症细胞, 如肿瘤相关巨噬细胞(Tumor-associated macrophage, TAM)和炎症因子参与构成TME, 诱导多种细胞因子、炎症细胞因子、白细

表 1 组织蛋白酶在不同肿瘤中的表达变化及结果**Table 1** Expression changes of cathepsin and their consequences in different tumors

酶类	肿瘤类型	表达变化	结果	文献
CTSA	肺癌	↑	组织蛋白酶A促进细胞增殖、迁移和侵袭	[55]
	乳腺癌	↑	组织蛋白酶A表明预后不良	[56]
	结直肠癌	↑	组织蛋白酶A与淋巴结和肝转移有关	[57]
	前列腺癌	↑	组织蛋白酶A促进增殖、EMT和肿瘤发生	[58]
	黑色素瘤	↑	黑色素瘤病变中检测到高组织蛋白酶A活性	[59,60]
CTSB	喉癌	↑	组织蛋白酶B与迁移、侵袭和增殖呈正相关	[61]
	胃癌	↑	组织蛋白酶B存在过表达与晚期肿瘤分期和进行性疾病正相关	[62]
	乳腺癌	↑	组织蛋白酶B在较大肿瘤中含量更高且是复发指征的预后标志物	[63]
	脑膜瘤	—	组织蛋白酶B在内皮和微血管中表达	[64]
	结直肠癌	↑	组织蛋白酶B(来自TAM)升高与转移相关	[65]
	黑色素瘤	↑	血清组织蛋白酶B表明转移性黑色素瘤和较短的总生存期	[66]
	前列腺癌	—	组织蛋白酶B和MMP-9与细胞存活、侵袭和血管生成正相关	[67]
	胰岛细胞癌	↑	组织蛋白酶B促进肿瘤形成、血管生成、侵袭和增殖	[40]
	胶质母细胞瘤	—	组织蛋白酶B和MMP-9促进肿瘤侵袭、生长和血管生成	[68]
	非小细胞肺癌	↑	组织蛋白酶B的活性在肿瘤中显著升高	[69]
CTSC	舌癌	—	组织蛋白酶C在舌癌中表达, 其高水平可预测患者的不良预后	[70]
	结直肠癌	—	组织蛋白酶C抑制阻断自噬并诱导内质网应激和细胞凋亡	[71]
	肾细胞癌	—	TSAII降低组织蛋白酶C的表达, 抑制细胞迁移和侵袭	[72]
	肝细胞癌	↑	组织蛋白酶C表达上调促进生长增殖和转移, 与不良预后相关	[73]
	胰岛细胞癌	↑	组织蛋白酶C在肿瘤组织中表达	[40]
	鳞状细胞癌	↑	组织蛋白酶C促进鳞状细胞癌变过程	[74]
	非小细胞肺癌	↑	组织蛋白酶C高表达与肿瘤复发相关	[75]
CTSD	胃癌	—	组织蛋白酶D参与癌症转移	[76]
	膀胱癌	—	组织蛋白酶D在某些组织中高度表达	[77]
	鼻咽癌	—	组织蛋白酶D上调表示转移和预后差	[78]
	乳腺癌	↑	组织蛋白酶D与较短的无复发生存期相关	[79]
	脑膜瘤	—	组织蛋白酶D在内皮和微血管中表达	[64]
	骨肉瘤	↑	组织蛋白酶D是骨肉瘤和肺转移瘤的生物标志物	[80]
	胰腺癌	—	组织蛋白酶D和组织蛋白酶原D促进癌症细胞扩散	[81]
	卵巢癌	↑	较高的组织蛋白酶D在浆液性卵巢癌中表达, 肿瘤上皮细胞中的组织蛋白酶D可能是有益的预后因素	[82]
	黑色素瘤	↑	组织蛋白酶D与肿瘤发展有关	[83]
	结直肠癌	↑	在患者血清中检测到组织蛋白酶D	[84]
	前列腺癌	—	组织蛋白酶D促进细胞增殖和侵袭	[85]
	肝细胞癌	↑	在患者血清中检测到组织蛋白酶D	[86]
	子宫内膜癌	↑	患者血清检测到组织蛋白酶D和IgG	[87]
	鳞状细胞癌	↑	组织蛋白酶D在低分化组织中强烈表达	[88]
	非小细胞肺癌	—	组织蛋白酶D淋巴结转移的预测因子	[89]
CTSE	胃癌	↑	组织蛋白酶E是印戒细胞癌和胃分化标志物	[90]
	胰腺癌	↑	在癌症中检测到组织蛋白酶E	[91]
	食道癌	↑	组织蛋白酶E在肿瘤组织中过表达	[92]
	膀胱癌	—	高组织蛋白酶E与更好的无进展生存率相关	[93]
	乳腺癌	—	组织蛋白酶E与良好的预后结果相关	[94]

(表1续)

酶类	肿瘤类型	表达变化	结果	文献
CTSF	胃癌	↓	组织蛋白酶F下调抑制细胞凋亡, 促进细胞增殖	[95]
	骨肉瘤	—	组织蛋白酶F与转移呈负相关	[96]
	宫颈癌	↑	组织蛋白酶F过表达参与宫颈癌的发病机制	[97]
CTSG	脑膜瘤	—	组织蛋白酶G在间质中表达	[64]
	舌鳞状细胞癌	—	组织蛋白酶G在肿瘤周围基质中表达	[98]
	胶质母细胞瘤	—	组织蛋白酶G在微血管中表达	[99]
	急性髓细胞白血病	—	组织蛋白酶G是生存率低的标志物	[100]
	急性淋巴细胞白血病	—	组织蛋白酶G预后不佳	[101]
CTSH	肺癌	↑	患者血清较组织中组织蛋白酶H较高	[102]
	肝细胞癌	—	组织蛋白酶B在HepG2中表达	[103]
	前列腺癌	—	组织蛋白酶H介导迁移和侵袭	[104]
	黑色素瘤	↑	组织蛋白酶H表明总生存率较低	[66]
	胰岛细胞癌	—	组织蛋白酶H促进肿瘤生长、血管生成并减少细胞凋亡	[104]
	基底细胞癌	↑	组织蛋白酶H(来自肿瘤周围细胞)促进肿瘤侵袭	[105]
	胶质母细胞瘤	↑	组织蛋白酶H促进肿瘤细胞侵袭	[106]
CTSK	胃癌	↑	组织蛋白酶K促进肿瘤复发	[76]
	乳腺癌	—	组织蛋白酶K促进细胞增殖和转移	[107]
	卵巢癌	↑	组织蛋白酶K促进肿瘤转移和不良预后相关	[108]
	黑色素瘤	↑	组织蛋白酶K是转移的独立预测因子	[109]
	前列腺癌	↑	组织蛋白酶K促进细胞侵袭	[110]
	结直肠癌	↑	组织蛋白酶K促进TAM的侵袭、M2样极化和不良结果	[111]
	颅底脊索瘤	↑	组织蛋白酶K与无进展生存率降低相关	[112]
	胶质母细胞瘤	↑	组织蛋白酶K与存活率无关	[113]
	口腔鳞状细胞癌	↑	组织蛋白酶K与淋巴结转移、神经侵袭和生存率低相关	[114]
CTSL	胃癌	↑	高组织蛋白酶L与转移、分化不良和弥漫性组织类型相关	[115]
	乳腺癌	—	组织蛋白酶L入核激活EMT相关活性	[116]
	胶质瘤	—	组织蛋白酶L促进细胞存活、迁移和侵袭	[117]
	胰腺癌	↑	高血清组织蛋白酶L与预后不良有关	[118]
	卵巢癌	↑	组织蛋白酶L过表达促进细胞增殖、迁移、侵袭和紫杉醇耐药性	[119]
	黑色素瘤	—	在细胞上清液中检测到组织蛋白酶L	[120]
	结直肠癌	↑	组织蛋白酶L与存活率呈负相关	[121]
	子宫颈癌	↑	组织蛋白酶L促进癌细胞的迁移和侵袭	[122]
	非小细胞肺癌	↑	突变的K-ras促进组织蛋白酶L的表达, 从而增强侵袭和迁移	[123]
CTSO	乳腺癌	—	组织蛋白酶O突变与较短的无病生存期和总生存期相关	无
CTSS	胃癌	↑	组织蛋白酶S与较高的TNM、晚期和较差的总生存率相关	[124]
	肝细胞癌	—	组织蛋白酶S抑制诱导细胞凋亡和化疗敏感性	[125]
	甲状腺癌	↑	组织蛋白酶S是进展和预后的预测标志物	[126]
	结直肠癌	↑	肿瘤巨噬细胞中组织蛋白酶S介导自噬促进M2极化加速肿瘤发展	[127]
	前列腺癌	↑	组织蛋白酶S(来自TAM)表达升高, 促进肿瘤进展	[128]
	非小细胞肺癌	—	在患者血清中检测到组织蛋白酶S活性	[129]
	三阴性乳腺癌	↑	组织蛋白酶S促进细胞生长和转移	[130,131]
CTSV	乳腺癌	↑	高组织蛋白酶V预测预后不良	[132]
	胸腺癌	—	组织蛋白酶V抑制肿瘤复发	[133]
	结直肠癌	↑	组织蛋白酶V在癌症中表达	[134]
	子宫内膜癌	↑	组织蛋白酶V的表达与生长调节基因表达相关	[135]

(表1续)

酶类	肿瘤类型	表达变化	结果	文献
CTSW	无	—	未发现组织蛋白酶W在肿瘤中的研究	无
CTSX	胃癌	—	组织蛋白酶X抑制G1期阻滞和凋亡	[136]
	乳腺癌	—	组织蛋白酶X参与EMT	[137]
	前列腺癌	↑	组织蛋白酶X在前列腺癌和前列腺上皮内瘤样病变中表达	[138]
	结直肠癌	—	在肿瘤发生过程中发现组织蛋白酶X(来自TAM)增加; 然而, 组织蛋白酶X的缺失与肿瘤的进展有关	[139]
	胶质母细胞瘤	↑	组织蛋白酶X含量高与生存率低相关	[113]

注: ↑表示表达上调, ↓表示表达下调, —表示变化未知

胞介素家族和转录因子NF- κ B以及趋化因子的表达, 促使细胞增殖并诱导血管生成, 从而促进肿瘤的发展及转移. 有研究表明, 组织蛋白酶也是驱动癌细胞生长和炎症发生中信号转导途径的重要组成部分^[158-161], 同时组织蛋白酶还可以活化肿瘤细胞中大量存在的炎症细胞和炎症因子, 使其产生多种促肿瘤生长因子、细胞因子和趋化因子来促进癌症的进展^[162,163]. 此外, 肿瘤中TAM的大量浸润与免疫抑制、肿瘤血管生成、肿瘤转移及不良预后相关^[164-166]. TAM来源的组织蛋白酶通过介导自噬和其他级联降解活动参与TAM极化调节, 以及极化以外的其他行为, 如调节TME^[167]、免疫介导、基质降解和血管生成, 从而促进肿瘤的发生和转移. 除在肿瘤转移过程中发挥重要作用外, 组织蛋白酶通过加工抗原以供MHC-II分子呈递, 参与适应性免疫反应^[168]. 此外, 在炎症过程中, 组织蛋白酶调节免疫细胞的激活和功能来调节免疫细胞的迁移^[169]. 这种调节可能在一定程度上影响肿瘤的转移过程, 因为免疫细胞的迁移和活性对于调节并控制肿瘤的生长和转移至关重要.

2.2 溶酶体相关膜蛋白对肿瘤发生和转移的影响及相关机制

虽然组织蛋白酶和其他溶酶体蛋白是癌症进展的基础, 但溶酶体膜蛋白也可以促进肿瘤恶性行为. 溶酶体相关膜蛋白LAMP包括五个家族成员: LAMP1, LAMP2, LAMP3, LAMP4, LAMP5, 是主要存在于溶酶体膜上的糖基化蛋白家族, 约占溶酶体膜蛋白的50%^[170]. 在溶酶体稳态、运动、分布和膜完整性中发挥重要作用. 有研究表明, LAMP对于溶酶体活性也有重要作用, 且其表达水平在不同组织存在差异. LAMP1和LAMP2在人体组织及细胞中普遍表达, 而

LAMP3, LAMP4和LAMP5是组织特异性蛋白. LAMP通过介导与其他细胞器的互作参与执行溶酶体信号传导^[2], LAMP还调控多种细胞过程, 如吞噬作用、溶酶体与自噬体的融合、脂质转运和衰老^[171], 维持溶酶体pH等. 有趣的是, 越来越多的研究表明, LAMP与肿瘤的发生及转移相关. Yousefi 等人^[172]研究表明, 高转移性的肿瘤细胞质膜比低转移性的肿瘤细胞质膜分布了更多的LAMP, 并且LAMP作为促侵袭及促转移因子发挥作用. 在TME中, LAMP1及LAMP2异常定位于质膜^[44,173,174], 通过形成保护性的糖萼来绕过酸诱导的质膜蛋白水解, 使癌细胞能够在恶劣的酸性微环境中存活^[174], LAMP1及LAMP2重新分布后其暴露的结构域将作为半乳糖凝集素-3、E-选择素的配体, 它们之间的相互作用促进肿瘤细胞与ECM蛋白的黏附加强癌细胞侵袭和转移, 并帮助癌细胞与内皮细胞结合. 与此同时, LAMP1和LAMP2表达均与白细胞内皮黏附能力和迁移能力正相关, 因此LAMP1A和LAMP2的高表达利于癌细胞的迁移^[175], 从而促进肿瘤转移^[176]. 然而, LAMP1和LAMP2在不同肿瘤中发挥作用, 例如, LAMP1的细胞膜表面移位与黑色素瘤、非小细胞肺癌和喉部鳞状细胞癌的转移潜力相关, 而LAMP2在以上几种肿瘤中则没有细胞膜表面移位现象^[177,178]. 有研究认为, LAMP1介导肿瘤转移与聚-N-乙酰基-乳糖胺的高表达有关, 聚-N-乙酰基-乳糖胺与LAMP1结合激活ERK和p38途径, 从而导致基质金属蛋白酶-9(Matrix metalloproteinases-9, MMP-9)的分泌和ECM重塑^[179,180]. LAMP1在一些浆液性卵巢恶性肿瘤中被报道参与调节EGF途径^[181], 可能的机制是LAMP1定位于质膜后激活生长因子及其信号传导通路, 从而在不同阶段调节癌症发展. 例如在胶质母细胞瘤、胰腺癌和卵巢癌等肿瘤中, LAMP1在癌症进展的早期阶段而

不是在转移过程中发挥作用^[181-183]。LAMP2的一个转录本LAMP2A可作为CMA的关键伴侣分子^[184,185],其表达上调与乳腺癌^[186-188]、胃癌^[189]和肝癌^[190]、结直肠癌^[191]等肿瘤的转移相关,此外TAM来源的LAMP2A^[192]在促进肿瘤转移中同样发挥重要作用。LAMP3被报道在子宫颈肿瘤^[193]、乳腺癌^[194,195]、卵巢癌^[196]、结直肠癌^[197]中过表达,有促进肿瘤侵袭转移的作用,并且与较差生存预后存在相关性。虽然LAMP3在促进肿瘤转移中的机制尚未完全阐明,但LAMP3可通过提高自噬通量^[198],移位到质膜增强肿瘤和内皮细胞的相互作用而促进肿瘤转移。LAMP4在溶酶体膜和质膜之间快速穿梭^[199]。研究表明,LAMP4与癌症的关联不仅与其在TAM中的表达有关,而且与其在肿瘤细胞中的表达有关^[200],例如LAMP4高表达与小胶质瘤恶性程度相关,并被认为是人类胶质瘤生存率降低的预后标志物^[201]。LAMP4作为几种恶性肿瘤的诊断和预后标志物,但这种蛋白在癌症中的作用仍有待解释^[202]。对于LAMP5在肿瘤进展中的影响,首先有研究表明,LAMP5与化学-放射影像治疗,简称为放化疗的II期胃癌患者不良预后相关^[203]。Umeda等人^[204]发现,在胃癌转移部位LAMP5过表达,高LAMP5 mRNA水平与更差的预后显著相关。也有报道称,癌细胞通过形成富含侵入性基质金属蛋白酶的F-肌动蛋白,在周围环境中附着,突破基底膜形成侵入性突起,依赖于LAMP作用下的溶酶体胞吐作用提供额外的膜部分^[205],促进突起的形成。此外,溶酶体膜蛋白糖基化模式的改变也可以增加癌细胞的转移能力^[49,179]。LAMP转运至质膜的确切机制尚未明确,但可能与质膜损伤引发的溶酶体融合和胞吐作为一种膜修复机制有关^[206]。某些研究提出了Rab3a依赖性复合体或肿瘤蛋白D52介导LAMP1和LAMP2转运至质膜的可能性^[44,173]。此外,体外研究表明,酸性微环境可能促使LAMP2移位,这可能支持质膜损伤导致溶酶体和相关膜蛋白招募至质膜的理论^[174]。综上所述,LAMPs家族都能促进肿瘤进展,它们大多在肿瘤发生及转移时移位到质膜来发挥作用,且均与EMT和ECM重排相关(图1),但在不同肿瘤中的作用机制仍有待探索。此外,肿瘤细胞会产生大量的ROS,引起氧化应激反应进而破坏溶酶体稳定,严重将导致溶酶体膜透化(Lysosomal membrane permeabilization, LMP)^[207]。有研究表明,当原癌基因,如*Src*和*Ras*转化为癌基因时,一些细胞系表现出溶酶体定位改

变和LAMP1及LAMP2的低表达,降低了溶酶体的稳定性导致LMP的产生使癌细胞敏感^[6],因此靶向LMP成为治疗肿瘤的新策略^[208],目前在乳腺癌、皮肤癌、宫颈癌、卵巢癌、前列腺癌、结肠癌、肺癌等癌症中已经被应用。溶酶体膜稳定剂,如羟氯喹(hydroxychloroquine)和氯喹(chloroquine)被广泛研究^[209]。其与LMP抑制剂是两种药物类型,前者可增强溶酶体稳定性抑制细胞内自噬过程,后者直接抑制LMP减少细胞死亡,它们在肿瘤治疗中的前临床和临床研究表现出潜在的抗肿瘤活性。

2.3 溶酶体功能在不同类型肿瘤转移中作用的研究进展

乳腺癌^[210]、结直肠癌^[197]、黑色素瘤^[211]作为常见的癌症类型,溶酶体相关活性对肿瘤转移的影响不断被证实。大量研究表明,组织蛋白酶及溶酶体相关蛋白作用下的溶酶体活性在肿瘤转移中起关键作用,其中组织蛋白酶对其他肿瘤进展的影响如表1所示。

乳腺癌被认为是一个全球性的健康问题,大约30%的患者会发生转移或复发^[188]。Wang等人^[212]研究表明,肿瘤诱导剂SYNJ2BP与LC3-II一起定位于自噬-溶酶体膜,然后介导PTEN聚集到溶酶体并降解,不仅依赖于泛素化蛋白酶体途径,激活PI3K/AKT/SNAI1信号通路,并在乳腺癌发展中促进EMT和肿瘤转移。Han等人^[188]研究发现,LAMP2A作为CMA途径的关键蛋白,其水平直接决定了CMA途径活性,体内及体外实验证明CMA途径在乳腺癌转移中活性升高,促进癌细胞迁移和侵袭,而对于正常乳腺上皮细胞无明显作用。他们还发现,CMA活性升高通过下调自噬相关基因5(Autophagy related genes 5, ATG5)依赖性巨噬的活性来影响人乳腺癌细胞的生长和转移。Zhang等人^[213]发现,定位于内质网及溶酶体膜上的跨膜蛋白(TM63A,作为一种新的致癌基因促进三阴性乳腺癌(triple negative breast cancer, TNBC)进展,内质网相关降解(Endoplasmic reticulum related degradation, ERAD)通路的核心成分VCP及DERL1影响TNBC进展,toll样受体互作蛋白TOLLIP介导的自噬-溶酶体降解途径使VCP-TM63A-DERL1信号轴增强促进TNBC进展。

结直肠癌是高发的消化道肿瘤之一。Xuan等人^[191]研究表明,表达量上调的LAMP2A可能在结直肠

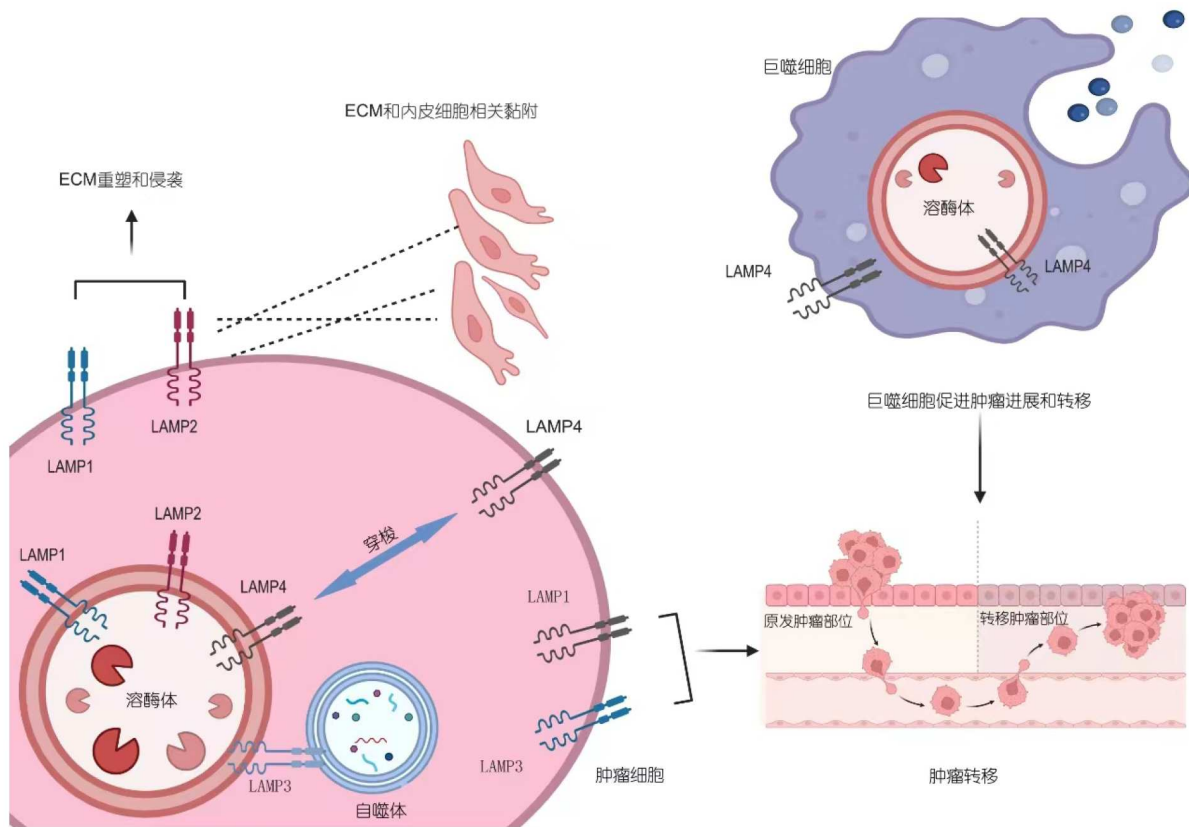


图 1 溶酶体相关膜蛋白与肿瘤发生及转移的关系

Figure 1 Relationship between lysosomal-associated membrane proteins and tumorigenesis and metastasis

癌发生和发展中起作用,抑制CMA活性能阻止结直肠癌肿瘤的生长和转移,并促进药物敏感性。Zhu等人^[197]揭示,结直肠癌细胞中蛋白RPL21的高表达激活了TFEB的转录功能,上调了LAMP3的表达,RPL21与LAMP3的直接相互作用抑制了泛素-蛋白酶体降解,激活了FAK/paxillin/ERK信号通路,增加了未成熟局灶黏连形成,从而促进结直肠癌细胞的迁移、侵袭和肿瘤转移。

恶性黑色素瘤转移造成的死亡人数占有皮肤癌相关死亡人数的75%以上^[211]。除组织蛋白酶外,Zhao等人^[214]研究发现,溶酶体酸性脂肪酶(LAL)及Rab7^[215],与内皮细胞(EC)及mTOR和溶酶体共定位,并与mTOR存在物理相互作用以影响其下游信号传导,具体机制是LAL缺乏导致的代谢重编程改变了Rab7的活性,增强了EC刺激黑色素瘤细胞增殖和转移的能力。对于LAL缺乏,Zhao等人^[216,217]也报道了小鼠的髓源性抑制细胞(MDSCs)在肿瘤发生发展过程中促进骨髓间充

质干细胞(MSCs)增殖,诱发炎症并促进B16黑色素瘤细胞的转移。Leclerc等人^[218]研究表明,小眼相关转录因(Microphthalmia-associated transcription factor, MITF)能调节黑色素瘤增殖及侵袭状态。鞘脂代谢中的关键酶酸性神经酰胺酶(ASAH1)作为MITF下游靶点起作用,ASAH1的低表达与整合素 α -5fak信号级联激活黑色素瘤侵袭行为有关,事实上溶酶体中鞘脂比例较其他膜性细胞器比例更加丰富^[2]。ASAH1的表达降低影响溶酶体稳定以促进黑色素瘤转移。Li等人^[219]证明,BRAFV600E-TFEB/ZKSCAN3-自噬-溶酶体轴是BRAFV600E协调TGF- β 信号和EMT的关键调控途径,导致黑色素瘤的肿瘤进展和转移。MCOLN1/TRPML1是位于溶酶体^[220]中的非选择性阳离子通道。它通过参与包括自噬在内的广泛细胞反应来维持溶酶体功能和细胞稳态^[221]。其中,Qi等人^[222]的研究已表明,MCOLN1的激活通过破坏细胞中自噬体和溶酶体之间的融合来抑制自噬,包括HeLa、HEK293T、胰腺

癌、乳腺癌和胃癌细胞。Xing等人^[223]研究表明, MCOLN1诱导的自噬抑制通过损伤恶性黑色素瘤和胶质瘤线粒体加剧ROS升高, 进而触发TP53活性, TP53的激活通过改变包括基质金属蛋白酶(Matrix metalloproteinase, MMPs)和上皮细胞中抑制EMT的因子(TWIST)在内的一系列转移相关基因的转录来控制癌细胞转移, 表明MCOLN1作为抗癌药物靶点具有巨大潜力。除MCOLN1外, D'Amore等人^[224]也通过实验证明, 溶酶体膜上的双孔通道2(Two-pore channels, TPC2)在人类黑色素瘤转移模型中, TPC2表达的缺失或减少会增加黑色素瘤细胞的侵袭性。除以上介绍的几种在特定肿瘤转移中发挥重要作用的溶酶体相关蛋白外, 鉴定出溶酶体蛋白跨膜-4β(LAPTM4B)基因, 该基因5'-UTR多态性区与肿瘤易感性相关。LAPTM4B在多种实体瘤中高表达促进肿瘤细胞的增殖, 促进侵袭和转移, 抵抗细胞凋亡, 启动自噬并协助耐药性, 可能成为癌症治疗的新靶点^[225]。

虽然对于肿瘤发生及转移的机制研究在逐渐深入, 然而对大多数癌症治疗药物的耐药性几乎是不可避免的, 这最终限制了晚期恶性肿瘤的成功治疗。肿瘤耐药性是肿瘤细胞对治疗药物逐渐失效或减弱的现象, 主要由遗传变异、药物代谢、肿瘤微环境、肿瘤细胞异质性和治疗策略等因素共同作用所致, 限制了肿瘤治疗的效果, 是肿瘤治疗中的重要挑战之一^[226]。溶酶体在肿瘤耐药性的形成和发展中发挥着重要作用, 成为克服肿瘤耐药性的潜在治疗靶点。由于溶酶体(pH 4.5~5)与细胞质(pH 7~7.5)之间存在巨大的pH差异, 溶酶体内部聚集了含胺亲脂性或两性亲分子, 药物通过被动扩散穿过溶酶体膜并进入溶酶体腔, 随后被质子化并保留在酸性环境中^[13]。一些化疗药物利用这种方式被隔离在溶酶体中, 包括顺铂、舒尼替尼、阿霉素和长春新碱。此外, 癌细胞可以诱导溶酶体膜高表达药物转运体, 主动将细胞毒性药物泵入溶酶体。ABC转运蛋白p-糖蛋白通常会诱导胞质膜外排, 从而导致对各种化疗药物的耐药性。它也可以在溶酶体膜中表达, 并介导药物转运进入溶酶体腔^[227]。药物在溶酶体内被隔离, 这阻碍了其到达细胞内的靶标, 进而降低了溶酶体的酸度和活性。为了弥补溶酶体功能缺陷, 细胞通过激活TFEB介导的溶酶体生物发生来产生更多的溶酶体。最终造成药物的隔离程度进一步增强, 加剧了化疗耐药性。溶酶体还可以迁移到质膜并将所含

药物分泌到细胞外环境, 作为另一种赋予耐药性的机制。溶酶体胞吐与治疗药物的耐药性见于多种癌症中, 如白血病、卵巢癌细胞和多形性肉瘤。在侵袭性肉瘤细胞中, 溶酶体重新分布到细胞边缘, 通过增加可溶性溶酶体水解酶和外泌体的胞吐, 导致侵袭性信号的扩散和传播, 同时通过化疗药物的分泌介导耐药。此外, LAMP1也可以通过增加溶酶体体积大小和溶酶体胞吐来促进耐药^[228]。

3 总结与展望

溶酶体内含多种水解酶使其成为细胞内回收废旧大分子的直接执行者, 溶酶体更重要的生理功能体现在其作为代谢的调控中心。在肿瘤中, 常规信号传导途径往往失调, 因此癌症发生发展中溶酶体的功能备受关注。大量研究表明, 溶酶体在癌症生物学中起着重要的作用, 可以影响肿瘤的发生和转移。如图2所示, 溶酶体组分复杂, 包括溶酶体水解酶和溶酶体相关膜蛋白, 它们都在肿瘤转移中起作用。组织蛋白酶作为溶酶体的关键水解酶, 其在肿瘤中表达上调往往促进肿瘤的发生和转移且与患者不良生存预后相关, 具有重要的临床意义。来源于肿瘤细胞或是TAM的组织蛋白酶往往能重塑ECM促进肿瘤的恶性表型, 包括侵袭、EMT、放疗抵抗、血管生成及转移。已有研究表明, 组织蛋白酶抑制剂确实在某些类型肿瘤中抑制肿瘤的进一步转移, 因此组织蛋白酶将是治疗肿瘤发生和转移的重要分子靶点。LAMPs的差异表达显著影响了癌症进展的各过程。LAMP1及LAMP2共同参与致癌过程, 如局部癌症进展、ECM黏附和重塑、转移等; LAMP3及LAMP4等在癌症发展中被激活与炎症相关, 但LAMP3表达影响肿瘤进展的机制仍有待阐明; 有趣的是, LAMP3, LAMP4及LAMP5往往在免疫细胞中高表达, 其在肿瘤细胞中表达量也增加。因此, 有必要深入研究癌症和免疫系统之间的关系, 并阐明LAMP蛋白是否可以在癌症的免疫反应中发挥直接作用。总之, 了解溶酶体水解酶和LAMP蛋白家族在癌症进展中的作用将会提供有价值的参考信息。在癌症治疗的个性化时代, 精确靶向亚细胞器的治疗策略为治疗带来了新的希望。过去几年里, 癌症治疗取得了显著进展, 但大多数治疗药物的耐药性仍然是一个挑战, 限制了晚期癌症的治疗效果, 其中溶酶体作为一个重

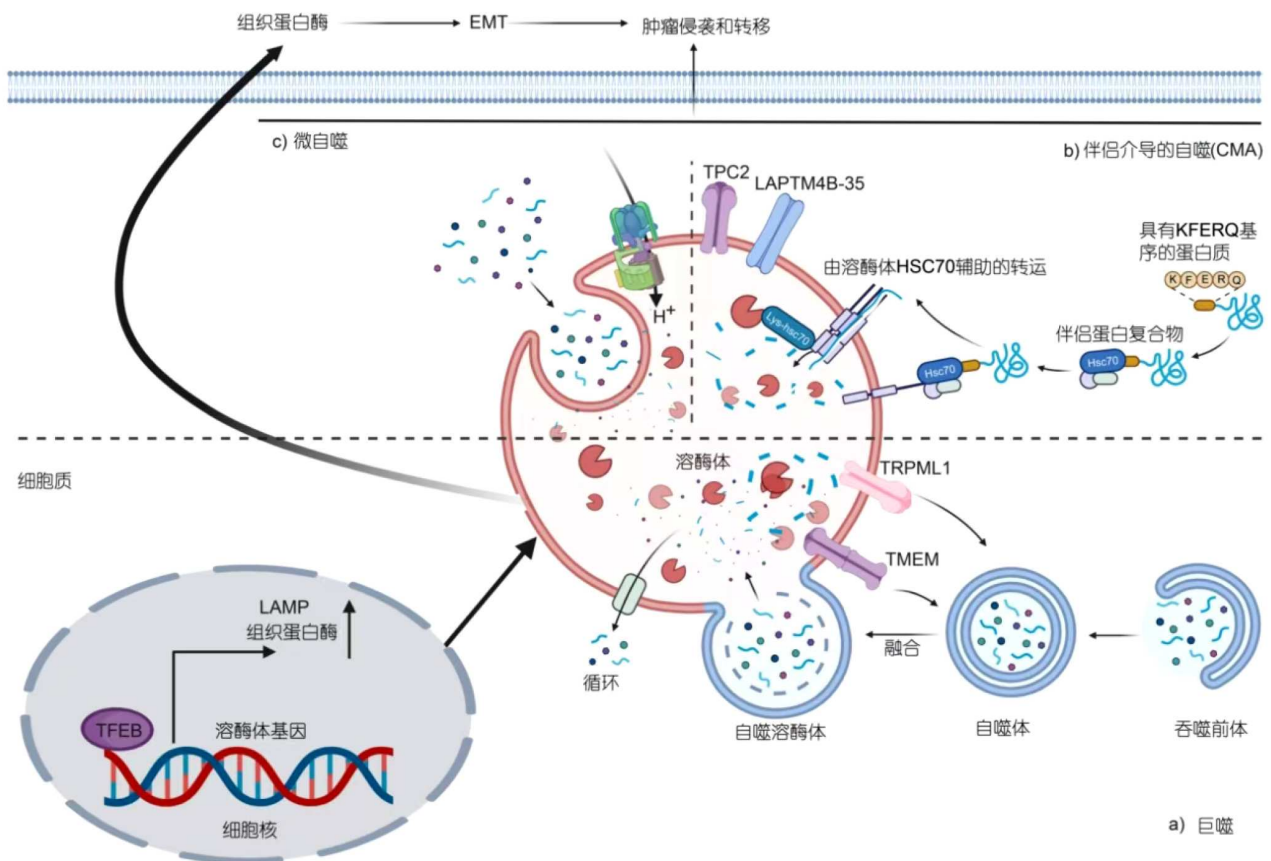


图 2 溶酶体组分与肿瘤转移的关系

Figure 2 Relationship between lysosomal components and tumor metastasis

要的治疗靶点备受关注。溶酶体在自噬过程中的作用对于开发自噬抑制剂用于治疗癌症具有实际意义。溶酶体通过将癌症药物隔离在其酸性环境中,降低了药物的作用效果,在癌症耐药性中起着重要作用。因此,溶酶体被认为是癌细胞的致命弱点。在癌细胞中,溶酶体的生物发生和自噬增加,为增加的代谢活动提供物质及能量,甚至在营养和缺氧条件下也能维持癌细胞增殖。然而,由于溶酶体功能的增强,癌细胞更容易受

到溶酶体膜渗透的影响,这为诱导细胞死亡提供了另一种策略。总的来说,溶酶体在癌症治疗中具有重要的作用,通过多种途径影响癌细胞的生存和耐药性,因此成为重要的治疗靶点。目前对于部分肿瘤,靶向溶酶体的治疗方法显示出良好效果,但相关机制仍有待确认。随着对溶酶体在肿瘤发展中作用机制的深入探究,靶向溶酶体的治疗手段有望进一步改善肿瘤转移的治疗效果。

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Role of lysosomes in tumorigenesis and metastasis

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Lysosomes are crucial for the main metabolic activities within cells, and their dysfunction is linked to various diseases. However, the association between lysosomes and tumor metastasis remains unclear. Tumor metastasis involves escape from the primary tumor site, local invasion, intravasation into circulation, survival in the systemic circulation, extravasation to distant organs, and colonization and growth at secondary tumor sites. Over 90% of cancer-related deaths are attributed to metastasis to distant target organs. The significance of lysosomes in metastasis has been highlighted; however, its underlying mechanisms remain unclear. This review examines the role and mechanisms of lysosomes in tumorigenesis and metastasis and provides insights for targeted therapeutic strategies aiming at lysosomes in cancer prevention and treatment.

lysosome, cathepsin, lysosomal-associated membrane protein, tumorigenesis, tumor metastasis

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