mTOR信号转导通路抑制剂及其与肿瘤耐药的研究进展

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摘要 哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)是一种特异性的蛋白激酶, 在调控细胞生长、增殖、代谢等多项生命活动中都具有重要意义。mTOR调控功能的失活与异常激活, 会导致相关肿瘤和疾病的发生。近年来已有多种mTOR抑制剂用于治疗该信号转导通路异常引起的肿瘤。该文探究多种调控mTOR的信号通路和mTOR抑制剂用于肿瘤治疗的最新进展, 还探讨肿瘤细胞对mTOR抑制剂产生耐药性的潜在机制和应对策略。因此, 对mTOR信号通路及其调控机制的探索有助于研发全新的肿瘤治疗技术。

关键词 mTOR信号转导通路; 肿瘤; 耐药性; 靶向治疗

Research Progress of Inhibitors in mTOR Signal Transduction Pathway and Drug Resistance in Tumor

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Abstract mTOR (mammalian target of rapamycin) is an evolutionary protein kinase that senses multiple upstream stimuli to regulate cell growth, proliferation, metabolism and many other vital activities. The inactivation and abnormal activation of mTOR regulatory functions will lead to the occurrence of related tumors and diseases. In recent years, a variety of mTOR inhibitors have been used to treat tumors caused by abnormal regulation of this signaling transduction pathway. The latest advances in mTOR inhibitors for tumor treatment are listed, and the potential mechanisms by which tumor cells develop resistance to mTOR inhibitors are also explored. Therefore, in-depth study of the mTOR signal transduction pathway and its regulatory mechanism contributes to the development of new tumor treatment technologies.

Keywords mTOR signal transduction pathway; tumor; drug resistance; targeted therapy

哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)是一种高度保守的特异性蛋白激酶, 可以磷酸化其下游底物的丝氨酸/苏氨酸残基以及酪氨酸残基[1]。mTOR响应氨基酸、营养物质、生长因子等环境信号以调控各项生命活动, 包括细胞生长、代谢、衰老、再生等[1]。mTOR以mTORC1/2

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复合体形式存在, mTORC1主要调节细胞生长和代谢, 而mTORC2主要控制细胞增殖和存活[2]。mTOR信号通路在调节哺乳动物的代谢和生理活动中具有关键作用, 其异常调控涉及许多病理生理状况, 例如衰老、阿尔茨海默病、糖尿病、肥胖症和肿瘤等, 尤其在肿瘤发生进程中起重要作用[3]。

mTOR抑制剂通常作为免疫抑制剂, 已被批准用于治疗人类恶性肿瘤。雷帕霉素及其同源物能抑制mTORC1活性, 而短期内不会抑制mTORC2活性[4]。mTOR激活可通过多种方式来促进肿瘤生长, 包括促进生长因子受体信号激活、血管生成、糖酵解代谢、脂质代谢、肿瘤细胞迁移等[5]。因此, mTOR是非常有前景的肿瘤治疗靶点, 尤其mTOR抑制剂广泛应用于肿瘤靶向治疗、器官移植、类风湿关节炎等的研究。这类抑制剂的临床研究证实了它们能有效遏制细胞生长和增殖。然而, mTOR抑制剂的潜在毒性使临床试验的结果并不可观, 需改善治疗策略以便从此类小分子化合物中获益。mTOR抑制剂的研究揭示了肿瘤的代谢可塑性, 可引发其他独立于mTOR的机制来补偿mTOR活性受阻, 从而使肿瘤细胞获得营养以促进其生长和增殖。本综述简要介绍了mTOR的结构和生物学功能, 以及肿瘤细胞对mTOR抑制剂产生耐药性的潜在机制和应对耐药性的有效策略。

1 mTOR及其复合体组装

1.1 mTOR蛋白结构

人源*mTOR*基因编码的蛋白质包含2 549个氨基酸, 并具有多个结构域, 主要包括N-HEAT(NH2-terminal HEAT)、M-HEAT(middle HEAT)、FAT(FRAP-ATM-TTRAP)、FRB(FKBP12-rapamycin-binding)结构域以及激酶结构域[6]。雷帕霉素与mTOR上的FRB结合, 使下游底物无法进入活性位点, 从而抑制mTOR激酶活性, 而ATP竞争性mTOR抑制剂Torin 1, 可直接靶向mTOR催化位点并抑制mTOR的激酶活性[7]。

1.2 mTOR的组装

目前研究发现, mTORC1复合体主要由五种亚基[包括核心催化亚基mTOR、调节亚基Raptor(regulatory-associated protein of mTOR)、结构亚基mLST8(mammalian lethal with SEC13 protein 8)、负调控亚基PRAS40(40 kDa proline-rich Akt substrate)和Deptor(DEP domain-containing protein 6)]组成[8]。mTORC1下游底物4E-BPs(eukaryotic translation initiation factor 4E binding proteins)和S6K1(ribosomal protein S6 kinase β-1)的磷酸化水平是检测其活性的标志[9]。催化亚基mTOR和调节亚基Raptor存在多种磷酸化位点, 如mTOR的S1261、T2164和Raptor的S696、T908等位点, 这些位点的磷酸化均能够影响mTORC1的活性。mTORC1的活性下调时, mTOR负调控亚基PRAS40和Deptor会被募集到mTORC1复合体上, 从而抑制mTORC1活性[10]; mTORC1的活性上调时, 能够利用自身的激酶活性来磷酸化负调控亚基PRAS40和Deptor, 从而减弱负调控亚基的抑制作用, 从而进一步增强mTORC1的活性[11]。

mTORC2复合体由六种亚基[催化亚基mTOR、结构亚基Rictor(rapamycin-insensitive companion of mTOR)、正调控亚基mSin1(mammalian stress-activated protein kinase-interacting protein 1)、mLST8(mammalian lethal with SEC13 protein 8)和Protor1/2(protein observed with Rictor 1/2), 以及负调控亚基Deptor]组成[12]。AGC激酶(cAMP-dependent protein kinase A/cGMP-dependent protein kinase G/protein kinase C)是mTORC2的下游底物。mTORC2的激活依赖于mSIN1的PH(pleckstrin homology)结构域与质膜上的磷脂酰肌醇3,4,5-三磷酸结合, 并且Rictor和mLST8上也存在多种磷酸化位点以调控mTORC2的活性[13]。

2 mTOR信号通路的调控

2.1 mTORC1活性的调控

mTORC1的活性受生长因子、细胞能量、应激和营养物质等多种信号调节(图1)。这些信号主要以两种方式调控mTORC1的活性, 一种是定位于膜表面的小GTP酶Rheb(Ras homolog enriched in the brain)响应上游信号如生长因子、细胞能量、应激等, 通过结合GTP或GDP分别处于活化或失活状态, 进而与mTORC1相互作用以调节其活性, 在此过程中TSC(tuberous sclerosis protein complex)发挥着重要的调节功能, 其作为Rheb酶活化蛋白促进与Rheb结合的GTP水解, 使得Rheb失活, 以实现对mTORC1活性的调节[14]; 一种是在营养物质如氨基酸充足的条件下, 小G蛋白Rags被激活, 结合mTORC1并协助其定位于溶酶体膜表面, 进而调控其活性[15]。目前的研究表明, 此过程由RagA/RagB和RagC/D异源二聚体介导, GTP

结合的RagA/RagB和GDP结合的RagC/D复合物被调节子锚定在溶酶体膜上，进而与Raptor相互作用，将mTORC1募集到溶酶体膜表面以调节其活性[16]。

生长因子激活mTORC1是通过依赖于溶酶体上的Rheb与mTOR的相互作用从而激活mTOR的[17]。生长因子受体如EGFR(epidermal growth factor receptor)和IGFR(insulin-like growth factor receptor)分别识别生长因子EGF和IGF而被激活，进一步激活PI3K(phosphatidylinositol-3-kinase)/PDK1(pyruvate dehydrogenase kinase 1)/Akt(protein kinase B)信号通路，上调mTORC1的活性[18]。生长因子受体GPCR(G protein-coupled receptor)下游的MAPK(mitogen-activated protein kinase)也可上调mTORC1的活性[19]。

mTORC1不仅能感知生长因子，也能感知细胞能量变化并作出反应。在细胞中低能量水平会提高AMP/ATP比例，进而激活能量传感器AMPK(AMP-dependent kinase)，活化的AMPK磷酸化TSC，从而下调mTORC1活性[20]。细胞能量缺乏通常会导致内质网应激，而ATF6(activating transcription factor 6)可通过诱导Rheb的表达来上调mTORC1的活性，进而促进细胞存活[21]。此外，mTORC1还能感知胞内氧气水平和DNA损伤等应激信号并作出响应。在缺氧的条件下，ATP水平的降低会激活AMPK，活化的AMPK促进TSC2的激活，从而抑制mTORC1的活性[22]；低氧还可以通过REDD1(regulated in development and DNA damage response 1)激活TSC，进而阻断mTORC1的激活[23]。DNA损伤应答途径可以通过诱导*p53*的靶基因*AMPKβ*(AMPK的调节亚基)和*TSC*的表达，导致TSC复合物的活性增强，从而抑制mTORC1活性[24]。

氨基酸调控mTORC1的活性是由溶酶体调节蛋白Rags介导的。Rags的活性受两种复合物GATOR1(GAP activity toward the Rag GTPases 1)和GATOR2的调控。GATOR1通过抑制RagA/B的GTP酶活性，从而抑制mTORC1的活性；GATOR2通过诱导DEPDC5(DEP domain-containing protein 5)降解来负调控GATOR1[25]。SESN2(sestrin2)作为亮氨酸传感器调控mTORC1的活性，亮氨酸直接与SESN2结合，导致SESN2从GATOR2上解离，释放GATOR2，从而上调mTORC1活性[26]。为了限制氨基酸对mTORC1的过度激活，E3泛素连接酶RNF152(ring finger protein 152)和SKP2(S-phase kinase-associated protein 2)诱导RagA的泛素化并促进RagA与GATOR1的结合，从而抑制mTORC1的活性[27]。此外，泛素连接酶TRAF6(TNF receptor associated factor 6)催化Akt和mTOR的K63泛素化，以促进氨基酸对Akt和mTORC1的激活[28]。

2.2 mTORC2活性的调控

mTORC2的激活主要由生长因子调控(图1)。经胞外信号激活的PI3K转化成PIP3，PIP3与mSIN1的PH结构域结合，以阻断mSIN1对mTOR活性的抑制，从而激活mTORC2[29]，同时PI3K还可通过促进mTORC2与核糖体的结合，来上调mTORC2活性[30]。激活的mTORC2位于质膜、线粒体和内体囊泡中[31]。此外，IKKα(IkappaB kinase-alpha)可与mTORC2相互作用并增强Akt的激酶活性[32]。

mTORC2活性也受细胞能量和营养的调控。能量传感器AMPK抑制mTORC1的活性，进一步减弱mTORC1对mTORC2的抑制，从而激活mTORC2，因而mTORC2可能有助于细胞适应低能量水平，并且谷氨酰胺饥饿处理会促进mTORC2的激活[33]。

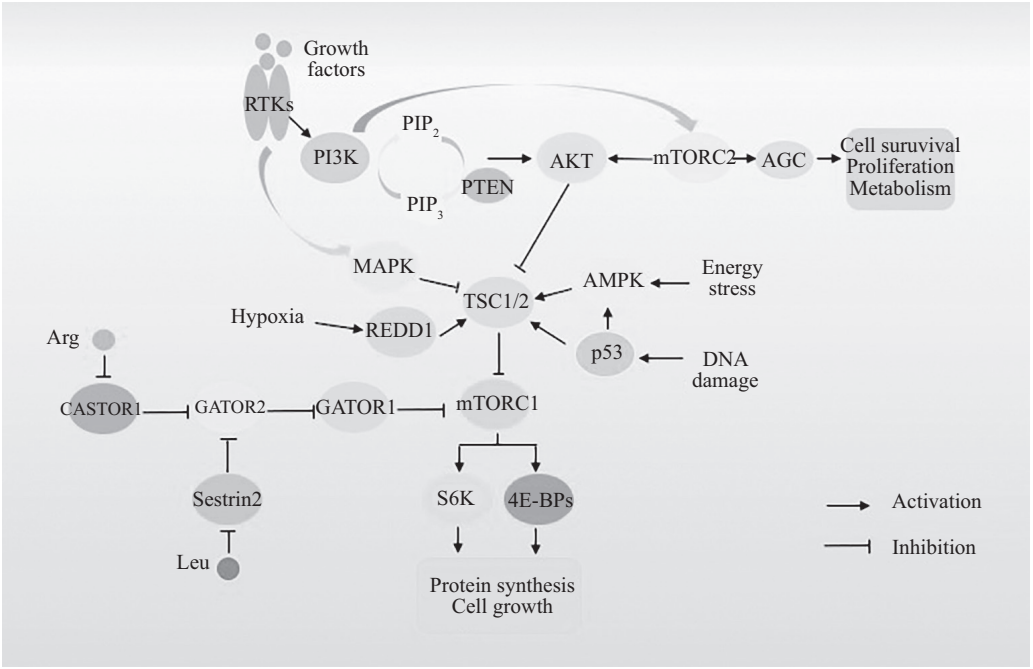
mTORC2复合体结构受磷脂酸的调控，且PA能维持其结构的稳定性[34]。mTORC2的活性还受mLST8泛素化的调控。E3泛素连接酶TRAF2(tumor necrosis factor receptor associated factor 2)正向调节mLST8的泛素化修饰，削弱mLST8与mSIN1的相互作用并损害mTORC2的完整性，从而抑制mTORC2的活性[35]。

3 mTOR与肿瘤疾病的关系

mTOR信号通路参与细胞内的多项生理活动，其失调会影响细胞的正常生理功能并导致人体免疫功能受到损害而引起肿瘤。人类肿瘤中mTOR的异常激活更多归因于mTOR通路激活突变、mTOR复合物组分的扩增或过度表达以及mTOR的负调节因子的突变或丢失。

3.1 mTOR上游信号通路的异常激活

RTKs(receptor tyrosine kinases)介导PI3K以调控mTORC1和mTORC2的活性。RTKs或mTOR其他上游成员如PIK3CA、RAS、Akt的异常激活以及PTEN(phosphatase and tensin homolog deleted on chromosome 10)的突变和丢失均能异常激活mTOR[36]。在人源肿瘤中经常发现*EGFR*基因发生突变而异常表达。*EGFR*突变在25%~82%的结直肠癌、30%~50%的胶质母细胞瘤和5%~20%的非



RTKs: 酪氨酸激酶受体; PI3K: 磷脂酰肌醇三羟基激酶; PIP_2: 磷脂酰肌醇二磷酸; PIP_3: 磷脂酰肌醇三磷酸; PTEN: 磷酸酯酶与张力蛋白同源物; Akt: 蛋白激酶B; TSC: 结节性硬化症蛋白复合体; MAPK: 有丝分裂原活性蛋白激酶; AMPK: 腺苷酸依赖性蛋白激酶; REDD1: 发育及DNA损伤反应调节基因1; mTORC1/2: 哺乳动物雷帕霉素靶蛋白复合体1/2; S6K: 核糖体S6K蛋白激酶; 4E-BPs: 真核翻译起始因子4E结合蛋白。

RTKs: receptor tyrosine kinases; PI3K: phosphatidylinositol 3-kinase; PIP_2: phospholipid phosphatidylinositol 4,5-bisphosphate; PIP_3: phosphatidylinositol 3,4,5-trisphosphate; PTEN: phosphatase and tensin homolog deleted on chromosome 10; Akt: protein kinase B; TSC: tuberous sclerosis complex; MAPK: mitogen-activated protein kinase; AMPK: AMP-activated protein kinase; REDD1: regulated in development and DNA damage response 1; mTORC1/2: mammalian target of rapamycin complex 1/2; S6K: ribosomal protein S6 kinase β-1; 4E-BPs: eukaryotic translation initiation factor 4E binding proteins.

图1 mTOR信号转导通路

Fig.1 mTOR signal transduction pathway

小细胞肺癌等中更常见[37]。在约5%的胃肠道间质癌中发现了*PDGFRα*(platelet-derived growth factor receptor alpha)突变, 在食管癌、脑恶性肿瘤和动脉内膜肉瘤中发现了5%~10%的*PDGFRα*扩增[38]。*FGFR*(fibroblast growth factor receptor)突变广泛存在于人源肿瘤中, 据报道*FGFR1/2/3*的突变在头颈癌、子宫癌和结肠癌等中经常发生, 并且*FGFR1/2*在乳腺癌中异常扩增[39]。*FGFR*基因片段易位也会致癌(包括多发性骨髓瘤)[40]。抑癌基因*PTEN*可负向调控PI3K、MAPK及FAK等信号通路, 而在人源恶性肿瘤(如胃癌、宫颈癌以及胶质瘤等)中经常出现PTEN的功能丧失或突变, 另外, *mTOR*基因经常发生失调, 导致多种恶性肿瘤(如肾上腺癌等)的发生[41]。

3.2 mTOR信号通路下游底物的激活

mTOR下游效应子S6K1、4EBP1和eIF4等[42]通过调节蛋白质合成、细胞存活和生长从而在肿瘤诱发中发挥重要作用。NAKAMURA等[43]发现, 来自乳腺癌细胞系和原发性肿瘤的S6K1高度过表达, 与正常组织相比, S6K1约在8%的原发性乳腺癌中扩增, 表明其在乳腺癌患者的肿瘤发生和预测中具有关键作用, 而且, S6K1已被证实与神经胶质细胞转化和肿瘤发生有关。JAFARI等[44]发现, S6K1介导的PIPK(phosphatidylinositol phosphate kinase)磷酸化对于肿瘤黏着斑和侵袭伪足形成至关重要, 是迁移和侵袭的关键机制。SEGATTO等[45]发现S6K1在细胞运动中起主导作用, 且对新开发的S6K1小分子抑制剂的临床测试表明, 该化合物可能潜在地抑制乳腺癌细胞的集落形成和不依赖贴壁的生长, 表明使用S6K1抑制剂有机会抑制乳腺癌的局部复发和转移。

对p-4EBP1进行的分析表明, p-4EBP1过表达与恶性肿瘤的形成直接相关, 并且p-4EBP1可能作为致癌信号的预测因子和肿瘤恶性能力的重要分子标志物, 特别是在致癌能力和促进增殖信号等方面[46]。此外, 已发现4EBP1水平可以影响肿瘤细胞对PI3K/Akt信号通路抑制剂的敏感性或抗性。ICHIYANAGI等[47]发现, 4EBP1/eIF4E的激活水平可预测肾细胞癌的早期和晚期复发。而且最近研究发现, p-4EBP1可能是卵巢癌患者预后分层和治疗决策的潜在生物标志物[48]。

4 用于肿瘤治疗的mTOR抑制剂

鉴于mTOR在肿瘤进展中发挥着关键作用，mTOR抑制剂有望用于肿瘤等疾病的治疗。雷帕霉素及其类似物(rapalogs)已被批准用于临床治疗，而且研究人员已经研发出了许多具有不同作用机制的mTOR抑制剂(表1)，其中一些正在被用于多种肿瘤疾病的临床试验[49]。

4.1 雷帕霉素及其类似物

雷帕霉素最初被确定为抗真菌药物、免疫抑制剂和抗增殖剂。由于雷帕霉素的溶解性和药代动力学较差，因此不适用于人类肿瘤的治疗。目前，已研发出的几种水溶性雷帕霉素类似物，如西罗莫司(Sirolimus)和依维莫司(Everolimus)表现出肿瘤抑制作用，均已在临床上用于肾细胞癌的治疗，并且已有临床试验结果表明rapalogs用于治疗胃癌、非小细胞肺癌和子宫内膜癌等均有可观的效用[50]。在临床试验中发现，仅雷帕霉素类似物能够辅助用于治疗实体瘤，然而雷帕霉素类似物对肿瘤的抑制作用是有限度的，而且其对mTOR的不完全抑制可能导致较低的临床试验成功率。

4.2 ATP竞争性mTOR抑制剂

为了更彻底地抑制mTOR，研究人员开发出了多种靶向mTORC1和mTORC2的ATP竞争性mTOR抑制剂。依赖于mTOR信号通路的肿瘤可能对这类抑制剂更加敏感，与雷帕霉素类似物不同，ATP竞争性mTOR抑制剂不仅能抑制细胞生长，还可以诱导细胞凋亡。MLN0128(Sapanisertib)是一种pan-mTOR抑制剂，在体外和体内均具有强效抗肿瘤作用，并且MLN0128在小鼠模式生物中已针对骨和软组织肉瘤、乳腺癌等实体瘤进行了实验[51]。FRICKE等[52]的研究表明，在*PIK3CA*突变的结直肠癌中，MLN0128可以克服肿瘤对Everolimus的耐药性并将肿瘤大小减少约20%。CHAMBERLAIN等[53]也发现，对于异种移植的胰腺神经内分泌肿瘤的患者，即使在Everolimus耐药的肿瘤中，MLN0128也可诱导肿瘤缩小。

另一种ATP竞争性mTOR抑制剂PP242(Tokinib)，对胃癌和结肠癌等多种恶性肿瘤均具有良好的抗肿瘤活性[54]。在依赖于Akt-mTOR信号通路的铂耐药肿瘤细胞中，研究人员发现PP242可以在体外和体内使铂耐药卵巢肿瘤细胞重新对卡铂敏感[55]。此外，AZD2014(Vistusertib)及其类似物作为ATP竞争性mTORC1/2抑制剂，在治疗雌激素受体阳性乳腺癌方面非常有效，还可以抑制对rapalogs和紫杉醇具有耐药性的乳腺癌[56]。

4.3 靶向PI3K/mTOR的抑制剂

与单独靶向mTOR相比，靶向PI3K和mTOR的抑制剂可能具有更好的抗癌活性。鉴于PI3K和mTOR的相似性，一些化学物可同时抑制PI3K和mTOR。NVP-BEZ235(Dactolisib)抑制多种PI3K异构体和mTOR，并具有有效的抗癌活性，可穿透血脑屏障，用于治疗胶质瘤和逆转胶质瘤对莫唑胺(muzolimine)的耐药性，且对于表现出PI3K/mTOR活性上调的一类胃癌，NVP-BEZ235能抑制其对紫杉醇产生耐药性的特性[57]。

SAR245409(Voxtalisib)是一种PI3K抑制剂，在多种人类肿瘤异种移植模型中显著抑制肿瘤生长。SAR245409与MEK(mitogen-activated protein kinase kinase)抑制剂Pimasertib可协同抑制某些子宫内膜瘤细胞的生长[58]。GSK2126458(Omipalisib)是一种可口服的PI3K和mTOR抑制剂，能有效减弱人横纹肌肉瘤细胞活力，并抑制体内横纹肌肉瘤的生长[59]。

表1 用于肿瘤治疗的mTOR抑制剂

Table 1 mTOR inhibitors for tumor treatment

mTOR抑制剂 mTOR inhibitor	类别 Category	肿瘤类型 Tumor type
Sirolimus	Rapalog	Renal cell carcinoma
Everolimus	Rapalog	Gastric cancer, non-small cell lung cancer
Sapanisertib	ATP-competitive	Bone and soft tissue sarcoma, breast cancer
Tokinib	ATP-competitive	Stomach and colon cancer
Vistusertib	ATP-competitive	ER-positive breast cancer
Dactolisib	Targeting PI3K and mTOR	Glioma, gastric cancer
Voxtalisib	Targeting PI3K and mTOR	Endometrioma
Omipalisib	Targeting PI3K and mTOR	Rhabdomyosarcoma

5 肿瘤对mTOR抑制剂产生耐药性的机制及治疗策略

耐药性是有效治疗肿瘤的主要难题之一。由于肿瘤的异质性, 一些肿瘤对给定的药物甚至没有反应。克隆选择、适应性进化和对细胞死亡的抵抗是肿瘤耐药的常见机制。由于信号网络的复杂性, 肿瘤细胞可能会通过靶向给定的信号通路, 来影响其他信号通路的激活, 进而适应一种或多种抑制剂。因此, 肿瘤对mTOR抑制剂产生耐药性的潜在机制的深入研究具有重要意义。如下列举了肿瘤对mTOR抑制剂产生耐药性的机制(图2)。

5.1 ABC转运蛋白介导的药物外流

ABC(ATP-binding cassette)转运蛋白的过度表达是多数肿瘤产生耐药性的机制之一。ABC转运蛋白可构成药物外排泵, 从而降低细胞内的药物水平, 影响肿瘤等疾病的治疗效果。事实上, mTOR抑制剂雷帕霉素和NVP-BEZ235分别是糖蛋白和乳腺癌耐药蛋白的底物[60]。HURVITZ等[61]的研究发现, 乳腺癌耐药蛋白在对Everolimus耐药的管腔乳腺癌细胞系中过度表达, 并且ABCG2的过表达赋予了肿瘤细胞对PI3K抑制剂PF-4989216的显著抗性, 而ABCG2抑制剂或竞争性底物能逆转此过程。对ABC转运蛋白的亲和力因不同的mTOR抑制剂而异, 因此降低其对ABC转运蛋白的亲和力或抑制ABC转运蛋白的活性可能会增强mTOR抑制剂的功效, 从而有效治疗肿瘤。

5.2 肿瘤干细胞

肿瘤干细胞(tumor stem cell, TSC)是肿瘤块中的一个亚群, 对肿瘤治疗具有极强的抵抗力。mTOR是增强肿瘤耐药性的转化生长因子-β信号通路的介质之一。转化生长因子-β可诱导上皮–间质转化, 从而促进肿瘤干细胞的生成[62]。已有研究表明, 一些mTOR抑制剂具有对肿瘤干细胞的抑制作用, 如PI3K/mTOR抑制剂VS-5584会降低多种人源肿瘤小鼠异种移植模型中的CSC水平[63]。VENKATESAN等[64]的研究表明, *TP53*(tumor suppressor p53)突变和BCL2(B-cell lymphoma 2)磷酸化影响胶质母细胞瘤对mTOR抑制剂的敏感性, 而且与*TP53*突变的胶质母细胞瘤干细胞相比, TP53野生型胶质母细胞瘤干细胞中的BCL2磷酸化导致胶质母细胞瘤对mTORC1/2抑制剂的敏感性降低。因此, 深入研究肿瘤的遗传背景和肿瘤干性通路, 将有利于研发更有效的mTOR抑制剂和小分子化合物以抵抗肿瘤耐药性。

5.3 mTOR突变

基因突变可能会影响药物的敏感性。已有多种mTOR的激活突变例如mTOR激酶结构域的突变M2327I、S2215Y、L2230V、E2388Q和V2046A等存在于人源肿瘤中, 可能对ATP竞争性抑制剂MLN0128产生抗性[65]。尽管已有所突破, 仍需要进一步深入研究以阐明在Raptor、Rictor和RHEB中哪些未知的肿瘤相关突变可能与mTOR抑制剂的耐药性有关。

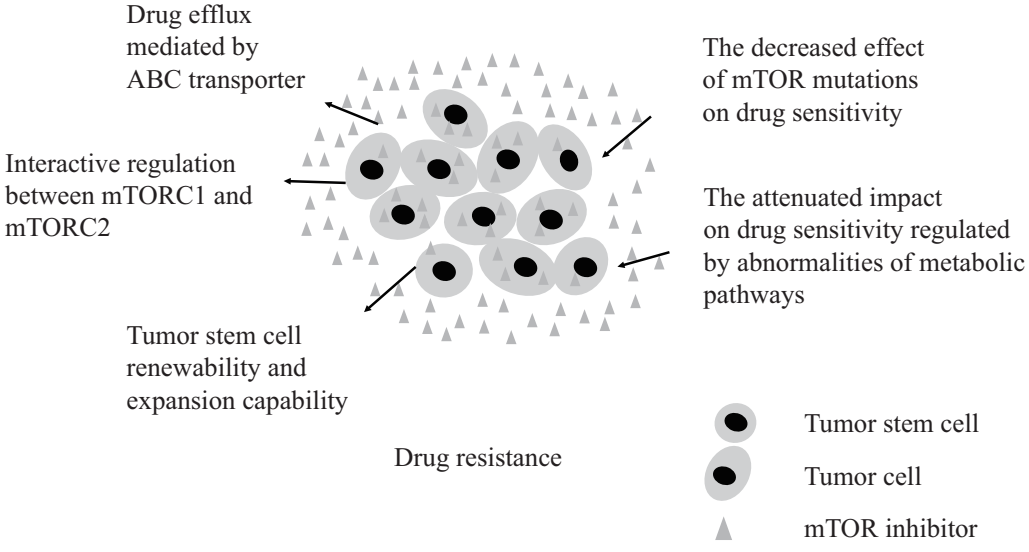


图2 肿瘤对mTOR抑制剂产生耐药性的机制

Fig.2 Mechanisms of tumor resistance to mTOR inhibitors

5.4 肿瘤代谢途径的异常

mTOR抑制剂的敏感性受其他肿瘤途径的调节。抑制mTOR可能导致MEK/ERK通路的激活, 通过CDK4/6(cyclin dependent kinase 4/6)抑制剂palbociclib可抑制ERK, 因而CDK4/6和mTOR抑制剂可协同抑制肿瘤生长[66]。转谷氨酰胺酶2(transglutaminase 2)是一种多功能酶, 参与多肽链的交联、细胞凋亡、信号转导等, 抑制转谷氨酰胺酶2可有效使mTORC1异常激活的肿瘤细胞对雷帕霉素敏感[67]。此外, 线粒体稳态对细胞生长和存活至关重要。线粒体过度融合是对mTOR抑制的适应性反应, 而这一过程会拮抗细胞凋亡, 使肿瘤细胞得以存活[68]。因此, 肿瘤代谢途径的异常及相互影响均会导致肿瘤产生耐药性。深入研究肿瘤代谢途径的复杂机制将有益于指导临床治疗中mTOR抑制剂的高效使用。

5.5 mTORC1与mTORC2的交互作用

mTORC1与mTORC2的交互调控也会影响肿瘤对mTOR抑制剂的敏感性。mTORC2通过PI3K响应生长因子而被激活, 激活的mTORC2磷酸化Akt, 上调mTORC1的活性, 使肿瘤细胞的生存能力和增殖能力得以增强, 从而使肿瘤细胞对药物产生一定的抵抗性[69]。同时, 活化的mTORC2通过抑制促凋亡microRNA(miR-9-3p)的表达, 从而削弱其对促存活因子E2F1(E2F transcription factor 1)的负调控, 以抑制肿瘤细胞的凋亡并且促进肿瘤细胞的存活[70]。mTORC2的活性还受mTORC1的底物S6K的调控。mTORC1下游底物S6K通过在不同部位磷酸化IRS1(insulin receptor substrate 1)以抑制胰岛素信号转导, 下调PI3K信号通路来抑制mTORC2活性。S6K还可分别磷酸化Rictor和mSin1, 以破坏mTORC2的稳定性[71]。故靶向mTORC1的抑制剂会解除mTORC1对PI3K/mTORC2信号的抑制, 从而导致肿瘤细胞存活能力增强[72]。因此, 进一步研究并阐明mTORC1与mTORC2间潜在的交互调控机制, 有利于mTOR抑制剂和小分子药物的合理使用以克服肿瘤耐药性。

6 讨论与展望

mTOR及mTOR信号通路的调节器和效应器的深入研究有益于阐明细胞信号转导的调控机制以及信号网络协同工作的复杂机制。mTOR及其在肿瘤发生中的重要作用的鉴定推动了mTOR抑制剂的研发。虽然一些mTOR抑制剂已被批准用于肿瘤治疗, 但更多的mTOR抑制剂正在接受临床检验, 以实现对肿瘤的有效治疗。最近的研究表明, mTOR抑制剂似乎在患有不同类型肿瘤的患者和患有相同类型肿瘤的患者中具有混合功效, 特别是肿瘤类器官可能有助于测试给定肿瘤对mTOR抑制剂的反应[73]。确定这些新兴技术能否有效应用于临床治疗将具有重要意义。

潜在的预测性生物标志物可用于指导临床试验和帮助肿瘤患者从mTOR抑制剂治疗中受益, 但是肿瘤患者对mTOR抑制剂的不同反应的复杂机制可能降低抑制剂的疗效。此外, 毒性是阻碍药物临床治疗的关键问题。尽管mTOR抑制剂在临床研究中具有一定的疗效, 但一些抑制剂对患者有严重的副作用而必须停用。因此, 阐明这些不良反应背后的机制将有助于在临床上合理应用此类小分子药物。

耐药性是成功治疗肿瘤的严峻挑战。进一步研究并阐明肿瘤发生的不同分子机制更有助于制定相应策略来克服肿瘤对mTOR抑制剂的耐药性。未来对于mTOR抑制剂与化学治疗剂或分子靶向药物的配合使用具有广阔前景。

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