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·综 述·

天冬酰胺与肿瘤关系的研究进展

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[摘 要] 天冬酰胺(Asn)作为一种非必需氨基酸,在疾病的发展过程中扮演着举足轻重的角色,尤其在肿瘤细胞代谢调控和免疫调节方面发挥着关键作用。本文围绕肿瘤代谢及转移侵袭等核心生物学过程,从信号通路和分子机制方面,系统阐述了Asn参与上述病理进程的具体作用机制。同时,本文总结了近年来Asn在肿瘤治疗领域的研究进展及临床应用成果,并深入分析了其在后续研究与临床推广中可能面临的挑战,旨在为Asn在医学领域的进一步应用研究提供有力线索,并为相关领域的研究者提供有益的参考。

[关键词] 天冬酰胺;肿瘤;mTOR;免疫;代谢调控
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Research progress on the relationship between asparagine and tumors

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Abstract: Asparagine (Asn), a non-essential amino acid, plays a pivotal role in the development of diseases, particularly in the metabolic regulation and immune modulation of tumor cells. This paper focuses on the core biological processes such as tumor metabolism and metastasis and invasion, and systematically elucidates the specific mechanisms of Asn participates in the above pathological processes from the perspectives of signaling pathways and molecular mechanisms. Meanwhile, this paper summarizes the research progress and clinical application achievements of Asn in the field of tumor therapy in recent years, and conducts an in-depth analysis of potential challenges in subsequent research and clinical promotion, aiming to provide valuable insights for further application studies of Asn in the medical field and offer useful references for researchers in related areas.

Keywords: asparagine; tumor; mTOR; immune; metabolic regulation

恶性肿瘤作为威胁全球人类健康的主要“元凶”之一,其复杂的发生发展机制一直是医学领域的研究重点。近年来,肿瘤细胞的代谢调控逐渐成为治疗肿瘤的关键靶点。天冬酰胺(asparagine,Asn)作为一种具有重要生理功能的氨基酸,已被证实与大多数类型肿瘤的发生、发展及转移过程密切相关。例如,在胃癌细胞中,Asn的含量显著增加,且其代谢水平与肿瘤的发生和发展密切相关[1]。此外,L-天冬酰胺酶(L-asparaginase,L-ASNase)作为一种能够水解Asn的关键酶,可影响白血病[2]、乳腺癌[3]等的发生和发展。Asn不仅参与肿瘤细胞的代谢途径,还可通过调控信号通路、影响肿瘤细胞微环境等参与肿瘤的发生、发展和转移过程。因此,深入研究Asn在肿瘤发生发展中的具体作用机制,不仅有助于更全面理解肿瘤生物学行为的复杂性,还可能为开发创新性的肿瘤治疗方法开辟全新路径,进而为肿瘤的临床治疗提供更加精准、有效的策略,从而显著改善肿瘤患者的预后和生活质量。

1 Asn与肿瘤代谢的关系

Asn因在肿瘤代谢中的作用而受到广泛关注,降低Asn水平已成为治疗急性髓细胞白血病的有效方法[4]。1970年,研究者首次发现白血病细胞对药物治疗的敏感性与其Asn生物合成能力之间呈显著负相关[5]。这为L-ASNase在儿童急性淋巴细胞白血病化疗方案中的广泛使用提供了理论基础[6-8]。其核心机制在于,恶性淋巴细胞依赖于从循环血浆中摄取Asn来保证代谢、生长和增殖[9],而天冬酰胺酶(asparaginase,ASNase)可通过消耗血液中的Asn间接发挥作用,从而抑制肿瘤细胞的增殖,起到抗肿瘤的作用[5]。

有研究发现,肿瘤抑制因子p53的缺失上调了天冬酰胺合成酶(asparagine synthetase,ASNS)的表达,从而影响小鼠血清中Asn的水平,及肿瘤细胞内外环境

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中Asn和天冬氨酸的平衡状态[10]。高水平Asn可维持肿瘤细胞的存活和增殖能力,而去除Asn会显著抑制肿瘤细胞的增殖并诱导其凋亡[11-13]。此外,Asn是线粒体呼吸功能与肿瘤细胞代谢调控通路之间的分子纽带:当线粒体的电子传输链受到抑制时,细胞内的天冬氨酸及其衍生的Asn水平会降低,导致转录激活因子4(activating transcription factor 4,ATF4)的水平升高,进而抑制哺乳动物雷帕霉素靶蛋白复合体1(mammalian target of rapamycin complex 1,mTORC1)的活性,影响核苷酸的合成,最终抑制肿瘤细胞的增殖;而外源补充Asn可在电子传输链受抑制的情况下恢复肿瘤细胞的增殖、ATF4和mTORC1的活性,以及mTORC1依赖的核苷酸合成[14]。这些研究均证实,Asn在肿瘤细胞的代谢和生长过程中发挥着关键作用[14]。

作为氨基酸感应网络的关键节点,Asn通过多机制特异性调控mTORC1的激活(图1),在肿瘤代谢适应中扮演特殊角色。mTORC1作为细胞代谢中枢,通过整合营养信号与生长因子刺激,驱动癌细胞代谢重编程以适应低营养微环境。其激活需要氨基酸特别是亮氨酸、精氨酸和谷氨酰胺通过Ras相关鸟苷三磷酸结合蛋白(Ras-related guanosine triphosphate-binding protein,RAG)家族[15]引导mTORC1向溶酶体定位[16]。Asn作为氨基酸交换因子,通过促进细胞内外丝氨酸、精氨酸等必需氨基酸的交换,间接激活mTORC1[13]。值得注意的是,Asn同时突破了传统RAG依赖机制,通过ADP核糖基化因子1(ADP-ribosylation factor 1,ARF1)的GTP水解循环介导mTORC1向核糖体表面定位,绕过RAG直接激活mTORC1[17-18]。

在肿瘤微环境中,癌细胞通过代谢重编程维持氨基酸稳态。ASNS表达上调使癌细胞能自主合成Asn[10],同时细胞膜氨基酸转运体溶质载体家族1成员5(solute carrier family 1 member 5,SLC1A5)介导Asn外排-摄取循环,形成促进mTORC1持续激活的正反馈回路[19-20]。这种Asn依赖的代谢适应机制,与磷脂酰肌醇3-激酶/蛋白激酶B信号通路(phosphoinositide 3-kinase/protein kinase B signaling pathway,PI3K/AKT signaling pathway)突变[21-22]及磷酸酶与张力蛋白同源物(phosphatase and tensin homolog,PTEN)失活[21]协同,共同维系癌细胞的合成代谢需求。

临床干预mTOR通路面临双重挑战:传统雷帕霉素类似物难以完全抑制真核翻译起始因子4E结合蛋白(eukaryotic translation initiation factor 4E-binding protein,4EBP)磷酸化,且可能引发Akt反馈激活[23];单纯靶向氨基酸代谢易导致旁路代偿。基于Asn的特殊调控机制,联合抑制ASNS与mTOR的活性,或阻断SLC1A5介导的氨基酸交换,可能打破肿瘤细胞的代谢-信号轴恶性循环,为癌症治疗提供新策略。

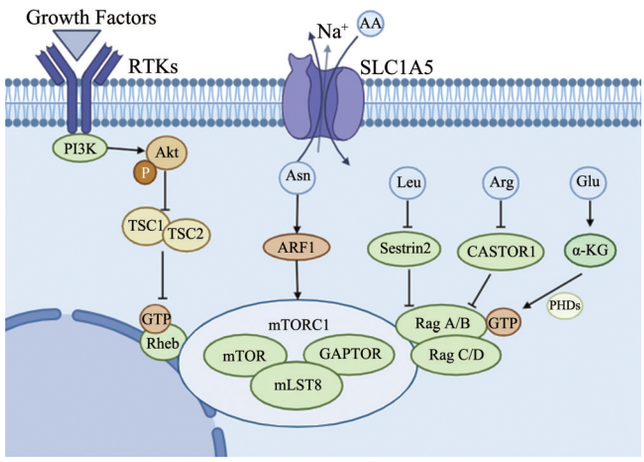


图1 Asn激活mTORC1复合物

2 Asn与肿瘤侵袭和转移的关系(图2)

Asn作为蛋白质合成的关键氨基酸,在肿瘤转移中展现出复杂的双向调控功能。Asn的生物利用度(即肿瘤细胞获取和利用Asn的能力)直接影响转移潜能[24],但具体作用机制因肿瘤类型而异。

在乳腺癌中,ASNS的高表达导致细胞内Asn水平升高,进而激活mTORC1信号通路,其表达水平与晚期肿瘤的转移、复发呈正相关[24]。通过敲低ASNS的编码基因[25]、应用ASNase治疗[25-26]或限制摄入Asn,可减少Asn的供应,进而调控外源性凋亡途径并诱导肿瘤细胞凋亡[27],最终抑制肿瘤细胞的迁移和侵袭能力。有研究发现,在乳腺癌小鼠模型中,抑制ASNS或限制Asn摄取可降低癌细胞对Asn的生物利用度,阻止间质基因表达模式的诱导,从而减少肺转移,但对小鼠原发性乳腺肿瘤的生长无明显影响[24]。

与乳腺癌相反,ASNS在肝细胞癌中呈高表达,且与肿瘤恶性程度呈负相关。敲低ASNS会增强肝细胞癌细胞迁移、侵袭及肺转移能力,提示Asn代谢在肝细胞癌中可能通过抑制上皮间质转化发挥保护作用[28]。

此外,在口腔鳞状细胞癌中,Asn可促进神经侵袭并作为神经周围浸润的诊断指标[29]。在食管鳞状细胞癌中,NRF2/ATF4/FOXM1通路的激活驱动ASNS上调,与癌症晚期转移密切相关[30-31];在结肠腺癌中,L-ASNase可通过阻断PI3K/Akt/mTORC1通路抑制细胞增殖,并激活自噬凋亡信号[32];同时Asn/Gln剥夺能够激活Erk磷酸化介导的促自噬途径[33],从而影响肿瘤细胞的生长与增殖。

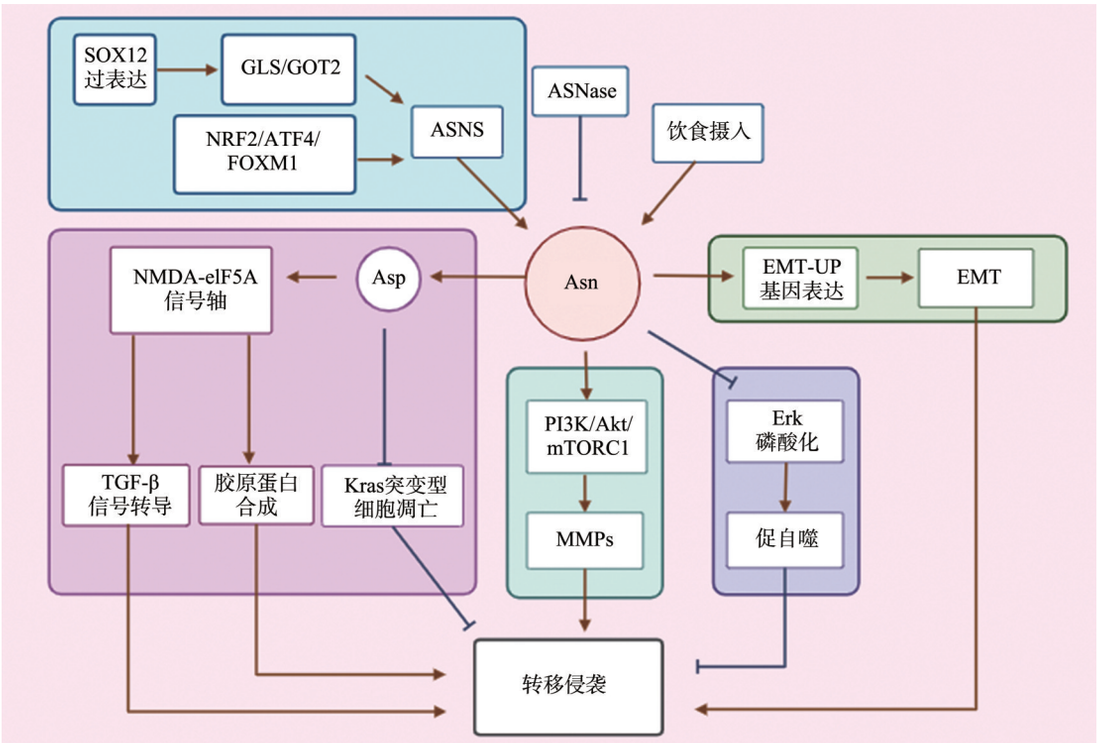


图2 Asn与肿瘤侵袭和转移的关系

3 Asn代谢靶向的肿瘤治疗策略

3.1 ASNase疗法

ASNase是一种可将非必需氨基酸Asn脱氨基的外源性酶[34]。肿瘤细胞自身合成Asn的能力有限,主要依赖外源性Asn供应[35]。ASNase可通过降低血液中的Asn水平,抑制肿瘤细胞的生长和增殖。目前,ASNase治疗已被广泛应用于急性淋巴细胞白血病的治疗,并取得了显著的疗效。然而,在治疗过程中,部分肿瘤细胞可能通过基因变异等方式,提高ASNS的活性,从而自行合成Asn,减少对外源性Asn的依赖[35-37],表明白血病细胞在药物压力下能够发展出抵抗机制[38]。Hinze等[36]发现,在ASNase耐药的急性白血病中,Wnt通路激活可能会改变细胞对Asn剥夺的代谢敏感性,使得原本对ASNase耐药的细胞,在Asn耗竭的压力下,无法通过代偿机制维持存活,最终触发凋亡,为治疗ASNase耐药性白血病提供了潜在的治疗靶点。

ASNS是肿瘤细胞合成Asn的关键酶[39]。ASNS的表达增强可以保护胰腺癌细胞免受葡萄糖剥夺和顺铂诱导的细胞凋亡[40]。ASNS在去势抵抗性前列腺癌中上调,使用ASNS抑制剂消耗Asn可能是一种靶向去势抵抗性前列腺癌细胞的新策略[41]。有研究显示,新型ASNS抑制剂Bisabosqual A能抑制人非小细胞肺癌A549细胞增殖和迁移[42]。这表明ASNS抑制剂的开发,可为肿瘤治疗领域带来新的希望和可能性。

3.2 代谢联合干预

二甲双胍是线粒体呼吸链复合体Ⅰ的抑制剂,可以通过抑制线粒体呼吸链,降低肿瘤细胞内的腺嘌呤核苷三磷酸水平,从而抑制肿瘤细胞的增殖[43]。研究表明,二甲双胍与限制Asn摄入联用可以显著延缓荷瘤小鼠体内肿瘤的生长[14]。

极光激酶A(aurora kinase A,AURKA)在非小细胞肺癌中显著上调并与不良预后相关[44]。抑制AURKA可导致纺锤体形成异常和有丝分裂缺陷,从而导致肿瘤细胞死亡[45-46]。有研究表明,AURKA抑制会抑制ASNS的表达,使得高表达ASNS的KEAP1缺陷型非小细胞肺癌细胞对AURKA抑制剂敏感[47]。同样,肿瘤转化基因1在肝癌组织中高表达,提示其在肝癌的发生发展中可能起重要作用。有研究发现,肿瘤转化基因1参与了Asn的代谢重编程,通过增加Asn水平激活mTOR通路进而促进肝细胞癌进展[48],可作为肝细胞癌的治疗和诊断靶点。

4 Asn与免疫调控

Asn能够通过上调淋巴细胞特异性蛋白酪氨酸激酶信号通路增强$CD8^+$ T细胞活性,从而增强免疫细胞功能,抑制肿瘤生长[49]。然而,在长时间刺激后,细胞内ASNS表达上调会驱动$CD8^+$ T细胞表型转变,使其不再严格依赖Asn存活[50]。对此,美国Ruoning Wang团队也提出了类似的观点,在$CD8^+$ T细胞的活化进程中,Asn对细胞的限制作用存在阶段特异性差异,即激

活早期与分化晚期所发挥的生物学效应完全相反[51]。

5 总结与展望

Asn在肿瘤发展的研究中虽已取得显著进展,但仍面临一些挑战。Asn通过多条途径进行调控的复杂机制,显著增加了研究的难度和复杂性。且不同的肿瘤细胞类型对Asn的依赖程度可能存在差异[52]。这种细胞类型特异性要求研究者针对不同类型的肿瘤进行个性化的研究。目前,非实体肿瘤中以Asn代谢为靶向的治疗方案已大范围推广应用,但对于实体肿瘤的作用效果并不明朗,这与实体肿瘤自身表达ASNS、对外源性Asn依赖性差有关[52-53]。

目前,用于降低Asn水平的药物(如ASNase)在临床应用中易引起过敏反应、胰腺炎等副作用[54]。另外,长期使用ASNase等药物可能导致肿瘤细胞产生耐药性,从而降低治疗效果[36]。为了克服这些问题,研究者们还需继续深入探索Asn在肿瘤代谢和信号传导中的作用机制,开发更加有效、安全的针对Asn代谢的肿瘤治疗方法。

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