靶向肌苷5′-单磷酸脱氢酶的抗肿瘤药物研究进展

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摘要: 细胞内嘌呤核苷酸稳态的维持对于正常生命活动的开展具有重要意义。肌苷5′-单磷酸脱氢酶 (inosine-5′-monophosphate dehydrogenase, IMPDH) 是嘌呤核苷酸从头合成途径 (*de novo* synthesis pathway) 的限速酶, 能够直接决定细胞内鸟嘌呤核苷酸的合成水平。在快速增殖的肿瘤细胞中, IMPDH会异常活化以维持其旺盛的核酸需求, 这使其成为肿瘤治疗的潜在靶标。尽管包括噻唑呋林 (tiazofurin) 在内多款药物已进入临床研究阶段, 但目前尚无靶向IMPDH的抗肿瘤药物上市, 该领域仍需更加深入系统的研究。本文综述了IMPDH的结构、功能和靶向IMPDH的抗肿瘤药物研究进展, 旨在为后续研究提供参考。

关键词: 核苷酸代谢; 从头合成途径; 肌苷5′-单磷酸脱氢酶; 抑制剂; 癌症治疗

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Research progress of anticancer drugs targeting inosine-5′-monophosphate dehydrogenase

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Abstract: Maintaining intracellular purine nucleotide homeostasis is critical for sustaining normal cellular physiology. Inosine-5′-monophosphate dehydrogenase (IMPDH) acts as the rate-limiting enzyme in the *de novo* purine nucleotide biosynthesis (DNPNB) pathway, directly regulating intracellular guanine nucleotide synthesis levels. In rapidly proliferating tumor cells, IMPDH is aberrantly activated to meet heightened nucleic acid demands, rendering it a promising target for cancer therapy. Despite the advancement of several candidates — including tiazofurin — into clinical trials, no IMPDH-targeted antitumor drugs have been approved for marketing, highlighting the need for more rigorous and systematic investigation in this field. This review summarizes the structural and functional properties of IMPDH and the progress in developing IMPDH-targeting anticancer drugs, with the aim of providing insights for future research.

Key words: nucleotide metabolism; *de novo* synthesis pathway; inosine-5′-monophosphate; inhibitor; cancer therapy

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核苷酸是核酸的基本组成单位, 也是所有细胞增殖的必需原料之一。核苷酸代谢 (nucleotide metabolism) 稳态的维持对生命活动的正常进行具有重要意义[1]。肿瘤细胞具有无限增殖的特征, 其通过广泛的代谢重编程以支持自身存活与快速增殖[2]。嘌呤核苷酸代谢重编程是肿瘤的核心特征之一, 通过调控增殖、免疫、转移等多环节促进肿瘤进展[3,4]。其中, 鸟苷三磷酸 (guanosine triphosphate, GTP) 是能量代谢的重要载体, 也是DNA和RNA合成的关键前体; 其细胞内水平的升高依赖于嘌呤核苷酸从头合成途径[5]。肌苷5′-单磷酸脱氢酶 (inosine-5′-monophosphate dehydrogenase, IMPDH) 是从头合成途径的关键限速酶, 能催化肌苷单磷酸 (inosinic acid, IMP) 不可逆氧化为黄嘌呤单磷酸 (xanthine monophosphate, XMP), 直接调控GTP合成的速率与整体水平[1]。IMPDH介导的嘌呤核苷酸从头合成途径异常激活已成为肿瘤的关键特征之一, 且与肿瘤的发生发展密切相关[2]。因此, 靶向IMPDH的药物有望成为癌症治疗的潜在策略。

1 嘌呤核苷酸代谢

胞内嘌呤核苷酸稳态的维持依赖从头合成途径和补救合成途径 (salvage synthesis pathway)[6,7]。补救合成途径通过回收胞内核苷酸分解产物或外源核苷完成嘌呤核苷酸再生; 而从头合成途径可利用氨基酸、5-磷酸核糖-1-焦磷酸 (phosphoribosyl pyrophosphate, PRPP)及碳酸氢盐等前体物质, 经多步酶促反应逐步组装嘌呤环, 最终生成IMP, 并进一步分支合成腺嘌呤核苷酸 (adenosine monophosphate, AMP) 和鸟嘌呤核苷酸 (guanosine monophosphate, GMP)[8,9]。补救合成途径能量消耗低, 主要满足分化成熟细胞的基础代谢需求; 从头合成途径主要在肝脏中进行, 能量消耗较高, 可满足快速增殖细胞 (如肿瘤细胞) 的大量嘌呤需求, 是体内嘌呤核苷酸的主要合成方式。

从头合成途径是维持细胞核苷酸稳态的关键, 在细胞内受到多层面协同调控: 在转录水平, 癌细胞中c-MYC (myelocytomatosis viral oncogene homolog) 和VGLL3 (vestigial like family member 3) 等转录因子可特异性激活通路关键基因的表达; 在蛋白水平, 不仅磷酸化和乙酰化等翻译后修饰可调控相关酶催化活性, 嘌呤核苷酸终产物 (如AMP和GMP) 也可通过负反馈机制抑制相关酶活性, 最终实现胞内嘌呤代谢的动态平衡[5]。此外, 从头合成途径的活性还受到细胞能量状态及其他信号通路的调控: 当细胞增殖需求旺盛或能量充足时, PI3K-PDK1信号通路激活, 促进嘌呤核苷酸从头合成途径相关酶组装形成功能性超分子复合物——嘌呤体 (purinosome), 显著提升通路催化效率; 而能量匮乏时, AMP依赖的蛋白激酶 (adenosine 5′-monophosphate-activated protein kinase, AMPK) 被激活, 通过抑制嘌呤体组装减少代谢消耗, 实现通路活性的精准下调。肿瘤细胞具有无限增殖特征和旺盛的能量需求, 其对鸟嘌呤核苷酸 [GMP→GDP (guanosine-5′-diphosphate) →GTP] 的需求显著升高[10], 进而导致从头合成途径异常激活。因此, 靶向嘌呤核苷酸代谢关键通路成为肿瘤治疗领域的新方向之一。

2 IMPDH的结构和功能

作为从头合成途径的限速酶, IMPDH是调控嘌呤核苷酸代谢的关键分子[11]。人类基因组编码两种IMPDH同工酶, 分别为位于7号染色体的IMPDH1 (inosine-5′-monophosphate dehydrogenase 1) 和3号染色体的IMPDH2 (inosine-5′-monophosphate dehydrogenase 2), 二者序列同源性高达84%[12]。IMPDH1和IMPDH2的表达与组织分布存在差异: IMPDH1主要存在于静态细胞中, 如视网膜、脾脏及静止的外周血单核细胞; IMPDH2则主要存在于快速增殖细胞中, 如肿瘤组织和活化的淋巴组织[13]。

IMPDH单体通常由400～500个氨基酸残基组成, 分为催化域 (catalytic domain) 和调控域 (regulatory domain) 两个结构域 (图1A～C)。催化域由 $(\beta/\alpha)_8$ 桶状结构构成, 即由8个β折叠形成桶状核心, 外侧环绕8个α螺旋 (图1C)。$(\beta/\alpha)_8$桶状结构是生物酶中常见的催化结构域折叠模式[14], 因首次在磷酸丙糖异构酶 (triose-phosphate isomerase, TIM) 中发现而得名, 是IMPDH结合底物并执行催化反应的核心区域。调控域长约120个氨基酸残基, 由两个胱硫醚β-合酶 (cystathionine β-synthase, CBS) 重复序列构成, 形成一个CBS对 (bateman结构域)[15]。调控域插入催化域的一个环区中, 对IMPDH的催化活性并非必需, 但对变构调节至关重要; 例如, bateman结构域可结合核苷酸类变构调节剂 (如ATP和GTP), 介导酶的构象变化[16]。IMPDH还具有一个特殊结构特征: 从TIM桶状结构C端表面伸出的扭曲β折叠, 该结构被称为“手指域”(finger domain)[17], 存在于所有已知IMPDH中, 且对变构调节不可或缺 (图1C)。此外, 手指域内存在一个关键功能环, 称为“催化瓣”(catalytic flap), 在催化循环过程中呈现不同构象 (图1C)[18]。通过各单体催化域的相互作用, IMPDH在溶液中以四聚体形式存在 (图1B), 这可能主要为实现功能上的协同效应和精密的变构调节。

IMPDH催化IMP氧化为XMP的机制如图1D所示: 首先, IMPDH中的319位半胱氨酸与IMP的C2位发生亲电加成反应, 通过重排将氢负离子转移至

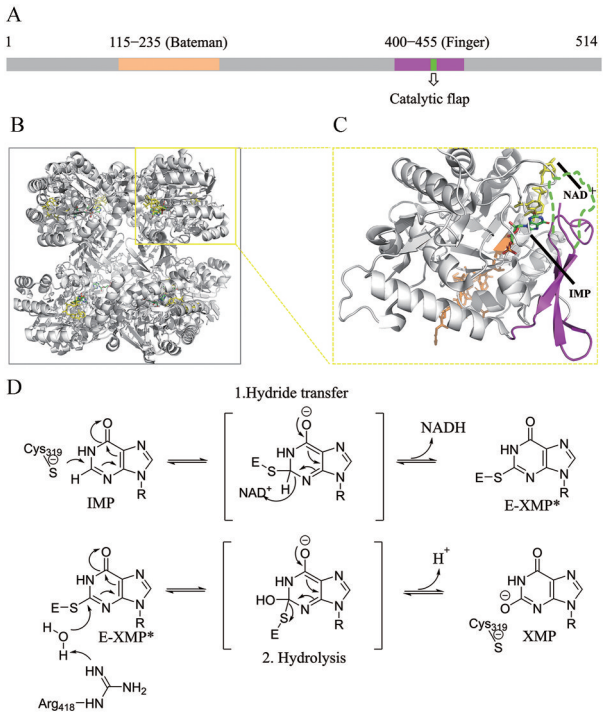


Figure 1 The structure and catalytic mechanism of inosine-5′-monophosphate dehydrogenase (IMPDH). A: Schematic representation of the structural and functional domains of IMPDH. Numbers correspond to the canonical variant of the human IMPDH2 enzyme; B: Ribbon representation of a tetramer of IMPDH (PDBID 1MEW); C: Ribbon representation of a monomer of IMPDH with the two substrates (IMP in a mixed color of blue, green and red sticks and NAD^+ in yellow sticks) bound. The catalytic flap is shown with a discontinuous green line to indicate that it is unstructured; D: The catalytic mechanism of IMPDH

NAD^+ (nicotinamide adenine dinucleotide) 生成NADH (nicotinamide adenine dinucleotide, reduced form), 同时形成硫代亚胺酯中间体E-XMP*, 随后NADH脱离活性位点; 随后, 在IMPDH中418位精氨酸的协助下, 活化水分子进攻E-XMP*中间体, 水解生成XMP[19]。IMPDH在催化过程呈现两种关键且互斥的构象: 一种为开放构象 (open conformation), 在脱氢酶反应步骤中可同时容纳底物与辅因子; 另一种为闭合构象 (closed conformation), 此时“催化瓣”移向辅因子结合位点以完成E-XMP的水解[18], 这种动态构象变化保证了整个催化循环的顺利进行。

3 IMPDH与肿瘤

在肿瘤细胞中, IMPDH表达明显上调[10], 持续激活嘌呤核苷酸从头合成途径, 进而参与调控肿瘤代谢、增殖、转移及耐药等关键进程, 最终促进肿瘤的发生与发展[20]。在achaete-scute同源蛋白-1低表达 (achaete-scute homolog-1 low expression, $ASCL1^{Low}$) 的小细胞肺癌 (small cell lung cancer, SCLC) 中, 过表达的MYC结合IMPDH启动子, 促进IMPDH上调, 从而激活鸟苷酸合成通路 (图2A)。抑制IMPDH可选择性降低$ASCL1^{Low}$细胞的RNA聚合酶I活性, 减少核糖体前体RNA (pre-ribosomal RNA, pre-rRNA) 合成, 阻断核糖体生物发生, 进而在体内外抑制肿瘤细胞生长 (图2A)[21]。在肝细胞癌中, 高表达的泛素特异性肽酶5 (ubiquitin specific peptidase 5, USP5) 通过对IMPDH2进行去泛素化修饰, 稳定并上调IMPDH2蛋白; IMPDH2进一步通过促进上皮间质转化 (epithelial-mesenchymal transition, EMT) 过程, 增强肝癌细胞的增殖与转移能力, 而敲低IMPDH2可增强索拉非尼 (sorafenib) 的抗肝癌效果[22] (图2B)。在胶质母细胞瘤 (glioblastoma, GBM) 中, 异常高表达的IMPDH2驱动GTP从头合成, 促进rRNA和tRNA合成及核仁异常活化, 进而加速肿瘤发生发展[23] (图2C); IMPDH抑制剂可特异性抑制GBM增殖, 而对正常胶质细胞无显著影响。在MLL融合型急性髓系白血病 (acute myeloid leukemia, AML) 中, IMPDH表达异常上调; 抑制IMPDH可诱导Toll样受体介导的TLR-TRAF6-NF-κB信号通路过度活化, 并上调血管细胞黏附分子-1 (vascular cell adhesion molecule 1, VCAM-1) 的表达, 最终发挥强效抗肿瘤活性[24] (图2D)。此外, 在膀胱癌中, 抑制IMPDH通过调控活性氧相关通路, 导致相关基因和代谢物失调, 最终促进膀胱癌细胞铁死亡和凋亡[25]。因此, IMPDH与肿瘤的发生发展密切相关, 是抗肿瘤药物的潜在靶标。

4 IMPDH抑制剂

靶向IMPDH的抑制剂根据结构特征可分为核苷类和非核苷类, 此外, 天然产物也是IMPDH抑制剂的重要来源。IMPDH发挥功能依赖催化域与调控域的协同作用, 其抑制剂根据作用机制可分为底物竞争性抑制剂和别构调节剂: 其中, 底物竞争性抑制剂是目前的研究主流, 而别构调节剂尚处于研究早期阶段。基于协同抗肿瘤策略, 靶向IMPDH的双靶点抑制剂也在探索中, 在增强疗效和克服耐药性方面展现出潜力。

4.1 核苷类IMPDH抑制剂

核苷类IMPDH抑制剂在体内经腺苷激酶 (adenosine kinase, AK) 催化磷酸化转化为活性磷酸中间体, 并在烟酰胺单核苷酸腺苷酸转移酶 (nicotinamide mononucleotide adenylyltransferase, NMNAT) 作用下进一步转化为IMP或NAD^+类似物; 后者通过占据底物结合位点阻断IMP氧化为XMP, 从而抑制IMPDH活性 (图3A)。尽管核苷类药物存在极性较强、脂溶性差及口服吸收困难等缺陷, 但其可能通过在肿瘤细胞中选择性活化, 降低对正常细胞的损伤。

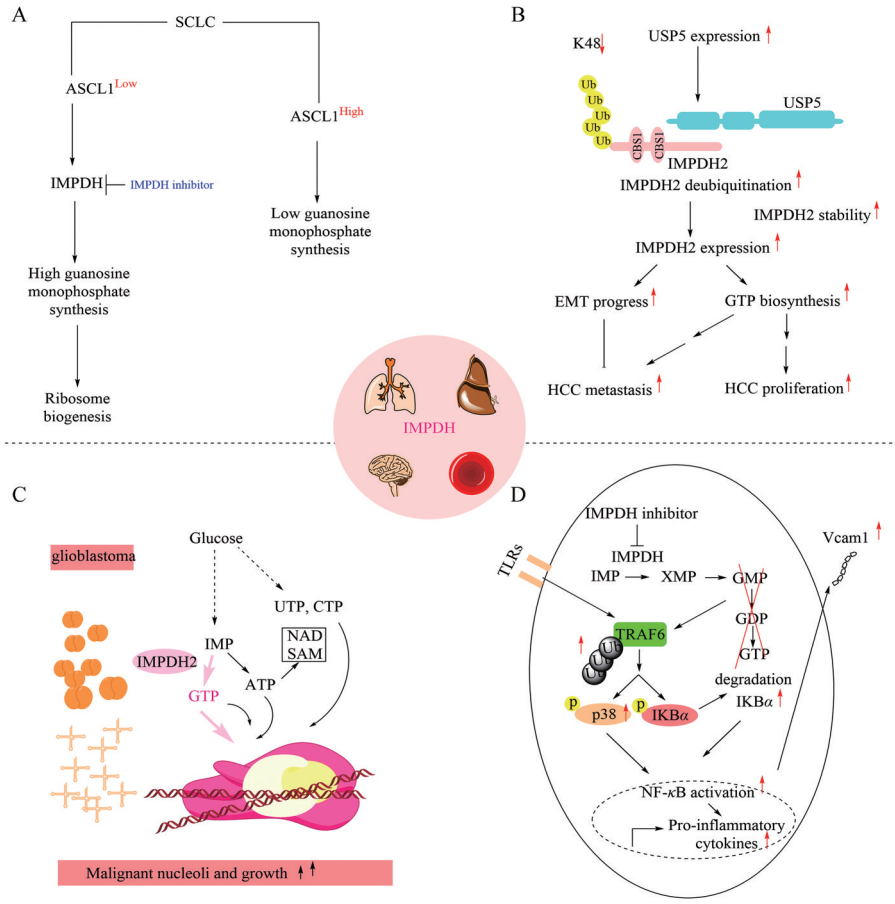


Figure 2 IMPDH and cancers. A: The high IMPDH expression promotes guanosine nucleotides synthesis in ASCL1^{Low} small cell lung cancer cells; B: The high IMPDH expression promotes hepatocellular carcinoma metastasis; C: The high IMPDH expression promotes glioblastoma progress; D: Inhibition of IMPDH suppress MLL fusion acute myeloid leukemia growth. ASCL1^{Low}: Achaete-scute homolog-1 low expression; SCLC: Small cell lung cancer; TRAF6: TNF receptor-associated factor 6; VCAM-1: Vascular cell adhesion molecule 1; USP5: Ubiquitin specific peptidase 5; EMT: Epithelial-mesenchymal transition; CTP: Cytidine triphosphate; UTP: Uridine triphosphate

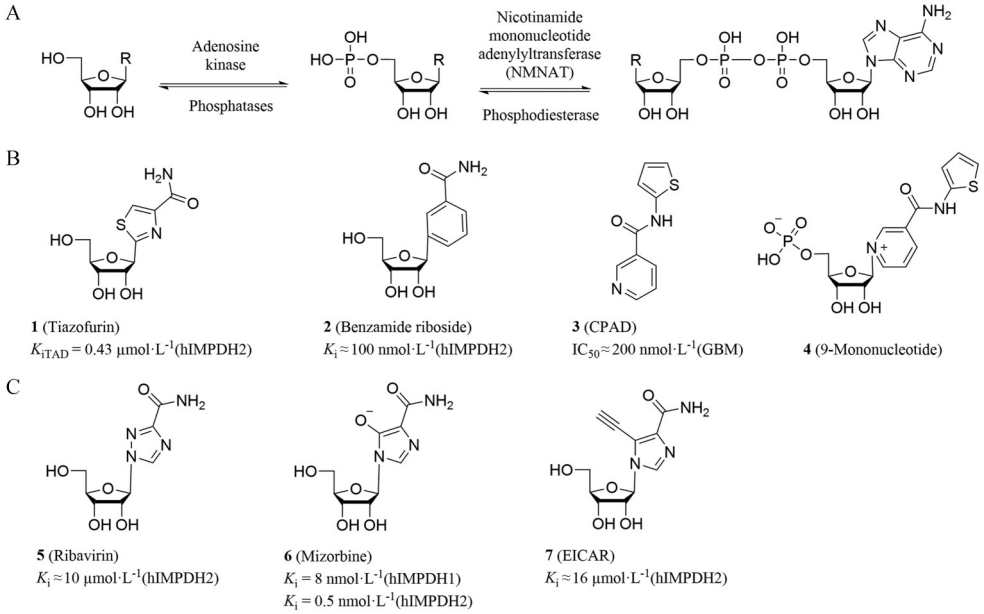


Figure 3 Nucleoside IMPDH inhibitors. A: The mechanism of nucleoside IMPDH inhibitors; B: Nucleoside IMPDH inhibitors occupying NAD^+ binding sites; C: Nucleoside IMPDH inhibitors occupying IMP binding sites

噻唑呋林 (**1**, tiazofurin) 是代表性C-核苷类IMPDH抑制剂 (图3B), 其在体内活化后形成活性代谢物, 噻唑呋林腺嘌呤二核苷酸 (thiazole-4-carboxamide adenine dinucleotide, TAD)[26], 后者占据NAD^+结合位点。作为首个展现抗肿瘤活性的IMPDH抑制剂, tiazofurin在治疗髓系恶性肿瘤的I/II期临床试验中, 对急变期慢性髓系白血病 (blast crisis of chronic myelogenous leukemia, CML-BC) 的总缓解率为48%, 并于2000年被FDA授予“孤儿药”资格, 用于治疗CML-BC[27]。然而, TAD可能脱靶作用于其他NAD^+依赖性酶, 引发潜在毒性; 此外, TAD代谢稳定性差, 易被NMNAT降解, 导致肿瘤细胞对tiazofurin耐药[28]。后因临床试验中存在缓解持续时间短及毒性反应显著等问题, tiazofurin的进一步研发被终止[29]。苯甲酰胺核苷 (benzamide riboside, **2**, BR) 是烟酰胺核苷的生物电子等排类似物, 作用机制与tiazofurin类似, 对人IMPDH2 (hIMPDH2) 具有良好抑制活性 ($K_i \approx 100\ nmol\cdot L^{-1}$), 对多种肿瘤细胞的抑制活性强于tiazofurin[30,31], 且对tiazofurin不敏感的人卵巢癌N.1细胞具有杀伤作用[32]。2024年, Chen等[33]通过高通量筛选鉴定出烟酰胺模拟前药gliocidin (**3**, CPDA), 其可选择性杀伤胶质母细胞瘤细胞 (IC_{50} = $200\ nmol\cdot L^{-1}$)。机制研究表明, gliocidin在烟酰胺磷酸核糖基转移酶 (nicotinamide phosphoribosyl transferase, NAMPT) 催化下生成中间体**4**, 最终转化为活性代谢物gliocidin-腺嘌呤二核苷酸, 通过抑制IMPDH2活性导致GBM细胞内鸟嘌呤核苷酸耗竭, 引发核苷酸失衡与复制应激, 最终诱导细胞死亡[34]。Gliocidin为肿瘤选择性激活前药的设计提供了新思路, 对肿瘤精准治疗方案的探索具有重要意义。

以利巴韦林 (**5**, ribavirin, RBV) 为代表的核苷类化合物, 在体内活化后可竞争性结合IMP位点。Ribavirin是人工合成的鸟苷类似物, 其活性代谢物对人源IMPDH2的抑制活性较弱 ($K_i \approx 10\ nmol\cdot L^{-1}$) [35]。Mizorbine (**6**, MZR) 是一种天然来源的咪唑核苷, 对IMPDH具有高亲和力 (hIMPDH1, $K_i = 8\ nmol\cdot L^{-1}$, hIMPDH2, $K_i = 0.5\ nmol\cdot L^{-1}$), 同时对GMP合成酶有较弱抑制作用 ($K_i = 10\ \mu mol\cdot L^{-1}$), 可双重阻断鸟嘌呤核苷酸合成。在携带5′-核苷酸酶细胞质II (5′-nucleotidase cytosolic II, NT5C2) 基因功能获得性突变的耐药急性B淋巴细胞白血病模型小鼠中, MZR表现出显著抗白血病效应[36]。EICAR (**7**) 是人工合成的咪唑核苷, 经活化后对IMPDH具有抑制活性, 对多种肿瘤细胞具有毒性[37]。尽管核苷类IMPDH抑制剂展现出良好的抗肿瘤潜力, 但毒性及代谢稳定性等问题促使研究者进一步探索非核苷类IMPDH抑制剂。

4.2 非核苷类抑制剂

4.2.1 霉酚酸及其衍生物 霉酚酸 (**8**, mycophenolic acid, MPA) 是一类非核苷类IMPDH抑制剂。其通过模拟NAD^+的烟酰胺单核苷酸结构, 选择性占据IMPDH的辅因子结合口袋, 从而抑制IMPDH活性[38]。晶体学研究显示: MPA的苯并内酯环可与IMP的次黄嘌呤基团形成π-π堆积作用, 内酯氧原子与Thr333残基形成氢键, 酚羟基与Gly326残基形成氢键; 羧基则与Ser276残基产生电荷−偶极相互作用 (图4A、B)。MPA不仅能抑制多种癌细胞的增殖, 还可诱导癌细胞分化并促进其凋亡, 具有良好的抗肿瘤潜力。然而, MPA的羧基和酚羟基在肝药酶催化下易发生葡萄糖醛酸化反应, 导致肾脏清除率较高, 难以维持有效的体内抗肿瘤活性; 此外, 其还存在剂量限制性胃肠道毒性[39]。因此, 需对MPA进行进一步化学修饰, 以开发疗效更优的抗肿瘤药物。

酯前药是羧酸类药物的常用修饰策略, 具有增加药物透膜性、延长半衰期、降低毒性及提高血脑屏障透过效率等优势。霉酚酸酯 (**9**, mycophenolic mofetil, MMF) 作为MPA的前药, 虽可提升口服生物利用度, 但无法避免MPA相关的胃肠道毒性[39]。在复发/难治性多发性骨髓瘤的I期临床试验中, 每日1～5 g剂量的MMF在患者中表现出良好耐受性, 且患者的临床反应与细胞内dGTP水平耗竭呈正相关, 提示其可能对骨髓瘤治疗具有潜在价值; 然而, 目前尚无IMPDH抑制剂获美国FDA批准用于血液瘤治疗。此外, 霉酚酸酯联合放疗 (NCT04477200) 或标准疗法 (NCT05236036) 治疗胶质母细胞瘤的研究正在进行中[40]。

MPA与IMPDH结合后, NAD^+结合口袋的“AMP亚口袋”(即NAD^+分子中腺苷单磷酸结合区域) 未被占据, 提示该位点存在进一步优化的潜力。1998年, Lesiak等[41]通过将NAD^+分子中的烟酰胺单核苷酸部分替换为MPA结构, 成功开发出霉酚酸腺嘌呤二核苷酸类似物**10** (MAD), 其对hIMPDH表现出强效抑制活性 (图4C)。在联合免疫缺陷的小鼠慢性粒细胞白血病 (chronic myeloid leukemia, CML) 模型中, 化合物**10**的抗癌活性是tiazofurin的4倍, 且毒性更低。此外, 化合物**10**不易发生葡萄糖醛酸化, 代谢稳定性更强; 同时, 其对tiazofurin耐药肿瘤细胞仍保持抑制活性[42]。

硝基吖啶/吖啶酮骨架具有DNA嵌入能力和强效细胞毒性, 是经典的抗肿瘤药效团[43,44], 2012年Cholewinski团队[45]合成10个MPA-硝基吖啶/吖啶酮缀合物 (图4C), 其中硝基吖啶类缀合物**11**～**15**对多种白血病细胞及MPA耐药细胞系表现出强效抑制活性, 且对正常免疫细胞毒性较低。2016年该团队[46]又合成10种

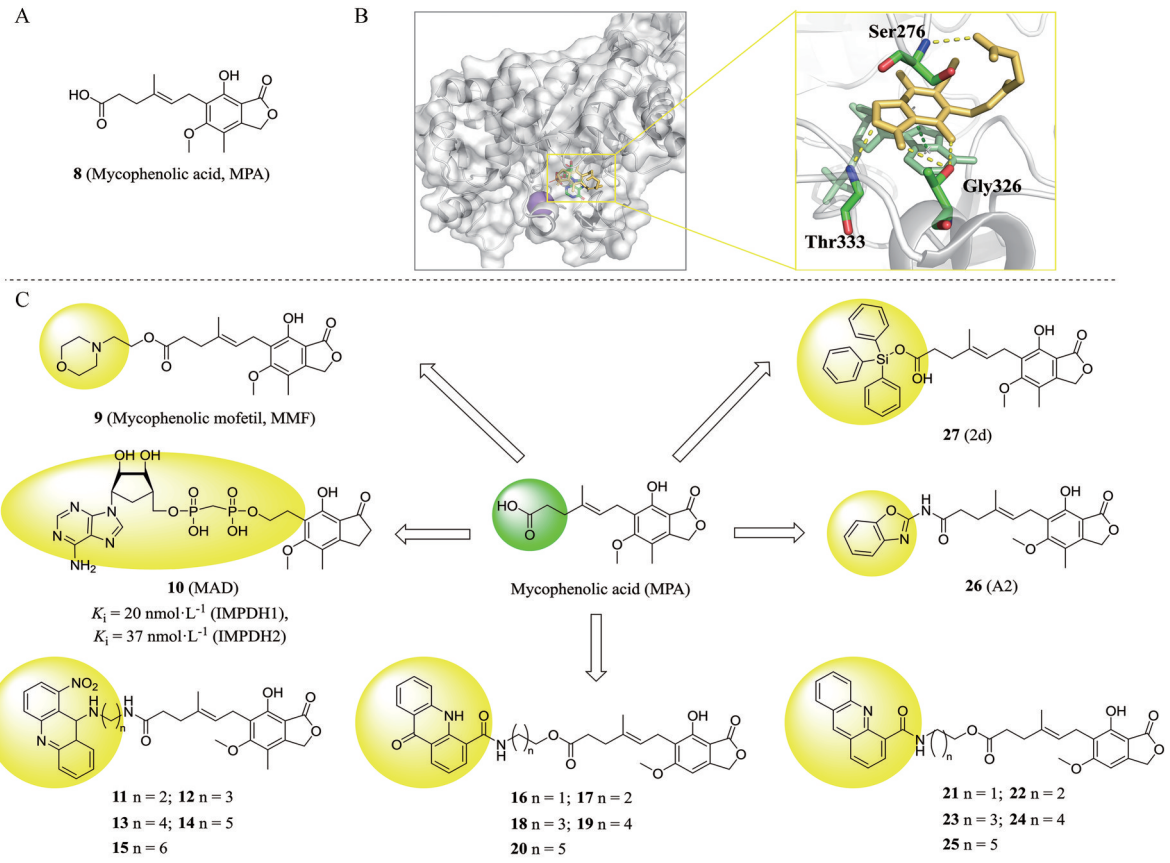


Figure 4 MPA and derivatives. A: The structure of MPA; B: Crystal complex of MPA and IMPDH (PDB: 1JR1); C: The structure of MPA and derivatives

MPA-吖啶/吖啶酮酯缀合物, 其中吖啶类缀合物 **17**～**20** (EC_{50} 0.01～0.02 μmol·L^{-1}) 活性优于吖啶酮类 **21**～**25** (EC_{50} 0.32～0.98 μmol·L^{-1})。2022 年 Walczak 等[47]将 MPA 与不同的杂环胺缩合, 得到了具有良好活性的苯并噁唑化合物 **26** (A2), 其在外周血单个核细胞和 T-Jurkat 细胞上具有和 MPA 相当的活性, 但毒性更低。分子对接显示, **26** 的苯并噁唑环和丝氨酸 276 和谷氨酰胺 441 可能有额外的相互作用, 这使其与 IMPDH 的结合能力比 MPA 更强。大体积基团的硅基的引入可提升化合物脂溶性和细胞穿透性, 以及通过多靶点增强抗肿瘤活性, Silalai 等[48]合成一系列 MPA-硅基衍生物, 其中三苯基硅基修饰的 **27** (2d) 具有最佳活性, 虽然 **27** 对 IMPDH2 的活性弱于 MPA (K_i, app = 1.8 *vs* 0.046 μmol·L^{-1}), 但 **27** 通过对血管内皮细胞生长因子受体 2 (vascular endothelial growth factor receptor-2, VEGFR-2)、细胞周期蛋白依赖性激酶 2 (cyclin-dependent kinase 2, CDK2) 和 IMPDH 多靶点协同作用, 对骨肉瘤细胞表现出强效抑制, 但对正常细胞表现出低毒性。

4.2.2 苯基噁唑脲类 IMPDH 抑制剂 为了克服传统 IMPDH 抑制剂 MPA 代谢不稳定和胃肠道毒性大的缺陷, 福泰制药公司 (Vertex Pharmaceuticals, Inc.) 通过基于结构的药物设计策略, 开发了一类苯基噁唑脲类 IMPDH 抑制剂, 该类化合物具有更优异的药代动力学性质和安全性 (图 5)。代表性化合物 VX-497 (**28**, merimepodib) 可与 IMPDH 催化反应中的关键中间体 E-XMP*结合, 阻断后续水解反应, 从而抑制 IMPDH 活性 (hIMPDH, K_i = 7 nmol·L^{-1})。分子对接结果显示: 分子中的苯基联噁唑片段与 XMP 嘌呤环存在疏水堆叠作用 (hydrophobic stacking); 噁唑环上的氮/氧原子可与 IMPDH 活性位点的 Gly326 和 Thr333 形成氢键; 脲键能与 Asp274 形成氢键; 甲氧基则嵌入 IMPDH 活性位点的疏水口袋中 (图 5A)[49,50]。为进一步优化化合物性质, 福泰制药对 VX-497 的四氢呋喃环及亚甲基碳连接子进行结构修饰, 通过引入氰基片段调节分子极性与疏水性, 改善了化合物的溶解性和透膜性, 最终获得强效口服 IMPDH 抑制剂 VX-944 (**29**)。VX-944 具有广泛的抗肿瘤活性, 可诱导多发性骨髓瘤细胞半胱天冬酶非依赖性凋亡[51]; 同时能抑制前列腺癌细胞的增殖, 诱导细胞周期 S 期阻滞, 并促进细胞分化与凋亡[52]。此外, 通过将 VX-497 的噁唑环进行生物电子等排替换为氰基, 得到 IMPDH 抑制剂 VX-148 (**30**), 其对

IMPDH2和IMPDH1的K_i值分别为6和14 nmol·L^{-1} [53]。百时美施贵宝公司 (Bristol Myers Squibb, BMS) 以VX-497为先导化合物, 通过生物电子等排策略将脲连接子 (-NH-CO-NH-) 替换为2-氨基噁唑结构, 并进一步引入亲水性吗啉环, 得到化合物BMS-337197 (**31**)。其中, 噁唑环增强了分子结构刚性, 以维持类似VX-497的活性构象; 同时抑制了脲键的水解, 提升了代谢稳定性。BMS-337197对IMPDH具有良好的抑制活性, 其对IMPDH2和IMPDH1的IC_{50}值分别为12和120 nmol·L^{-1} [54]。

4.2.3 其他非核苷酸类IMPDH抑制剂 Watterson等[55]通过高通量筛选发现吖啶酮类化合物**32**是潜在的先导分子 (图6A), 但进一步结构鉴定发现杂质**33** (含量约为12%) 是主要活性来源, 其对IMPDH2的IC_{50}为0.059 μmol·L^{-1}。以化合物**33**为先导化合物, 在乙酯端引入不同的酰胺取代基, 其中**34**对IMPDH2的活性显著提升 (IC_{50} = 19 nmol·L^{-1})。随后, 在吖啶酮母核引入氟原子, 限制酰胺键的旋转自由度, 增强与IMPDH2的疏水相互作用, 得到化合物**35**, 其对人外周血单个核细胞的增殖抑制活性进一步提升 (IC_{50} = 0.59 μmol·L^{-1})。将苯环经生物电子等排替换为吡啶环, 化合物**36**的增殖抑制活性提升至IC_{50}值为0.14 μmol·L^{-1}。最后, 在吡啶基中引入不同极性基团, 以改善化合物的理化性质和代谢稳定性, 得到最优化合物**37** (BMS-566419), 其对IMPDH2的IC_{50}为17 nmol·L^{-1}, 活性与MPA相当。此外, BMS-566419不仅具有良好的口服生物利用度, 还无MPA中易被代谢的酚羟基结构, 提高了代谢稳定性, 降低了胃肠道相关毒性风险。

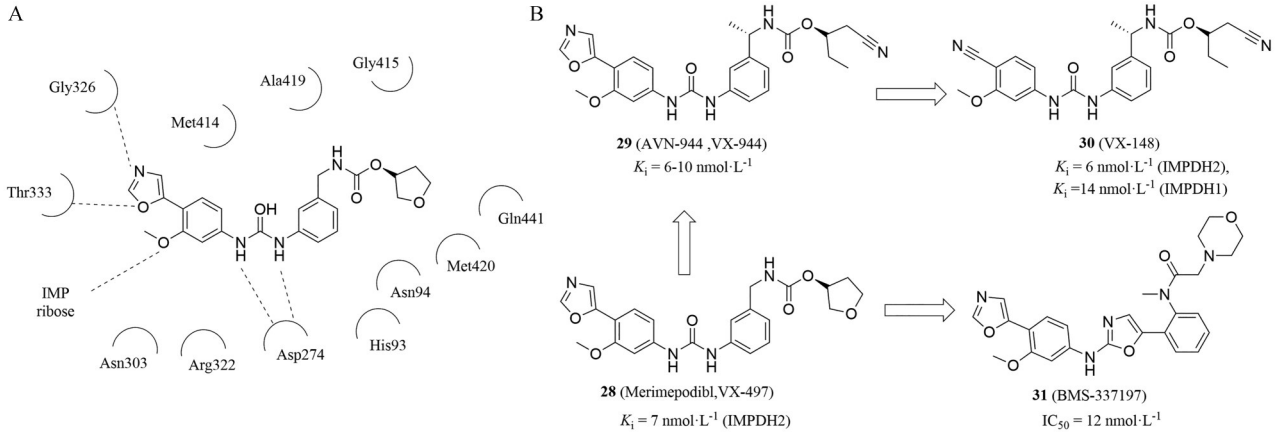


Figure 5 Structure and interactions of phenyl oxazole urea IMPDH inhibitors and derivatives. A: The interaction between VX-497 and IMPDH predicted by molecular docking; B: The structure of IMPDH inhibitors **28**–**31**

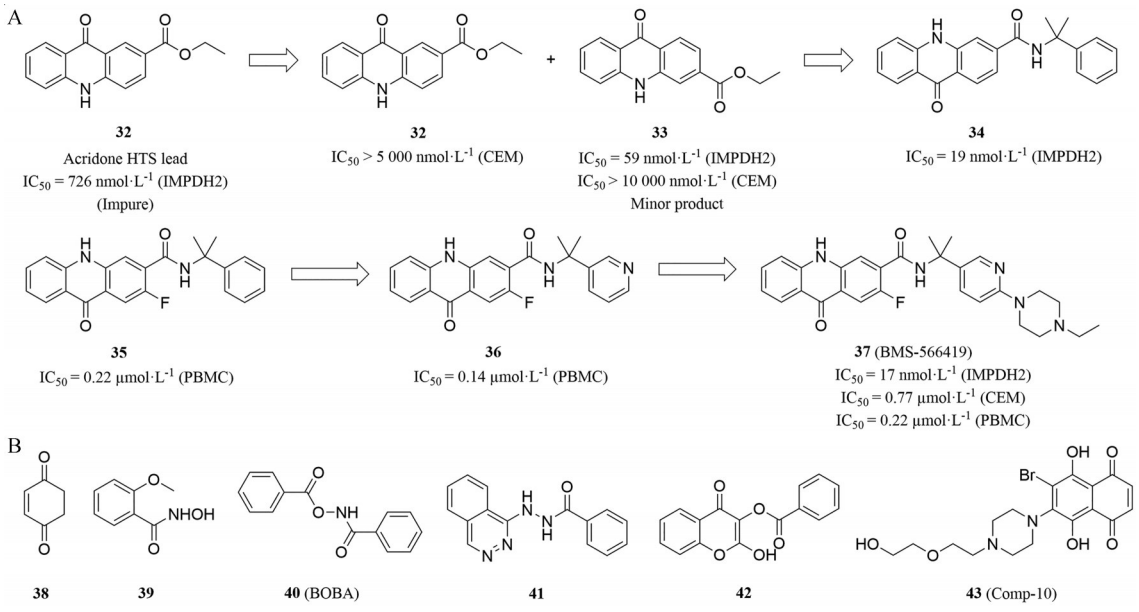


Figure 6 The structures of other non-nucleoside inhibitors. A: The optimization process of BMS-566419; B: The structure of compound **38**–**43**

2001年, Hall等[56]发现马来酰肼 (**38**)、苯氧肟酸 (**39**) 和*N*-(苯甲酰氧基)苯甲酰胺 [**40**, *N*-(benzoyloxy) benzamide, BOBA] 可通过竞争性抑制方式特异性抑制白血病细胞中IMPDH2的活性。其中, BOBA对IMPDH2的K_i值为2.57 μmol·L^{-1}, 抑制效果优于利巴韦林, 但弱于MPA。随后, Floresta等[57]以BOBA为先导化合物, 采用骨架跃迁 (scaffold hopping) 策略生成两类共1 000个衍生物, 经筛选获得与IMPDH结合能力更优的化合物**41**和**42** (图6B)。2025年Pattabiraman等[58]针对IMPDH2的变构域进行基于结构的虚拟筛选, 发现IMPDH别构抑制剂Comp-10 (**43**) 对IMPDH2的IC_{50}约为260 nmol·L^{-1}, 该化合物还能够降低IMPDH蛋白水平, 且对ALK/BTK抑制剂耐药的淋巴瘤有效。

天然产物具有结构多样性和广泛的生物活性, 是新型先导化合物的重要结构来源[59] (图7A)。2016年, Pan等[60]通过筛选发现, 膳食黄酮类化合物杨梅素 (**44**, myricetin) 对hIMPDH1/2均具有强效抑制活性, 并能以剂量依赖方式抑制白血病K562细胞增殖, 诱导细胞S期阻滞与凋亡。随后, Wang等[61]又通过扩大筛选范围发现, 紫草素 (**45**, shikonin) 同样为IMPDH抑制剂, 其可结合IMP活性口袋, 通过干扰鸟嘌呤核苷酸合成发挥抗三阴性乳腺癌活性。2023年, He等[62]对2 800个天然产物进行基于结构的虚拟筛选, 从中发现中药黄连成分小檗红素 (**46**, berberrubine) 是新型选择性IMPDH2抑制剂: 其对IMPDH2的IC_{50}为2.37 ± 0.04 μmol·L^{-1}, 对IMPDH1的IC_{50} > 30 μmol·L^{-1}, 可通过选择性抑制IMPDH2进而抑制结直肠癌生长。

Bateman结构域是IMPDH的变构调节核心, 且其在不同IMPDH家族成员中序列差异显著, 为IMPDH亚型选择性抑制剂的发现提供了结构基础。2017年, Liao等[63]发现, 从苏木中提取的sappanone A (**47**, SA) 可与hIMPDH2中保守的Cys140残基发生共价结合, 通过变构调节机制诱导IMPDH2失活, 进而有效抑制神经炎症反应。Sanglifehrin A (**48**, SFA)[64,65]是一种由聚酮合酶与非核糖体肽合酶协同合成的天然产物, 其大环核心结构能与亲环素A (cyclophilin A) 结合, 亲和力达亚纳摩尔级; 而侧链结构可特异性结合IMPDH2的bateman结构域, 但不影响IMPDH2的酶活性 (图7B)。Sanglifehrin A能与IMPDH2及cyclophilin A形成sanglifehrin A-cyclophilin A-IMPDH2三元复合物, 进而调控细胞生长[66]。

4.2.4 双靶点IMPDH抑制剂 肿瘤细胞的生存与增殖依赖复杂的信号网络, 其可通过“通路代偿”和“突变逃逸”等机制导致单靶点药物疗效降低或产生耐药性。将具有协同作用的不同药物分子的药效团进行融合, 可获得双靶点抑制剂, 这类分子具有增强疗效和克服耐药的潜在优势[67-69]。

组蛋白去乙酰化酶 (histone deacetylase, HDAC) 是一类重要的表观遗传调控酶, 参与广泛的基因表达调控, 是肿瘤治疗的潜在靶标[70]。2007年, Chen等[71]将MPA与HDAC抑制剂SAHA的骨架融合, 得到化合物**49** (图8), 其对IMPDH和HDAC均保持良好抑制活性, 抗增殖活性优于单一的IMPDH或HDAC抑制剂。此外, 通过将IMPDH抑制剂VX-497与SAHA骨架融合, 获得了强效IMPDH/HDAC双靶点抑制剂**50**[72]。2025年, Deng等[73]将吲哚类hIMPDH抑制剂的吲哚核心结构 (负责结合hIMPDH) 与HDAC抑制剂SAHA的异羟肟酸核心结构通过合适的连接子拼接, 得到IMPDH2/HDAC1双靶点抑制剂**51** (C12)。C12对hIMPDH2和HDAC1均具有强效抑制活性, IC_{50}值分别为84.69 nmol·L^{-1}和81.75 nmol·L^{-1}; 相较于MPA和SAHA, C12对K-562白

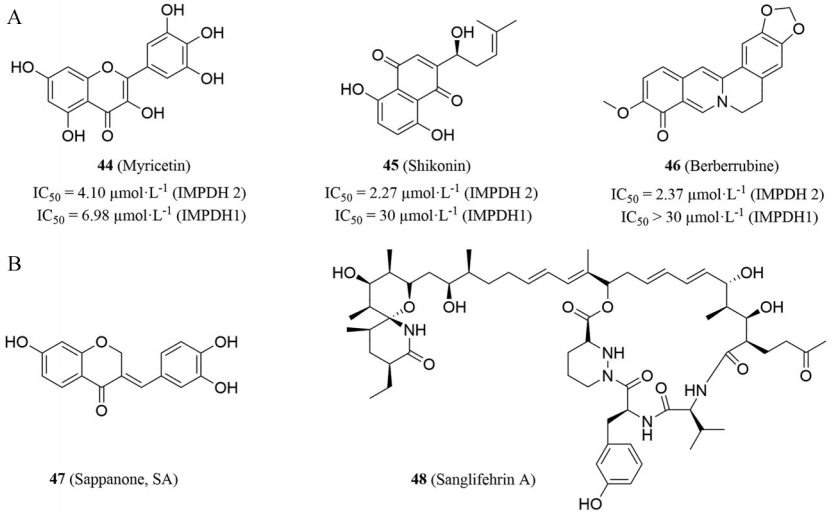


Figure 7 The IMPDH inhibitors from natural products. A: Substrate competitive IMPDH inhibitors; B: Allosteric IMPDH inhibitors

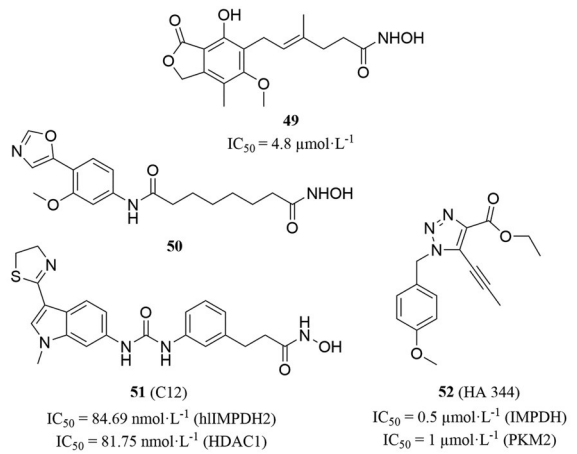


Figure 8 The structure of IMPDH dual-target inhibitors **49**–**52**

血病细胞的增殖抑制活性显著增强。

肿瘤细胞通过诱导肌肉型丙酮酸激酶同工酶M2 (pyruvate kinase isozyme typeM2, PKM2) 高表达进行代谢重编程, 进而导致肿瘤耐药[74]。2021年, Zerhouni等[75]通过筛选及结构优化, 开发了共价型IMPDH2/PKM2双靶点抑制剂HA344 (**52**)。HA344不仅能通过共价结合PKM2的半胱氨酸Cys424位点抑制其活性, 减少细胞糖酵解与氧化磷酸化水平, 还可抑制IMPDH2活性, 导致IMP积累并阻断嘌呤合成通路, 从而在体内外有效抑制皮肤转移性黑色素瘤细胞的生长 (图8)。

5 总结与展望

IMPDH是鸟嘌呤核苷酸代谢通路的核心调控因子, 但其功能尚未被充分阐明, 且活性受到多重复杂机制的精准调控。IMPDH的异常活化与肿瘤的发生及恶性进展密切相关, 这使其成为肿瘤治疗的潜在靶标, 并推动了靶向IMPDH的抗肿瘤药物研发。

目前已开发的靶向IMPDH抑制剂可分为核苷类、非核苷类、天然产物类及双靶点抑制剂。其中, 核苷类抑制剂在体内活化后能模拟天然核苷底物, 具有良好抑制活性, 但毒性和代谢稳定性问题是其临床应用的主要挑战; 而开发可在肿瘤组织中选择性活化的前药, 有望扩大治疗窗口并实现肿瘤精准治疗。在非核苷类抑制剂中, 以MPA为代表的IMPDH抑制剂显示出治疗潜力, 但其代谢稳定性差和胃肠道不良反应是需重点关注的问题。通过对MPA进行结构修饰及发现具有更高化学结构多样性的抑制剂, 部分候选药物已实现疗效、代谢稳定性及安全性的显著提升。天然来源的IMPDH抑制剂不仅拓展了现有抑制剂的结构多样性, 还为IMPDH别构调节剂的研发提供了线索。最后, 基于协同抗肿瘤策略开发的IMPDH双靶点抑制剂在增强疗效和克服耐药方面具有潜力, 但其已知的协同作用靶标仍较为有限。

目前靶向IMPDH的抗肿瘤药物研究已取得显著进展, 但尚无药物获批上市。未来研究需重点关注以下方向: 首先, 深入解析IMPDH同工酶的结构与功能差异, 基于亚型特异性位点开发选择性抑制剂, 以实现对特定肿瘤类型的精准治疗; 其次, 系统阐明IMPDH的调控机制, 发掘催化结构域的变构口袋并评估其成药性, 开发基于新作用机制的高效别构调节剂; 最后, 探索IMPDH与其他关键抗肿瘤靶点的协同作用机制, 发现新型联合用药方案及双靶点抑制剂, 拓展靶向IMPDH药物的治疗应用场景。总之, 通过持续深入解析IMPDH的结构–功能关系及肿瘤代谢网络调控机制, 并结合新型药物设计技术与策略, 靶向IMPDH的抑制剂有望成为肿瘤治疗的重要新策略。

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References

[1] Thomas WT. Physiological concentrations of purines and pyrimidines [J]. Mol Cell Biochem, 1994, 140: 1-22.

[2] Sting ZE, Schug ZT, Salvino JM, et al. Targeting cancer metabolism in the era of precision oncology [J]. Nat Rev Drug Discov, 2022, 21: 141-162.

[3] Lu ZR, Li JY, Liu Y, et al. Purine metabolism in tumorigenesis and its clinical implications [J]. Semin Oncol, 2025, 52: 152409.

[4] Wang XY, Zhang J, Li Y, et al. Research progress on the regulation of tumor metabolism, tumor immunotherapy and new analytical methods [J]. Acta Pharm Sin (药学学报), 2020, 55: 2080-2091.

[5] Ayoub N, Gedeon A, Munier-LEhmann H. A journey into the regulatory secrets of the *de novo* purine nucleotide biosynthesis [J]. Front Pharmacol, 2024, 15: 1329011.

[6] Chanedl NS. Nucleotide metabolism [J]. Cold Spring Harb Perspect Biol, 2021, 13: 449-460.

[7] Du DY, Liu C, Qin MY, et al. Metabolic dysregulation and emerging therapeutical targets for hepatocellular carcinoma [J]. Acta Pharm Sin B, 2022, 12: 558-580.

[8] An S, Kumar R, Sheets ED, et al. Reversible compartmentalization of *de novo* purine biosynthetic complexes in living cells [J]. Science, 2008, 320: 103-106.

[9] Ogawa-Iio A, Takeuchi K, Shigemi K, et al. IMPDH and GTP metabolism in cancer: Mechanisms, regulation, and translational scope [J]. Cancer Sci, 2025, 116: 3250-3265.

[10] Kofuji S, Hirayama A, Eberhardt AO, et al. IMP dehydrogenase-2

drives aberrant nucleolar activity and promotes tumorigenesis in glioblastoma [J]. Nat Cell Biol, 2019, 21: 1003-1014.

[11] Zhang YW, Zhang D, Sun H. The basic functions of inosine 5′-monophosphate dehydrogenase and its application in drug discovery [J]. Acta Pharm Sin (药学学报), 2014, 49: 285-292.

[12] Chen LQ, Gao GY, Felczak K, et al. Probing binding requirements of type I and type II isoforms of inosine monophosphate dehydrogenase with adenine-modified nicotinamide adenine dinucleotide analogues [J]. J Med Chem, 2007, 50: 5743-5751.

[13] Jain J, Almquist SJ, Ford PJ, et al. Regulation of inosine monophosphate dehydrogenase type I and type II isoforms in human lymphocytes [J]. Biochem Pharmacol, 2004, 67: 767-776.

[14] Nagano N, Orengo C, Thornton JM. One fold with many functions: The evolutionary relationships between TIM barrel families based on their sequences, structures and functions [J]. J Mol Biol, 2002, 321: 741-765.

[15] Bateman A. The structure of a domain common to archaebacteria and the homocystinuria disease protein [J]. Trends Biochem Sci, 1997, 22: 12-13.

[16] Buey RM, Ledesma-Amaro R, Velázquez-Campoy A, et al. Guanine nucleotide binding to the bateman domain mediates the allosteric inhibition of eukaryotic IMP dehydrogenases [J]. Nat Commun, 2015, 6: 8923.

[17] Zhang RG, Evans G, Rotella FJ, et al. Characteristics and crystal structure of bacterial inosine-5′-monophosphate dehydrogenase [J]. Biochemistry, 1999, 38: 4691-4700.

[18] Makowska-Grzyska M, Kim YC, Wu RY, et al. *Bacillus anthracis* inosine 5′-monophosphate dehydrogenase in action: The first bacterial series of structures of phosphate ion-, substrate-, and product-bound complexes [J]. Biochemistry, 2012, 51: 6148-6163.

[19] Buey RM, Fernández-Justel D, Jiménez A, et al. The gateway to guanine nucleotides: Allosteric regulation of IMP dehydrogenases [J]. Protein Sci, 2022, 31: e4399.

[20] Ikeda Y, Hirayama A, Kofuji S, et al. SI-MOIRAI: A new method to identify and quantify the metabolic fate of nucleotides [J]. J Biochem, 2022, 170: 699-711.

[21] Huang F, Ni M, Chalishazar MD, et al. Inosine monophosphate dehydrogenase dependence in a subset of small cell lung cancers [J]. Cell Metab, 2018, 28: 369-382.e5.

[22] Jiang SY, Jiang LY, Xu YY, et al. USP5 deubiquitinates and stabilizes IMPDH2, to promote hepatocellular carcinoma progression [J]. Oncogene, 2025, 44: 1936-1948.

[23] Liu XQ, Wang JY, Wu LJ, et al. IMPDH inhibition decreases TERT expression and synergizes the cytotoxic effect of chemotherapeutic agents in glioblastoma cells [J]. Int J Mol Sci, 2024, 25: 5992.

[24] Liu XX, Sato N, Yabushita T, et al. IMPDH inhibition activates TLR-VCAM1 pathway and suppresses the development of MLL-fusion leukemia [J]. EMBO Mol Med, 2023, 15: e15631.

[25] Liu SS, Lei KY, Li G, et al. The integration of transcriptomics and metabolomics elucidates the antitumor mechanisms of mycophenolic acid in bladder cancer cells [J]. BMC Cancer, 2025, 25: 1463.

[26] Gebeyehu G, Marquez VE, Van Cott A, et al. Ribavirin, tiazofurin, and selenazofurin: Mononucleotides and nicotinamide adenine dinucleotide analogues. Synthesis, structure, and interactions with IMP dehydrogenase [J]. J Med Chem, 1985, 28: 99-105.

[27] Grifantini M. Tiazofurine ICN pharmaceuticals [J]. Curr Opin Investig Drugs, 2000, 1: 257-262.

[28] Jayaram HN. Biochemical mechanisms of resistance to tiazofurin [J]. Adv Enzyme Regul, 1985, 24: 67-89.

[29] Jayaram HN, Zhen WN, Gharehbaghi K. Biochemical consequences of resistance to tiazofurin in human myelogenous leukemic K562 cells [J]. Cancer Res, 1993, 53: 2344-2348.

[30] Grusch M, Rosenberger G, Fuhrmann G, et al. Benzamide riboside induces apoptosis independent of Cdc25A expression in human ovarian carcinoma N.1 cells [J]. Cell Death Differ, 1999, 6: 736-744.

[31] Hunáková L, Bies J, Sedlák J, et al. Differential sensitivity of ovarian carcinoma cell lines to apoptosis induced by the IMPDH inhibitor benzamide riboside [J]. Neoplasma, 2000, 47: 274-279.

[32] Gharehbaghi K, Sreenath A, Zhang H, et al. Comparison of biochemical parameters of benzamide riboside, a new inhibitor of IMP dehydrogenase, with tiazofurin and selenazofurin [J]. Biochem Pharmacol, 1994, 48: 1413-1419.

[33] Chen YJ, Iyer SV, Hsieh DC, et al. Gliocidin is a nicotinamide-mimetic prodrug that targets glioblastoma [J]. Nature, 2024, 636: 466-473.

[34] Theodoropoulos PC, Guo HH, Wang WT, et al. Thiophenyl derivatives of nicotinamide are metabolized by the NAD salvage pathway into unnatural NAD derivatives that inhibit IMPDH and are toxic to peripheral nerve cancers [J]. ACS Chem Biol, 2024, 19: 1339-1350.

[35] Stanimirović V, Stanimirović B, Nikolić D, et al. A phase II trial of ribavirin (Virazole®) in patients with genital infection caused by human papillomaviruses [J]. Archive Oncol, 2001, 9: 89-94.

[36] Tzoneva G, Dieck CL, Oshima K, et al. Clonal evolution mechanisms in NT5C2 mutant-relapsed acute lymphoblastic leukaemia [J]. Nature, 2018, 553: 511-514.

[37] Minakawa N, Takeda T, Sasaki T, et al. Nucleosides and nucleotides. 96. Synthesis and antitumor activity of 5-ethynyl-1-β-*D*-ribofuranosylimidazole-4-carboxamide (EICAR) and its derivatives [J]. J Med Chem, 1991, 34: 778-786.

[38] Sintchak MD, Fleming M, Futer O, et al. Structure and mechanism of inosine monophosphate dehydrogenase in complex with the immunosuppressant mycophenolic acid [J]. Cell, 1996, 85: 921-930.

[39] Behrend M. Adverse gastrointestinal effects of mycophenolate

mofetil: Aetiology, incidence and management [J]. Drug Saf, 2001, 24: 645-663.

[40] Takebe N, Cheng XF, Wu S, et al. Phase I clinical trial of the inosine monophosphate dehydrogenase inhibitor mycophenolate mofetil (cellcept) in advanced multiple myeloma patients [J]. Clin Cancer Res, 2004, 10: 8301-8308.

[41] Lesiak K, Watanabe KA, Majumdar A, et al. Synthesis of a methylenebis(phosphonate) analogue of mycophenolic adenine dinucleotide: A glucuronidation-resistant MAD analogue of NAD [J]. J Med Chem, 1998, 41: 618-622.

[42] Rejman D, Olesiak M, Chen LQ, et al. Novel methylenephosphophosphonate analogues of mycophenolic adenine dinucleotide. Inhibition of inosine monophosphate dehydrogenase [J]. J Med Chem, 2006, 49: 5018-5022.

[43] Petrelli R, Vita P, Torquati I, et al. Novel inhibitors of inosine monophosphate dehydrogenase in patent literature of the last decade [J]. Recent Pat Anticancer Drug Discov, 2013, 8: 103-125.

[44] Cholewiński G, Dzierzbicka K, Kołodziejczyk A. Natural and synthetic acridines/acridones as antitumor agents: Their biological activities and methods of synthesis [J]. Pharmacol Rep, 2011, 63: 305-336.

[45] Malachowska-Ugarte M, Cholewinski G, Dzierzbicka K, et al. Synthesis and biological activity of novel mycophenolic acid conjugates containing nitro-acridine/acridone derivatives [J]. Eur J Med Chem, 2012, 54: 197-201.

[46] Cholewinski G, Iwaszkiewicz-Grzes D, Trzonkowski P, et al. Synthesis and biological activity of ester derivatives of mycophenolic acid and acridines/acridones as potential immunosuppressive agents [J]. J Enzyme Inhib Med Chem, 2016, 31: 974-982.

[47] Walczak J, Iwaszkiewicz-Grześ D, Ziomkowska M, et al. Novel amides of mycophenolic acid and some heterocyclic derivatives as immunosuppressive agents [J]. J Enzyme Inhib Med Chem, 2022, 37: 2725-2741.

[48] Silalai P, Teeyakasem P, Pruksakorn D, et al. Design and synthesis of mycophenolic acid analogues for osteosarcoma cancer treatment [J]. ACS Bio Med Chem Au, 2025, 5: 106-118.

[49] Markland W, McQuaid TJ, Jain J, et al. Broad-spectrum antiviral activity of the IMP dehydrogenase inhibitor VX-497: A comparison with ribavirin and demonstration of antiviral additivity with alpha interferon [J]. Antimicrob Agents Chemother, 2000, 44: 859-866.

[50] Sintchak MD, Nimmesgern E. The structure of inosine 5′-monophosphate dehydrogenase and the design of novel inhibitors [J]. Immunopharmacology, 2000, 47: 163-184.

[51] Jain J, Ma JG, Furey BF, et al. The IMPDH inhibitor VX-944 demonstrates *in vivo* efficacy in an aggressive leukemia model [J]. Blood, 2004, 104: 25-30.

[52] Hamilton JM, Harding MW, Genna T, et al. A phase I dose-ranging study of the pharmacokinetics, pharmacodynamics, safety, and tolerability of AVN944, an IMPDH inhibitor, in healthy male volunteers [J]. J Clin Pharmacol, 2009, 49: 30-38.

[53] Jain J, Almquist SJ, Heiser AD, et al. Characterization of pharmacological efficacy of VX-148, a new, potent immunosuppressive inosine 5′-monophosphate dehydrogenase inhibitor [J]. J Pharmacol Exp Ther, 2002, 302: 1272-1277.

[54] Dhar TG, Shen ZQ, Guo JQ, et al. Discovery of *N*-[2-[2-[[3-methoxy-4-(5-oxazolyl) phenyl] amino]-5-oxazolyl] phenyl]-*N*-methyl-4-morpholineacetamide as a novel and potent inhibitor of inosine monophosphate dehydrogenase with excellent *in vivo* activity [J]. J Med Chem, 2002, 45: 2127-2130.

[55] Watterson SH, Chen P, Zhao YF, et al. Acridone-based inhibitors of inosine 5′-monophosphate dehydrogenase: Discovery and SAR leading to the identification of *N*-[2-[6-(4-ethylpiperazin-1-yl) pyridin-3-yl] propan-2-yl]-2-fluoro-9-oxo-9, 10-dihydroacridine-3-carboxamide (BMS-566419) [J]. J Med Chem, 2007, 50: 3730-3742.

[56] Hall IH, Barnes B, Ward ES, et al. Specific inhibition of type II inosine monophosphate dehydrogenase activity of Tmolt4 T cell human leukaemia cells by 3-methoxy and di-benzohydroxamic acids, maleic hydrazide and malonic acids [J]. J Pharm Pharmacol, 2001, 53: 749-755.

[57] Floresta G, Patamia V, Mazzeo PP, et al. Structural, morphological, and modeling studies of *N*-(benzoyloxy) benzamide as a specific inhibitor of type II inosine monophosphate dehydrogenase [J]. J Mol Struct, 2024, 1303: 137588.

[58] Pattabiraman N, Lobello C, Rushmore D, et al. A novel allosteric inhibitor targeting IMPDH at Y233 overcomes resistance to tyrosine kinase inhibitors in lymphoma [J]. Cancers (Basel), 2025, 17: 3389.

[59] Barnes EC, Kumar R, Davis RA. The use of isolated natural products as scaffolds for the generation of chemically diverse screening libraries for drug discovery [J]. Nat Prod Rep, 2016, 33: 372-381.

[60] Pan HL, Hu Q, Wang JY, et al. Myricetin is a novel inhibitor of human inosine 5′-monophosphate dehydrogenase with anti-leukemia activity [J]. Biochem Biophys Res Commun, 2016, 477: 915-922.

[61] Wang WY, Wu Y, Chen S, et al. Shikonin is a novel and selective IMPDH2 inhibitor that target triple-negative breast cancer [J]. Phytother Res, 2021, 35: 463-476.

[62] He XL, Cui JY, Ma H, et al. Berberrubine is a novel and selective IMPDH2 inhibitor that impairs the growth of colorectal cancer [J]. Biochem Pharmacol, 2023, 218: 115868.

[63] Liao LX, Song XM, Wang LC, et al. Highly selective inhibition of IMPDH2 provides the basis of antineuroinflammation therapy [J]. Proc Natl Acad Sci U S A, 2017, 114: E5986-E5994.

[64] Sanglier JJ, Quesniaux V, Fehr T, et al. Sanglifehrins A, B, C and D, novel cyclophilin-binding compounds isolated from *Streptomyces* sp. A92-308110. I. Taxonomy, fermentation, isolation and

biological activity [J]. J Antibiot (Tokyo), 1999, 52: 466-473.

[65] Zenke G, Strittmatter U, Fuchs S, et al. Sanglifehrin A, a novel cyclophilin-binding compound showing immunosuppressive activity with a new mechanism of action [J]. J Immunol, 2001, 166: 7165-7171.

[66] Pua KH, Stiles DT, Sowa ME, et al. IMPDH2 is an intracellular target of the cyclophilin A and sanglifehrin A complex [J]. Cell Rep, 2017, 18: 432-442.

[67] Morphy R, Rankovic Z. Designed multiple ligands. An emerging drug discovery paradigm [J]. J Med Chem, 2005, 48: 6523-6543.

[68] Qi XF, Kang Y, Qi JG. Synthesis and antitumor activity evaluation of dual-target inhibitors for tubulin and c-Src [J]. Acta Pharm Sin (药学学报), 2025, 60: 1778-1790.

[69] Shen J, Hu WJ, Dong GQ, et al. Advances in research of dual inhibitors targeting Janus kinase and histone deacetylase [J]. Acta Pharm Sin (药学学报), 2024, 59: 3057-3073.

[70] Zhang XH, Qin M, Wu HP, et al. A review of progress in histone deacetylase 6 inhibitors research: Structural specificity and functional diversity [J]. J Med Chem, 2021, 64: 1362-1391.

[71] Chen LQ, Wilson D, Jayaram HN, et al. Dual inhibitors of inosine monophosphate dehydrogenase and histone deacetylases for cancer treatment [J]. J Med Chem, 2007, 50: 6685-6691.

[72] Chen LQ, Petrelli R, Gao GY, et al. Dual inhibitors of inosine monophosphate dehydrogenase and histone deacetylase based on a cinnamic hydroxamic acid core structure [J]. Bioorg Med Chem, 2010, 18: 5950-5964.

[73] Deng FB, Jia HW, Hu DX, et al. Design, synthesis and antitumor activity evaluation of novel IMPDH II and HDAC1 dual inhibitor [J]. RSC Med Chem, 2025, 7: 685-691.

[74] Gao J, Zhao YW, Li T, et al. The role of PKM2 in the regulation of mitochondrial function: Focus on mitochondrial metabolism, oxidative stress, dynamic, and apoptosis. PKM2 in mitochondrial function [J]. Oxid Med Cell Longev, 2022, 2022: 7702681.

[75] Zerhouni M, Martin AR, Furstoss N, et al. Dual covalent inhibition of PKM and IMPDH targets metabolism in cutaneous metastatic melanoma [J]. Cancer Res, 2021, 81: 3806-3821.