结构药理学驱动的转录因子靶向药物研究进展

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摘要: 转录因子 (transcription factors, TFs) 是一类特异性识别并结合DNA序列、调节基因转录、影响细胞一系列生理活动和功能的蛋白质。近年来, 结构药理学技术的飞速发展极大推动了对转录因子构象变化机制、配体识别特性及其与共调节因子相互作用模式的解析, 从而为靶向药物的设计提供了关键的结构基础。核受体是一类结构保守、功能多样的配体调控型转录因子, 广泛参与发育、代谢、免疫、炎症和肿瘤等重要生理与病理过程。本文梳理了典型核受体结构域组成及其配体结合域的构象变化特征, 回顾近年来核受体在结构药理学领域的研究进展。本文还探讨了“类核受体”转录因子作为新型靶点的结构基础与成药潜力, 并总结了该家族中缺氧诱导因子、芳香烃受体等代表性靶点的药物开发实例。此外, 本文还概述了STAT3、p53/MDM2及MYC/MAX等其他转录因子靶点在结构指导下的靶向化合物的研究进展。最后, 本文对人工智能辅助结构预测及动态构象模拟等新兴技术在转录因子靶向药物研发中的应用前景进行了展望。

关键词: 转录因子; 核受体; 类核受体; 配体结合域; 结构药理学; 药物设计

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2026)06-1950-18

Progress in structural pharmacology-driven drug discovery targeting transcription factors

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Abstract: Transcription factors (TFs) constitute a class of proteins that regulate gene transcription through sequence-specific DNA binding and thereby govern a broad spectrum of cellular processes and functions. Recent rapid advances in structural pharmacology have substantially enhanced mechanistic understanding of TF conformational transitions, ligand recognition features, and interaction networks with coregulatory partners, establishing a critical structural framework for rational targeted drug design. Nuclear receptors represent a structurally conserved yet functionally diverse family of ligand-regulated TFs that are extensively involved in major physiological and pathological processes, including development, metabolism, immunity, inflammation, and tumorigenesis. This review systematically summarizes the domain organization of prototypical nuclear receptors and the conformational characteristics of their ligand-binding domains, and highlights recent progress in nuclear receptor structural pharmacology. It further examines the structural basis and therapeutic potential of "nuclear receptor-like" family proteins as emerging drug targets, with representative examples drawn from hypoxia-inducible factors (HIF) and the aryl hydrocarbon receptor (AHR). In addition, advances in structure-guided discovery of compounds targeting other TF systems, including STAT3, p53/MDM2, and MYC/MAX, are discussed. Finally, the review provides a forward-looking perspective on the application of emerging technologies,

收稿日期: 2026-02-05; 修回日期: 2026-05-11.

基金项目: 国家自然科学基金面上项目 (82373876); 济南市“新高校20条”自主培养创新团队 (202228080).

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DOI: 10.16438/j.0513-4870.2026-0165

such as AI-assisted structure prediction and dynamic conformational simulation, in TF-targeted drug discovery.

Key words: transcription factor; nuclear receptor; nuclear receptor-like; ligand-binding domain; structural pharmacology; drug design

转录因子 (transcription factor, TF) 是一类在细胞中调控基因表达的蛋白质。它们通过蛋白–核酸及蛋白–蛋白相互作用精准调控基因转录的起始、延伸与终止, 进而广泛参与细胞增殖、分化、代谢、免疫应答等多种生物学过程, 其功能异常与肿瘤等重大疾病密切相关[1-6]。尽管转录因子在疾病治疗中具有重要潜力, 但由于其大多缺乏典型的小分子结合口袋, 且调控机制复杂, 长期以来被认为是“难以靶向”的靶点[7-9]。

核受体 (nuclear receptors, NRs) 是一类结构域保守、依赖配体激活的转录因子。与大多数转录因子不同, 核受体的配体结合结构域 (ligand binding domain, LBD) 具有明确的可容纳小分子的口袋, 能够响应激素、维生素及代谢产物等内源性信号分子, 并通过其DNA结合结构域 (DNA binding domain, DBD) 识别相应的响应元件调控下游基因表达, 参与机体代谢稳态、免疫调节及肿瘤发生等过程[10]。正是基于这种独特的配体激活机制, 核受体成为转录因子家族中药物研发最为成熟、临床应用最为广泛的一类药物靶点[11-13]。

与经典核受体类似, bHLH-PAS (basic helix-loop-helix-PER-ARNT-SIM) 家族蛋白也是一类能够结合小分子配体的转录因子, 其保守的PAS结构域同样含有配体结合口袋, 并依赖配体诱导的构象变化调节蛋白–蛋白相互作用及下游基因表达[1]。然而, 两者在进化来源、结构组织及DNA识别方式上存在本质差异: 核受体通常含有结构特征明显的LBD和DBD, 并以单体或同源/异源二聚体形式直接结合特定响应元件; 而bHLH-PAS蛋白则依赖bHLH结构域识别DNA序列, 并通过PAS结构域介导异源二聚化及配体结合。尽管bHLH-PAS家族在结构域组成、二聚化方式和配体结合方式上与核受体有一定不同, 但其整体结构框架及转录调控方式与核受体相似, 因此可被称为“类核受体”, 成为继核受体之后第二个典型的药物靶向转录因子家族。

在靶向核受体和类核受体的药物发现过程中, 结构药理学方法通过解析蛋白–小分子复合物结构, 在原子水平阐明配体与靶蛋白之间的相互作用机制, 对药物设计与优化起到关键指导作用。近年来, 随着冷冻电镜分辨率的显著提升以及AlphaFold等蛋白质结构预测技术的突破, 结构药理学研究取得了多项进展。与此同时, 分子动力学模拟等计算方法的进步, 为揭示小分子或DNA与蛋白质之间的动态相互作用提供了有力工具; 而蛋白质从头设计等人工智能辅助计算策略则为蛋白–配体及蛋白–蛋白相互作用的理性调控提供了新的技术路径。

本综述旨在全面回顾核受体、类核受体及其他典型转录因子作为药物靶点的研究进展, 重点总结近年来结构药理学如何推动新型靶向药物发现和设计, 以期为开发更有效、更具特异性的基因表达调控药物提供思路。

1 核受体

核受体通过响应小分子配体来调节基因表达, 参与细胞分化、代谢、生长发育等基础生理过程, 其功能异常与糖尿病、癌症、心血管疾病等多种疾病的发生发展密切相关[14]。目前已知的核受体有300余种, 其中48种存在于人体中, 如糖皮质激素受体 (glucocorticoid receptor, GR) 和雌激素受体 (estrogen receptor, ER) 等[15,16]。

核受体通常包含A～E五个保守的功能结构域 (图1A)[13,17,18]。A/B区为N端调节结构域 (N-terminal regulatory domain, NTD), 其内含的转录激活功能区域1 (activation function 1, AF-1) 可通过与其他辅助激活蛋白互作以调节不同基因的转录。C区是高度保守的DBD, 包含两个锌指结构 (zinc finger), 负责识别并结合靶DNA序列。D区为铰链区 (hinge region), 是一段连接DBD与LBD的柔性短链, 在部分核受体中, D区还含有翻译后修饰位点和核定位信号序列 (nuclear localization sequence, NLS)。E区为结合配体的LBD, 结构相对保守, 由11～13个α螺旋 (α-helix) 和若干β折叠 (β-strand) 组成三层结构, 其底部形成疏水性配体结合口袋。配体结合后, 可引起LBD C端的12号α螺旋 (α-helix 12, H12) 发生构象变化, 进而像开关一样切换核受体的转录活性状态。此外, E区还含有与辅助激活蛋白相互作用的转录激活功能区域2 (activation function 2, AF-2)。早期研究曾将NRs C末端的序列定义为F区, 该区域氨基酸序列不保守, 在后续研究中多被并入E区一并讨论[13,18-20]。

在核受体的LBD中, H12扮演着“分子开关”的核心角色, 其构象变化直接决定了受体在配体结合后的功能状态。不同类型核受体的转录活性均通过特异性小分子配体的调控, 实现对相应下游靶基因的激活或

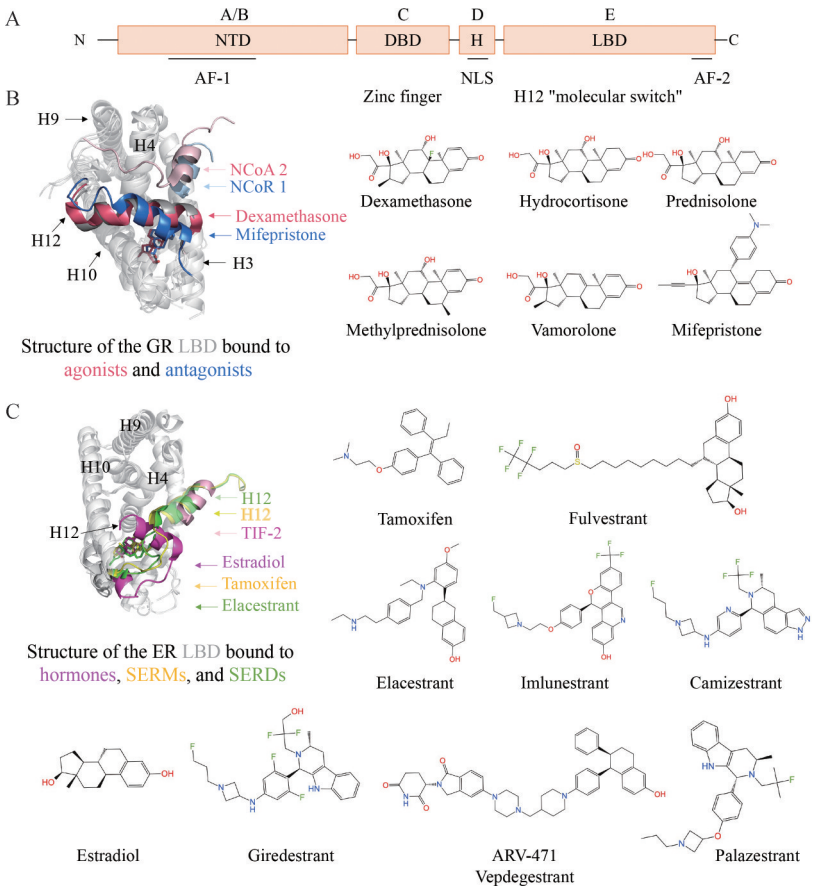


Figure 1 Structural organization of nuclear receptors GR and ER and ligand-induced conformational regulation mechanisms. A: Schematic representation of the canonical domain architecture of nuclear receptors, including the AF-1 (containing NTD), DBD (containing zinc-finger motifs), hinge region (harboring NLS), and LBD (containing H12 and AF-2). Within the LBD, H12 acts as a key conformational element functioning as a "molecular switch" to regulate coregulator binding; B: Ligand-dependent conformational changes of the GR LBD and representative ligand structures. Agonists (e.g., dexamethasone, hydrocortisone, prednisolone, and methylprednisolone) stabilize H12 in an active conformation, whereas antagonists (e.g., mifepristone) induce an alternative H12 arrangement that disrupts coactivator recruitment. GR, NCoA2, and NCoR1 are shown as cartoon mode, while dexamethasone and mifepristone in co-crystal structure are displayed as stick models. The co-crystal structure of GR-NCoA2-dexamethasone is colored gray/magenta, pink, and magenta, respectively, whereas the GR-NCoR1-mifepristone complex is colored gray/blue, light blue, and blue; C: Ligand-dependent conformational changes of the ER LBD and representative ligand structures. ER ligands differentially regulate H12 conformation, thereby determining receptor activation, antagonism, or degradation. ER and TIF-2 are shown as cartoon mode, and ER ligands in co-crystal structure are displayed as stick models. The co-crystal structures of ER-estradiol, ER-4-hydroxytamoxifen, and ER-elacestrant are colored gray/magenta, gray/yellow, and gray/green, respectively. NTD: N-terminal transactivation domain 1; AF-1: Activation function 1; DBD: DNA-binding domain; NLS: Nuclear localization signal; LBD: Ligand-binding domain; H12: Helix 12; GR: Glucocorticoid receptor; NCoA 2: Nuclear receptor coactivator 2; NCoR 1: Nuclear receptor corepressor 1; ER: Estrogen receptor; TIF-2: Transcriptional intermediary factor 2; SERMs: Selective estrogen receptor modulators; SERDs: Selective estrogen receptor degraders; PROTAC: Proteolysis targeting chimera

抑制。在众多核受体中, GR和ER具有丰富的配体复合物结构及明确的构象调控机制, 并在不同疾病领域实现了成功的临床转化, 因此本文以GR和ER作为核受体结构药理学研究与药物开发的典型代表进行综述。

1.1 GR GR是最早被发现的核受体之一, 在多种组织中广泛表达, 参与炎症抑制、免疫调控、代谢稳态及细胞命运调控等关键生理过程[21,22]。在未结合配体时, GR在细胞质中与伴侣蛋白Hsp70 (heat shock protein 70)、Hsp90、p23 (prostaglandin E synthase 3) 等形成多聚体复合物, 以维持其构象稳定; 当配体与GR的LBD结合后, GR构象发生改变并转位入核, 形成同源二聚体并结合糖皮质激素响应元件 (glucocorticoid response element, GREs), 调控下游基因表达[23,24]。基于这一经典信号通路, GR长期以来一直是抗炎与免疫抑制治疗中最重要的药物靶点之一。

靶向GR的药物早期以糖皮质激素类药物为代表，如地塞米松 (dexamethasone)、氢化可的松 (hydrocortisone)、泼尼松龙 (prednisolone) 和甲泼尼龙 (methylprednisolone) 等 (图1B)。这类药物能够高效激活GR, 广泛应用于哮喘、自身免疫疾病、器官移植及血液系统疾病等领域, 成为现代抗炎治疗的基础[22,25]。然而, 由于这类经典激动剂的广谱激活作用, 患者在长期使用中普遍伴随骨质疏松、糖代谢紊乱及库欣综合征等不良反应, 后续药物多向“功能选择性调控”方向发展[25]。

对GR LBD与小分子配体共晶结构的解析, 为深入理解其转录调控机制提供了关键依据 (图1B)。从结构机制上看, 激动剂通过与GR LBD内关键残基形成稳定的相互作用网络, 维持受体活化构象。以地塞米松为代表，该化合物通过氢键 (Asn564、Gln570、Arg611、Gln642 和 Thr739 等) 和疏水相互作用 (Phe623、Leu732、Tyr735和Phe749等) 稳定配体结合口袋, 促使H12稳定于完全闭合构象, 从而形成完整的AF-2共激活因子结合界面, 激活下游转录程序 (PDB: 1M2Z)[26]。

库欣综合征相关高血糖由GR过度激活引起, 米非司酮 (mifepristone) 是治疗该疾病的代表性GR拮抗剂 (图1B)。共晶结构显示, 米非司酮与GR激动剂相似, 仍可与GR的Gln570、Arg611及Gln642等关键残基形成相互作用, 但其11β位二甲氨基苯基取代基会干扰H12的正确定位, 诱导H12处于开放构象, 破坏Glu755与转录共激活因子TIF2 (transcriptional intermediary factor 2) 之间的相互作用, 并招募NCoR 1等转录共抑制因子阻断转录激活 (PDB: 3H52)[27]。在此基础上, 第二代选择性GR拮抗剂如relacorilant进一步提高了靶点选择性并改善安全性, 已于2026年3月获美国食品药品监督管理局 (Food and Drug Administration, FDA) 批准, 用于联合白蛋白结合紫杉醇 (nab-paclitaxel) 治疗铂类耐药的上皮性卵巢癌, 标志着GR靶向策略由代谢性疾病拓展至肿瘤治疗领域[28]。

在经典激动与拮抗之外, 选择性糖皮质激素受体调节剂 (selective glucocorticoid receptor modulator, SEGRMs) 通过调控受体构象, 实现对不同转录程序的选择性激活或抑制, 从而在保留抗炎活性的同时降低代谢相关不良反应。伐莫洛龙 (vamorolone) 是该策略的代表性成果, 其与GR的复合物结构 (PDB: 6W9M) 表明, 该分子在维持部分关键氢键 (Gln570、Arg611、Thr739) 识别的同时, 失去与Asn564的关键氢键相互作用, 使H12处于部分开放的中间状态, 削弱了GR招募共抑制因子的能力, 从而显著降低代谢和骨质疏松等相关的不良反应[29]。基于这一特性, 伐莫洛龙于2023年获得FDA批准, 用于治疗2岁及以上患者的杜氏肌营养不良症[30]。这一结果表明, GR的功能可以通过精细调控配体–受体相互作用网络加以重塑, 而非简单依赖于完全激活或完全抑制。

GR的功能调控并不限于其经典的配体结合位点。借助冷冻电镜技术, 研究人员解析了GR-Hsp90与免疫亲和蛋白FKBP51 (FK506 binding protein 51) 或FKBP52形成的高分辨率复合物结构, 从而分别阐明了FKBP51抑制与FKBP52激活GR的具体机制, 这些新发现的蛋白互作界面为开发新型GR靶向药物提供了潜在的作用位点 (PDB: 8FFV, 8FFW)[23,24]。此外, GR与14-3-3蛋白的复合物晶体结构 (PDB: 8A9G) 揭示, GR Thr524位点的磷酸化能促进GR与14-3-3结合; 在此基础上, 研究人员进一步设计了能够选择性靶向GR/14-3-3相互作用界面的分子胶 (molecular glue), 为干预GR功能开辟了新途径[31,32]。

GR靶向药物的研发正由传统激动/拮抗主导的广谱调控, 转向以构象选择性为核心的精细调节。不同配体通过改变Asn564、Glu755等极性识别残基及周围疏水口袋的相互作用网络, 调控H12构象和AF-2界面稳定性, 诱导受体招募不同共调节因子, 从而产生具有偏向性的转录调控效应[21,22,25]。GR药物设计已从单纯追求活性强弱, 转向对构象偏向性的精准调控, 为药物设计提供结构基础, 确保在保留药物抗炎活性的同时降低代谢不良反应。

1.2 ER ER包括ERα (ESR1) 和ERβ (ESR2)[33,34]。ER不同亚型 (如ERα36、ERα46和ERβ1～β5等) 广泛分布于乳腺、子宫、卵巢、骨骼、肝脏、心血管系统及中枢神经系统等多种组织中, 这些变体在不同组织中的表达存在显著差异, 并因此赋予其不同的转录活性和配体敏感性[35-37]。在众多表达组织中, 乳腺组织对雌激素高度敏感, ESR1过度激活与乳腺癌的发生发展密切相关, 因而成为乳腺癌药物研发的重要靶点[38-40]。乳腺癌是全球发病率最高的恶性肿瘤, 其中约80%为ER阳性乳腺癌[41]。靶向ER的治疗能够显著改善此类患者的生存预后, 已成为肿瘤靶向治疗中最成功的范式之一。

大量ESR1配体与受体复合物的共晶结构系统揭示了不同类型药物调控ER活性的分子基础, 配体通常通过与Glu353、Arg394形成保守氢键网络, 并嵌入由Leu387、Leu525、Met421等构成的疏水口袋实现高亲和力识别, 而H12螺旋作为分子开关, 通过构象变化决定AF-2的开放或关闭, 从而调控转录活性[42]。经典选择性雌激素受体调节剂 (selective estrogen receptor modulators, SERMs) 以他莫昔芬 (tamoxifen) 为代表

(图 1C), 其活性代谢物 4-羟基他莫昔芬 (4-hydroxytamoxifen) 与 ERα LBD 复合物结构 (PDB: 3ERT) 显示, 该配体占据 LBD 内部配体结合口袋, 并通过其侧链基团向外延伸并产生空间位阻, 将 H12 推离激动构象位置, 从而阻断共激活因子结合 ER, 维持 ER 的拮抗状态[42]。

相比之下, 选择性雌激素受体降解剂 (selective estrogen receptor degraders, SERDs) 在拮抗基础上进一步诱导受体降解。氟维司群 (fulvestrant) 结构类似物 ICI164384 及其衍生物与 ER 的复合物结构 (PDB: 1HJ1、7R62) 可在一定程度上反映氟维司群与 ER 的结合模式; 氟维司群 C7 位长链侧链可能以类似方式扰乱 H12 稳定性并破坏 AF-2 界面, 从而抑制 ER 二聚化和转录活性, 并促进 ER 降解; 在 Y537S、D538G 等 ESR1 突变背景下, 氟维司群仍保留一定抑制活性[43,44]。与氟维司群相比, 口服 SERD 艾拉司群 (elacestrant) 在生物利用度及安全性方面均有所提升, 其共晶结构 (PDB: 7TE7) 显示, 该分子在维持关键氢键识别的同时, 通过疏水相互作用网络间接扰动 H12 构象。不同于氟维司群直接将 H12 推离激动构象, 艾拉司群使 H12 处于动态不稳定状态, 从而阻碍 AF-2 界面形成并促进 ER 降解, 同时在 ESR1 突变背景下仍保持较高活性 (图 1C)[43,44]。总体而言, 这些结构研究表明, ESR1 不同类型药物通过诱导 H12 不同程度的位移或动态构象变化, 从而实现调节、拮抗或降解功能, 为基于结构的药物设计提供了关键分子基础。

艾拉司群于 2023 年获 FDA 批准, 用于 ER 阳性/HER2 (human epidermal growth factor receptor 2) 阴性且携带 ESR1 突变的晚期或转移性乳腺癌, 标志着口服 SERD 正式进入临床应用阶段; 随后, 基于 ESR1 配体结合口袋特征的结构−活性关系优化, 研究者开发出具有良好口服药代性质并能高效诱导 ER 降解的非甾体 SERD imlunestrant。该分子在体外表现出显著的 ESR1 降解活性, 并在体内具有良好的口服暴露和持续抑制作用, 于 2025 年获批用于类似适应症, 进一步验证了基于 ER 降解策略在内分泌耐药人群中的临床价值[45], 其结构机制研究也为后续第二代 SERD 及 PROTAC (proteolysis-targeting chimera)-ER 降解剂的开发奠定了基础[46]。

在此基础上, 多种新一代口服 SERD 或 ER 拮抗剂已进入关键临床阶段 (表 1)。卡米司群 (camizestrant, AZD9833) 在 III 期临床研究中显著延长了晚期乳腺癌患者的无进展生存期。当 ctDNA 检测筛选出患者 ESR1 突变后, 卡米司群在调整治疗策略的患者中显示出更好的疗效, 提示基于分子分型的动态治疗模式是 ER 靶向治疗的重要发展方向[47]。吉瑞司群 (giredestrant) 在针对 HR 阳性/HER2 阴性早期乳腺癌术后患者辅助治疗的 III 期临床研究中, 显示出降低癌症复发风险的能力。这些结果共同表明, ER 靶向药物的应用范围正由晚期乳腺癌逐步向疾病早期阶段拓展[48]。

Table 1 Representative pharmacological modalities targeting transcription factors that are approved or under clinical development

Target	Drug	Mechanism	Development status	Clinical indication
GR	Dexamethasone	GR agonist	Approved (1958)	Anti-inflammatory and immunosuppressive; potent long-acting benchmark glucocorticoid
	Prednisone	GR agonist	Approved (1955)	Widely used oral glucocorticoid; prodrug converted to prednisolone; autoimmune diseases, asthma, hematologic disorders
	Prednisolone	GR agonist	Approved (1955)	Active form; no hepatic activation required; suitable for liver dysfunction; local therapy
	Hydrocortisone	GR agonist	Approved (1952)	Closest to endogenous cortisol; adrenal replacement; mild-to-moderate inflammation
	Methylprednisolone	GR agonist	Approved (1957)	Enhanced anti-inflammatory activity; reduced fluid retention; severe inflammation, transplant rejection
	Mifepristone	GR antagonist	Approved (2012)	Cushing's syndrome-associated hyperglycemia; limited selectivity (also targets PR)
	Vamorolone	SEGRM	Approved (2023)	Duchenne muscular dystrophy; dissociates transactivation/transrepression; reduced side effects
	Relacorilant	SGRM	Approved (2026)	Platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
	Miricorilant	SGRM	Phase II-III	Metabolic diseases (e.g., NASH); modulates GR signaling
ER	Tamoxifen	SERM	Approved (1977)	ER^+ breast cancer; tissue-selective ER modulation; foundational therapy
	Lasofoxifene	SERM	Phase III	$ER^+/HER2^-$ ESR1-mutant breast cancer; active in endocrine resistance; bone and urogenital benefits

Continued

Target	Drug	Mechanism	Development status	Clinical indication
	Fulvestrant	SERD	Approved (2002)	ER^+ metastatic breast cancer; induces ER degradation; injection, limited exposure
	Elacestrant	Oral SERD	Approved (2023)	$ER^+/HER2^-$ advanced breast cancer (esp. ESR1 mutants); improved exposure and degradation
	Imlunestrant	Oral SERD	Approved (2025)	$ER^+/HER2^-$ ESR1-mutant advanced breast cancer
	Camizestrant (AZD9833)	Oral SERD	Phase III	$ER^+/HER2^-$ breast cancer; precision medicine with ESR1 mutation monitoring
	Giredestrant	Oral SERD	Phase III	$ER^+/HER2^-$ breast cancer; mixed clinical results
	Rintodestrant	Oral SERD	Phase I	$ER^+/HER2^-$ advanced breast cancer; next-generation SERD
	H3B-6545	Covalent ER antagonist	Phase I	ER^+ and ESR1-mutant breast cancer; irreversible inhibition
	Palazestrant (OP-1250)	Full ER antagonist/SERD-like	Phase III	ER^+ breast cancer; complete antagonism *via* conformational remodeling
	Vepdegestrant (ARV-471)	PROTAC ER degrader	Approved (2026)	$ER^+/HER2^-$ breast cancer; E3 ligase recruitment; superior efficacy in ESR1 mutants
HIF-2α	Belzutifan (MK-6482, PT2977)	HIF-2 inhibitor (blocks HIF-2α/ARNT dimerization)	Approved (2021); phase III (RCC)	VHL-associated tumors, RCC; first-in-class HIF-2α inhibitor
	NKT2152	HIF-2 inhibitor	Phase II (terminated)	ccRCC; next-generation inhibitor; PAS-B pocket strategy
	Casdatifan (AB521)	HIF-2 inhibitor	Phase III	Advanced ccRCC; mono- and combination therapy
AHR	Tapinarof	AHR agonist	Approved (2019)	Plaque psoriasis (approved: China, 2019; US, 2022); atopic dermatitis (approved: China/US, 2024)
	BAY 2416964	AHR antagonist	Phase I (terminated)	Solid tumors; limited efficacy; challenges in translation
	IK-175	AHR antagonist	Phase I/Ib completed	Urothelial and head & neck cancers; combination with nivolumab
STAT3	Danvatirsen (AZD9150)	STAT3 antisense oligonucleotide	Phase II	Lymphoma, solid tumors; reduces STAT3 expression
	TTI-101 (C188-9)	STAT3 inhibitor	Phase I/II	Solid tumors; SH2 targeting strategy
	OPB-31121	STAT3 inhibitor	Phase I (terminated)	Solid tumors; severe toxicity
	OPB-51602	STAT3 inhibitor	Phase I (terminated)	Solid tumors; metabolic toxicity
	SD-36	STAT3 PROTAC degrader	Preclinical	Not yet clinical; overcomes lack of binding pocket
p53/MDM2	RG7112	Nutlin-class inhibitor	Phase I (terminated)	Hematologic and solid tumors; first clinical validation of PPI targeting
	Idasanutlin (RG7388)	Nutlin-class inhibitor	Phase III failed	AML; hematologic toxicity; limited efficacy
	SAR405838 (MI-77301)	MDM2 inhibitor	Phase I/II	Solid and hematologic tumors; dose-limiting toxicity
	HDM201 (Siremadlin)	Selective MDM2 inhibitor	Phase II	Solid and hematologic tumors; intermittent dosing
	Milademetan (DS-3032)	MDM2 inhibitor	Phase III failed	Liposarcoma; limited efficacy
	Navtemadlin (KRT-232)	MDM2 inhibitor	Phase II/III	Myelofibrosis, solid tumors; effective in p53 WT patients
	Brigimadlin (BI 907828)	MDM2 inhibitor	Phase III	MDM2-amplified tumors; improved PK/toxicity balance
	ALRN-6924	MDM2/MDMX stapled peptide	Phase II	Solid tumors, lymphoma; dual targeting strategy
MYC/MAX	Omomyc (OMO-103)	Engineered MYC mutant protein	Phase I	Solid tumors; disrupts MYC/MAX interaction
	MYCi361/MYCi975	MYC/MAX inhibitor	Preclinical	Multiple tumor models; targets dimer interface
	10058-F4	MYC/MAX inhibitor	Preclinical	Mechanistic studies; poor PK
	10074-G5	MYC/MAX inhibitor	Preclinical	Disrupts MYC structure; limited stability
	KJ-Pyr-9	MYC/MAX inhibitor	Preclinical	Early inhibitor; validates targetability
	MYCMI-6	MYC/MAX inhibitor	Preclinical	Leukemia and solid tumors; early-stage

目前, ER靶向治疗仍受获得性耐药、药代动力学限制及作用机制单一等因素制约。新一代以结构为基础的ER靶向药物不断涌现, 如分子胶、PROTAC等[49,50]。其中, PROTAC分子ARV-471 (vepdegestrant)近期于2026年5月获FDA批准上市, 用于ER阳性、HER2阴性、ESR1突变的晚期或转移性乳腺癌患者[51,52]。此外, palazestrant是一种正处于III期临床研究阶段的新型口服ER完全拮抗剂, 其通过更有效地阻断ER与共激活因子的相互作用并改善口服药代动力学特性, 实现了更充分且持续的ER信号抑制, 从而在

内分泌耐药乳腺癌中展现出潜在治疗优势[53]。

总体而言, ER靶向药物的临床发展正经历由单纯抑制雌激素信号向同时兼具拮抗与受体降解作用的机制转变, 同时患者选择也逐步由基于临床特征转向以ESR1突变等分子标志物为依据的分层策略, 治疗应用则由晚期阶段逐渐向一线乃至辅助治疗延伸。上述进展表明, 围绕ER配体结合域构象调控, 尤其是H12构象稳定性及AF-2界面状态的结构药理学研究, 已成为推动新一代内分泌治疗药物开发与临床转化的重要基础, 为克服耐药并实现精准治疗提供了支撑。

2 类核受体

2.1 概述 类核受体即bHLH-PAS家族是一类高度保守的转录因子, 广泛参与发育、昼夜节律、氧感应、毒物代谢、免疫调控等多种生理过程。

目前已知类核受体 (bHLH-PAS) 转录因子在不同物种中约有数十种, 其中人类约有16个成员, 代表性包括缺氧诱导因子 (hypoxia-inducible factors, HIFs) 和芳香烃受体 (aryl hydrocarbon receptor, AHR) 等 (图2A)。该家族蛋白通常由class I与class II成员形成异源二聚体并结合DNA调控转录, 在结构上通常包含bHLH结构域、PAS-A/PAS-B结构域和C端转录激活结构域 (transcriptional activation domain, TAD, 图2B)[54]。其中, bHLH结构域介导蛋白二聚化及缺氧反应元件 (hypoxia response element, HRE) 等DNA识别, PAS结构域参与环境信号感应及蛋白−蛋白相互作用, 并与bHLH协同稳定异二聚体, 而C端TAD多为内在无序区 (intrinsically disordered region, IDR), 通过募集共调控因子调节转录活性[55-58]。

2.2 缺氧诱导因子 (HIF-2α) HIFs是一类由HIF-α亚基与芳香烃受体核转位蛋白 (aryl hydrocarbon

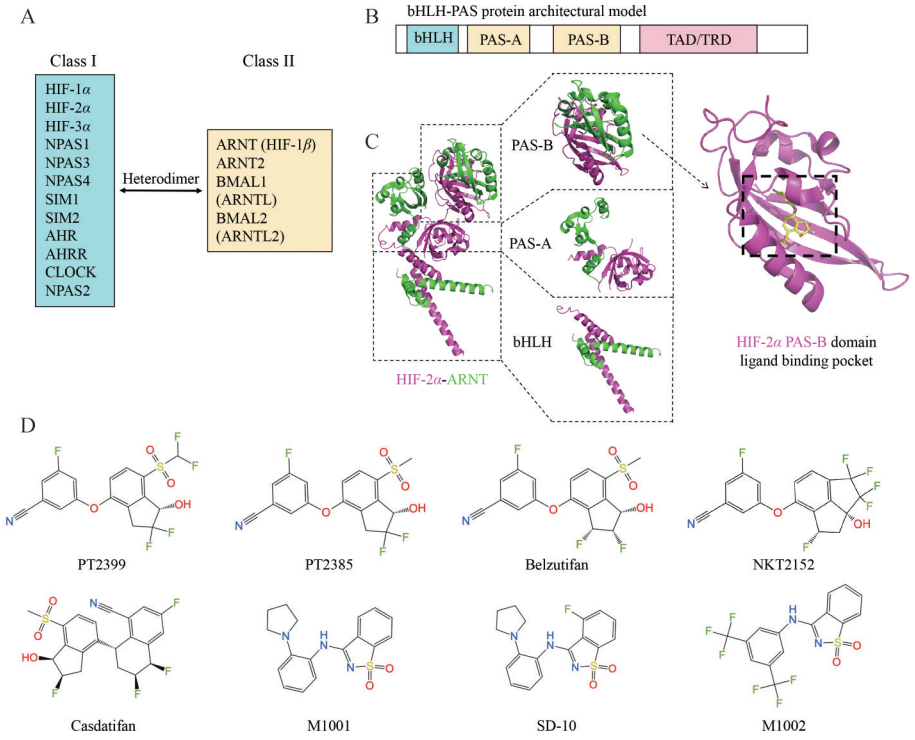


Figure 2 Structural organization of bHLH-PAS family proteins, HIF-2α structure and representative HIF-2α -targeting ligands. A: Schematic classification of nuclear receptor-like family proteins. Class I proteins (including HIF-1α, HIF-2α, HIF-3α, and AHR) function through heterodimerization with class II partners (ARNT, ARNT2, BMAL1, and BMAL2) to regulate transcription; B: Domain organization of nuclear receptor-like family proteins. These proteins typically comprise bHLH, PAS-A, PAS-B, and TAD/TRD domains; C: Structure of the HIF-2α-ARNT-belzutifan complex. The crystal structure (PDB: 7W80) includes the bHLH, PAS-A, and PAS-B regions. The right panel shows the co-crystal structure of the small molecule belzutifan bound to the HIF-2α PAS-B domain. The black dashed box highlights the allosteric ligand-binding pocket within HIF-2α PAS-B; D: Chemical structures of representative small-molecule ligands targeting the HIF-2α PAS-B domain, including inhibitors (PT2399, PT2385, belzutifan, NKT2152, and casdatifan) and agonists (M1001, M1002, and SD-10). HIF-1α: Hypoxia-inducible factor-1α; NPAS1: Neuronal PAS domain protein 1; SIM1: Single-minded protein 1; AHR: Aryl hydrocarbon receptor; AHRR: AHR repressor; CLOCK: Clock circadian regulator; ARNT: Aryl hydrocarbon receptor nuclear translocator; BMAL1: Brain and muscle ARNT-like protein 1; bHLH: Basic helix-loop-helix; PAS: PER-ARNT-SIM; TAD: Transcriptional activation domain; TRD: Transcriptional repression domain

receptor nuclear translocator, ARNT) 组成的异源二聚体转录因子, 是细胞感知氧浓度变化的核心调控分子(图2A)。在常氧条件下, HIF-α亚基经脯氨酸羟化酶催化发生羟基化修饰, 随后被希佩尔–林道 (von Hippel-Lindau, VHL) 抑癌蛋白识别并介导泛素化降解[59]; 而在缺氧条件下, HIF-α得以稳定存在并转位入核, 与ARNT形成活性复合物, 识别HRE并募集共调节因子, 激活包括血管生成、糖代谢重编程及肿瘤进展相关基因在内的转录程序[57]。

在人体中, HIF-α家族主要包括HIF-1α、HIF-2α和HIF-3α三种亚型[54,60]。HIF-1α广泛表达于多种组织, 而HIF-2α则具有更明显的组织特异性, 主要分布于肾脏、肝脏及神经系统等组织, 并在血管新生、红细胞生成及代谢调控中发挥关键作用[56,61]。尽管三种亚型均包含PAS-B结构域并具有潜在的小分子结合能力, 但HIF-1α的PAS-B口袋较小, 且药物靶向HIF-1α易引发全身代谢紊乱, 而HIF-3α虽可结合内源性配体, 但其剪接变体众多且功能复杂, 相关配体开发较少[57,62,63]。当前HIF-α相关的药物研发主要集中于成药性更佳的HIF-2α[64-67]。

结构药理学研究在HIF-2α靶向药物开发中发挥了决定性作用。早期晶体结构解析发现, HIF-2α的PAS-B结构域内存在一个可被小分子占据的疏水口袋, 配体结合后可诱导构象变化, 进而破坏HIF-2α与ARNT的异二聚化 (图2C)[61,68,69]。化合物PT2385/PT2399及其与HIF-2α的共晶结构证实, 其结合可诱导关键残基 (如M252、H293等) 发生构象重排, 这些残基位于HIF-2α-ARNT二聚界面, 从而通过变构机制削弱异源二聚体稳定性, 最终抑制下游转录活性。这一发现从结构层面揭示了该转录因子可通过变构调控实现药物干预的可能性, 从而推动了结构驱动的HIF-2α抑制剂研发。

基于上述发现, HIF-2α抑制剂的研发经历了由靶点可成药性验证到临床应用的逐步演进。早期先导分子PT2399在VHL缺失型肾透明细胞癌模型中表现出显著抗肿瘤活性, 首次完成了HIF-2α靶点的概念验证。在此基础上, 第一代临床候选药物PT2385进入临床研究, 验证了抑制HIF-2α-ARNT二聚化在晚期肾透明细胞癌中的安全性与初步疗效。然而, PT2385存在明显的药代动力学局限, 如葡萄糖醛酸化代谢导致的体内暴露不足及个体差异较大, 从而限制了其临床应用。

针对上述瓶颈, 通过结构优化获得的第二代分子贝组替凡 (belzutifan, 也称MK-6482或PT2977, 图2C) 显著改善了口袋占据能力及代谢稳定性, 实现了持续有效的体内暴露, 并最终获得监管批准, 成为首个上市的HIF-2α抑制剂。其适应证已从VHL相关肿瘤扩展至既往接受免疫治疗及抗血管生成治疗后的晚期肾透明细胞癌 (renal clear cell carcinomas, ccRCC), 并进一步拓展至中枢神经系统血管母细胞瘤、胰腺神经内分泌肿瘤和嗜铬细胞瘤/副神经节瘤。同时, 贝组替凡的开发已由单药治疗逐步发展至联合治疗及辅助治疗, 显示出其在肾癌治疗体系中的潜在应用价值。然而, 该药亦存在机制相关毒性, 如贫血和低氧血症, 以及单药疗效在复杂肿瘤微环境中的局限性, 促使后续研究进一步优化分子性质及治疗策略。

除贝组替凡之外, 一种新型口服HIF-2α抑制剂NKT2152在既往治疗失败的晚期透明细胞肾癌患者中显示出初步抗肿瘤活性, 目前处于临床I/II期研究阶段 (NCT05119335)[70], 但相关项目因管线策略调整而终止, 这提示在已有成熟药物背景下, 新分子需具备明确的差异化优势方能持续推进。相比之下, casdatifan (AB521, 图2D) 作为当前最具潜力的后续候选分子之一, 已进入III期临床研究 (NCT07011719), 其开发重点包括与酪氨酸激酶抑制剂 (如cabozantinib) 联合以提升疗效, 同时也在探索与免疫治疗联合构建无TKI的一线治疗方案, 以期降低相关毒性负担并优化治疗策略[71]。

除抑制剂之外, HIF-2α PAS-B口袋同时也可容纳激动剂, 通过改变不同关键氨基酸的构象 (如Y281), 从而实现对HIF-2α活性的双向调控[56]。HIF-2α激动剂研究仍处于早期探索阶段, 开发结构新颖的激动剂并评估其在肾性贫血中的治疗潜力具有重要意义。2019年, 本课题组率先报道了HIF-2α激动剂M1001及M1002, 并通过该化合物与HIF-2α-ARNT的共晶结构揭示了M1001通过变构效应增强HIF-2α-ARNT异源二聚体稳定性, 从而提高HIF-2α转录活性的分子机制(图2)[56]。此后, Yu等[72]基于M1002开发了一系列衍生物, 其中用溴取代三氟甲基的衍生物ZG-2006相较于M1002表现出改善的激动活性。2021年, 该团队又报道了新型HIF-2α激动剂ZG-2033, 其与PHD抑制剂伐度司他 (vadadustat) 联用可提高小鼠血浆中的EPO水平[73]。此外, 本课题组优化了M1002的杂环骨架、连接基团和苯环, 并通过构效关系分析表明, 在M1002的A环上添加卤素可增强其活性[74]。2025年, 本课题组基于HIF-2α激动剂M1001优化得到化合物SD-10, 该化合物能够稳定PAS-B结构域构象并增强HIF-2α-ARNT异二聚体转录活性。SD-10与达普司他 (daprodustat) 可以联用协同促进促红细胞生成素 (erythropoietin, EPO) 分泌, 有望成为治疗肾性贫血的

新型HIF-2α靶先导化合物[75]。

HIF-2α靶向药物的成功开发确立了转录因子中靶向变构口袋的重要药物设计范式。小分子配体诱导PAS-B结构域内疏水口袋中关键氨基酸构象重排, 削弱HIF-2α-ARNT二聚界面稳定性, 从而实现对转录活性的变构调控。这一机制突破了传统靶向蛋白互作界面的药物设计思路, 证明在表面平坦的转录因子中仍可能存在可利用的隐蔽调控位点。贝组替凡等药物以HIF-2α PAS-B口袋的结构为基础, 对药物构效关系进行多轮优化, 构建了从先导化合物到临床药物的完整路径, 也为其他bHLH-PAS蛋白乃至更广泛转录因子的药物开发提供了可借鉴的策略。

2.3 AHR AHR是一种配体依赖型转录因子, 广泛表达于肝脏、肺、肠道及免疫系统, 在外源化合物代谢、免疫调节和屏障功能维持中发挥重要作用。AHR能够感知多种外源性芳香族化合物和内源性色氨酸代谢物, 激活下游转录程序, 调控细胞色素P450酶 (如CYP1A1)、炎症因子及黏膜屏障相关基因的表达。近年来的研究表明, AHR在肿瘤发生、代谢稳态和神经系统功能调控中具有情境依赖性的双向调节作用, 如在乳腺癌和结直肠癌中影响细胞分化状态, 在肠道炎症及“脑−肠轴”调控中参与微生态与神经功能的协调等[76-78]。

AHR最初被认为是感知二噁英等环境毒性污染物的关键受体, 后续研究逐渐证实其在内源代谢、免疫调控及组织稳态中均具有重要作用[79]。结构药理学研究表明, AHR PAS-B结构域内部形成一个体积约为350～450 Å^{3}的疏水性口袋, 具有较高的构象柔性和配体适配能力, 可容纳多种芳香族和杂环化合物。未结合配体前, AHR在细胞质中以多蛋白复合物形式存在, 与Hsp90、XAP2 (X-associated protein 2) 和p23结合以维持其构象稳定; 当配体结合AHR PAS-B口袋后, AHR发生构象重排, 暴露核定位信号并转位入核, 与ARNT形成异源二聚体, 从而启动特异性的转录调控程序 (图3)[80]。本课题组的研究结果进一步揭示, 不同类型的配体结合AHR PAS-B结构域后可引发不同的构象调整, 这些构象变化可能改变其与异二聚体蛋白或共调节因子的相互作用界面, 从而影响下游信号传导的选择性与调控模式[78]。

基于上述功能与结构特征, 当前AHR靶向药物的研发逐渐形成两条主要路径: 一类为激动剂, 主要用于炎症性疾病; 另一类为抑制剂或拮抗剂, 主要应用于肿瘤治疗。

在炎症性疾病领域, 本维莫德 (tapinarof, 图3) 的上市验证了AHR作为治疗靶点的可行性, 并为转录因子靶向干预提供了新的方向。本维莫德可直接激活AHR信号通路, 促进角质形成细胞分化, 诱导filaggrin等屏障相关蛋白表达, 同时抑制IL-17、IL-22等炎症因子介导的免疫反应, 从而实现对皮肤屏障功能和炎症状态的双重调控[81]。该药已分别于2019年在中国、2022年在美国获批用于治疗银屑病, 后又于2024年底在两国获批治疗特应性皮炎等适应症[82]。结构药理学研究表明, 本维莫德的芳香环可深度嵌入PAS-B疏水口袋, 其羟基与口袋内极性残基形成稳定氢键, 从而破坏AHR与XAP2之间的相互作用, 促进其构象激活和核转位[78]。

与此不同, 在肿瘤微环境中, AHR往往作为免疫抑制信号的整合节点发挥作用。色氨酸代谢产生的犬

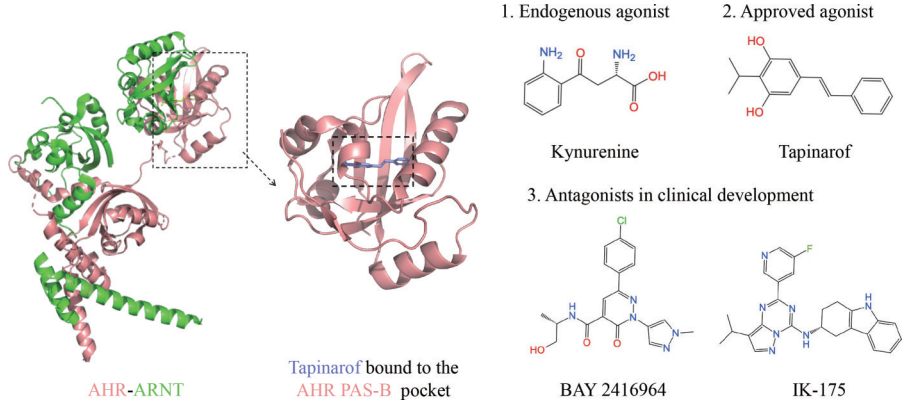


Figure 3 Co-crystal structure of the AHR-ARNT-tapinarof complex and chemical structures of representative AHR-targeting compounds. The heterodimeric structure of AHR-ARNT-tapinarof complex is shown on the left (PDB: 8XS6), with the dashed box highlighting the AHR-ARNT PAS-B domains. The middle panel presents the AHR PAS-B domain, with the dashed box indicating its ligand-binding pocket. The right panel illustrates representative AHR-targeting ligands of different classes, including the endogenous agonist kynurenine, the approved agonist tapinarof, and the clinical-stage antagonists BAY 2416964 and IK-175. In the structure, AHR and ARNT are depicted as cartoon mode, whereas tapinarof is shown as stick mode. AHR is colored in salmon, ARNT in green, and tapinarof in slate

尿氨酸 (kynurenine, 图3) 可作为内源性配体持续激活AHR, 从而抑制效应T细胞功能并促进免疫耐受[83]。代表性分子如BAY 2416964 (图3) 已进入I期临床研究, 通过抑制AHR的转录活性, 进而缓解肿瘤微环境中的免疫抑制状态 (NCT04069026)[84]; IK-175 (图3) 等分子则进一步与免疫检查点抑制剂联合应用, 通过阻断AHR信号增强抗肿瘤免疫反应, 显示出一定的协同治疗潜力 (NCT04200963)[85,86]。

总体而言, AHR配体结合口袋具有良好的可塑性, 为小分子设计提供了空间, 但配体结构多样性及其诱导的构象差异也带来了选择性和安全性方面的挑战。研究表明, AHR配体的组织选择性并非仅由结合亲和力决定, 还与其诱导的受体构象及共调节因子招募密切相关, 这为功能偏向性配体的设计提供了结构依据[87]。目前, AHR PAS-B结构域在配体结合过程中的动态构象变化仍有待进一步阐明[78], 未来的研究可着眼于识别新的变构调控位点、靶向AHR与其伴侣蛋白或共调节因子的相互作用界面, 并融合AI辅助结构预测与药效学模型构建技术, 以期实现对AHR更精准的组织与功能特异性调控[79]。

3 其他转录因子靶点

大部分转录因子因其结构高度柔性, 且在不同类型细胞中可能通过不同机制发挥转录活性, 这些特性给靶向药物的设计带来了显著挑战[88]。然而, 随着蛋白质降解技术 (如PROTAC和分子胶) 和高通量筛选等实验方法的快速发展, 越来越多曾被视为“难以靶向”的转录因子正逐步展现出潜在的可靶向性[89]。

3.1 STAT3 (signal transducer and activator of transcription 3) STAT家族是一类介导细胞信号转导的转录因子, 包含STAT1至STAT6六种亚型。其中, STAT3在肿瘤发生发展、免疫调控及炎症反应中发挥关键作用[90]。在经典JAK-STAT通路中, 细胞因子或生长因子与受体结合后激活Janus激酶 (Janus kinases, JAK), 进而磷酸化STAT3的Tyr705位点, 促使STAT3形成同源二聚体并转位入核 (图4A), 识别γ-干扰素激活序列 (gamma-activated sequence, GAS) 从而驱动下游基因转录[91]。激活后的STAT3可调控细胞增殖、血管新生和免疫抑制等多个肿瘤相关的过程。STAT3在多种实体瘤和血液系统肿瘤中均表现为异常激活状态, 并与肿瘤进展、免疫逃逸和耐药密切相关。尽管STAT3具有明确的生物学功能和治疗潜力, 但与核受体及类核受体不同, STAT3不依赖内源性小分子配体调控, 且缺乏深而稳定的配体结合口袋, 其SH2结构域 (Src homology 2 domain) 介导的二聚界面相对平坦且高度保守, 长期被视为“难以靶向”的转录因子之一[92]。

STAT3抑制剂的设计思路主要分为四种, 靶向SH2结构域抑制二聚化、阻断DNA结合活性、下调STAT3表达水平, 以及诱导STAT3选择性蛋白降解[93]。近年来, STAT3靶向药物的临床研究经历了由早期小分子抑制剂向核酸药物及结构导向优化分子的逐步演进, 但尚未有获批上市的STAT3靶向药物。早期代表性化合物OPB-31121和OPB-51602等首次在人体中验证了STAT3抑制的可行性, 但均受到药代动力学不足及剂量限制性毒性 (如乳酸性酸中毒及神经毒性) 的限制, 未能进一步推进[94-96]。相比之下, 基于结构导向设计的SH2结构域抑制剂TTI-101 (C188-9, 图4A) 在I期临床试验中表现出较好的安全性及一定抗肿瘤活性, 尤其在肝癌中观察到持续获益信号, 成为当前最具代表性的STAT3靶向候选药物[94-96]。WP1066作为STAT3/JAK2双重抑制剂, 目前处于临床II期试验用于治疗胶质母细胞瘤, I期临床数据显示该药物在儿童脑肿瘤中持续保持稳定疗效, 提示STAT3抑制策略可能在特定肿瘤类型中具有更高应用潜力[97]。与此同时, 反义寡核苷酸danvatirsen (AZD9150) 通过下调STAT3 mRNA水平, 在早期研究中显示出一定的肿瘤抑制活性, 并尝试与免疫检查点抑制剂联合以增强抗肿瘤免疫, 但后续II期临床研究总体疗效有限, 尚未建立明确临床优势[98,99]。

近年来, 基于PROTAC技术的STAT3靶向降解研究也取得了实际进展, 代表性化合物有SD-36 (图4A) 和KT-333[100,101]。结构药理学研究为STAT3靶向药物的理性设计提供了重要依据, 如STAT3与SD-36的复合物结构表明, SD-36可模拟磷酸酪氨酸的构象, 与Arg609、Ser611、Glu612及Ser613等关键残基形成稳定的氢键网络, 并延伸至Ile659、Met660、Leu666等疏水口袋以增强结合亲和力 (PDB: 6NJS, 6NUQ)[100]。配体还可诱导STAT3局部loop区域发生构象重排, 使SH2口袋由开放构象转变为半闭合状态, 从而削弱其二聚界面的稳定性。上述结合模式表明, STAT3 SH2口袋本质上由“极性磷酸酪氨酸识别区”与“疏水辅助口袋”共同构成, 该口袋特征决定了小分子设计需同时满足电荷匹配与疏水互作, 这也是STAT3抑制剂开发难度较高的结构基础。

尽管STAT3靶向研究取得持续进展, 其药物开发仍面临多重挑战。一方面, STAT3通过SH2介导的二聚界面整体较为平坦, 且在STAT家族成员间高度保守, 导致亚型选择性难以实现; 另一方面, STAT3在免疫调控与代谢稳态中具有重要生理功能, 其长期、系统性抑制可能带来潜在的安全性风险[102]。因此, 未来的

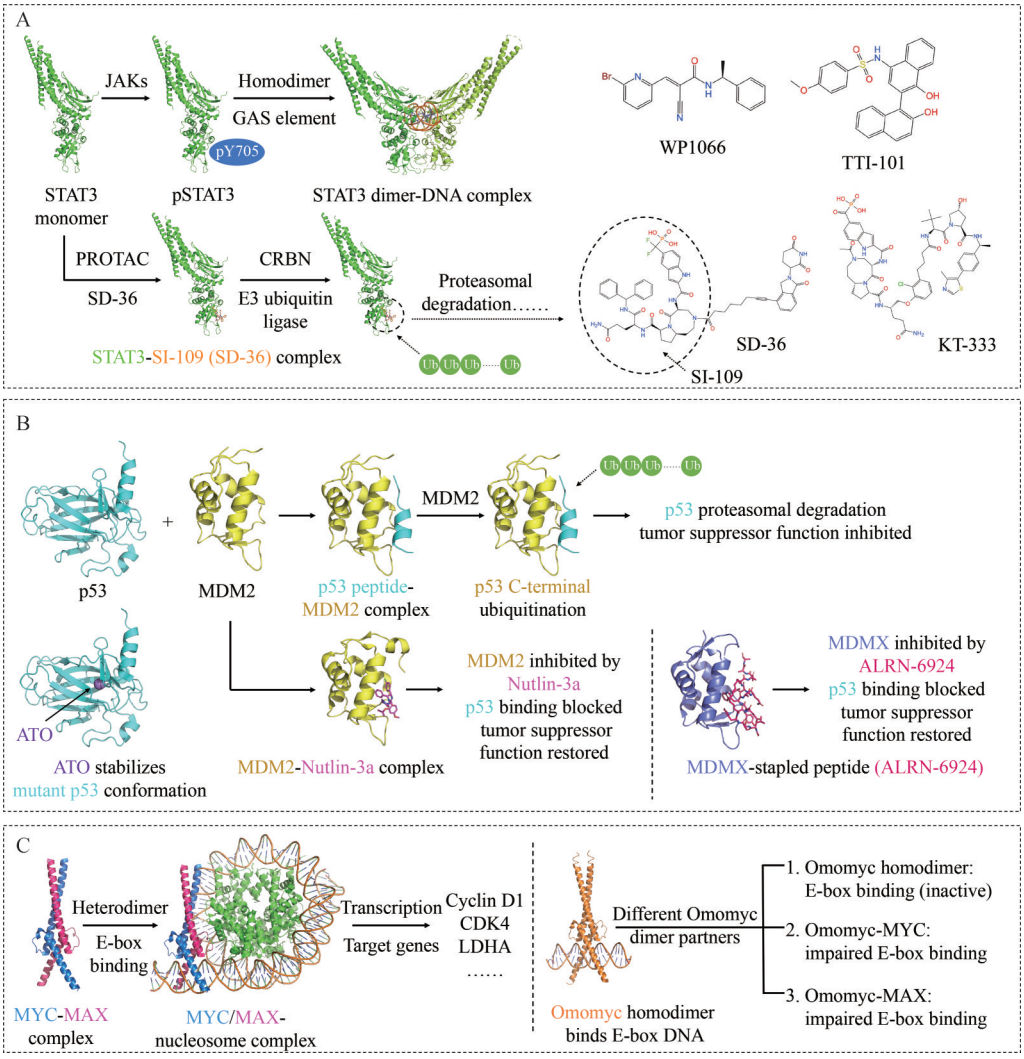


Figure 4 Structures of other traditional transcription factors and their targeting compounds. A: Schematic representation of the STAT3 signaling pathway and structures of its inhibitors. Upon phosphorylation of Tyr705 by JAK, STAT3 forms a homodimer and binds to target DNA (PDB: 6QHD), thereby promoting downstream gene expression. The PROTAC molecule SD-36 binds STAT3 (PDB: 6NJS) and recruits the E3 ubiquitin ligase CRBN, leading to STAT3 ubiquitination and proteasomal degradation; SI-109 represents the STAT3-binding moiety of SD-36. STAT3 is shown as green and lemon cartoon mode, while SI-109 and DNA are displayed as orange stick models. Chemical structures of STAT3 inhibitors napabucasin, WP1066, TTI-101, SD-36, and KT-333 are shown on the right; B: Schematic of the p53 regulatory axis and its pharmacological interventions. The E3 ubiquitin ligase MDM2 binds and ubiquitinates p53 (PDB: 1YCR), promoting its proteasomal degradation. ATO binds to mutant p53 DBD, stabilizing its conformation and restoring tumor suppressor activity (PDB: 7DHY). The MDM2 inhibitor nutlin-3a competitively occupies the p53-binding pocket of MDM2 (PDB: 4HG7), thereby blocking the p53-MDM2 interaction, reducing p53 degradation, and preserving its tumor suppressor function. The stapled peptide ALRN-6924 competitively binds to the p53-binding pocket of MDMX (PDB: 8GJS), disrupting the p53-MDMX interaction and similarly preventing p53 degradation. In the figure, p53 is shown as cyan cartoon mode, MDM2 in yellow cartoon mode, ATO as purple sphere mode, and nutlin-3a as magenta stick mode; MDMX is shown as slate cartoon mode, and ALRN-6924 is displayed as a hot pink stick model; C. Schematic illustration of MYC/MAX-mediated transcriptional activation. The MYC/MAX heterodimer binds E-box sequences (PDB: 8OTS), thereby initiating transcriptional programs of downstream genes, including genes involved in cell cycle and metabolism such as cyclin D1, CDK4, and LDHA. The engineered MYC mutant Omomyc can form homodimers (PDB: 5I50) or heterodimers with MYC or MAX, generating transcriptionally inactive complexes that competitively bind E-box sites and inhibit downstream gene transcription. MYC is shown as cyan cartoon mode, MAX in magenta cartoon mode, nucleosomes in green cartoon mode, DNA in orange stick mode, and Omomyc in orange cartoon mode. JAK: Janus kinase; STAT3: Signal transducer and activator of transcription 3; GAS: Gamma-activated sequence; CRBN: Cereblon; MDM2: Mouse double minute 2 homolog; MDMX: Mouse double minute X homolog; Ub: Ubiquitin; ATO: Arsenic trioxide; MYC: Myelocytomatosis oncogene; MAX: MYC-associated factor X; CDK4: Cyclin-dependent kinase 4; LDHA: Lactate dehydrogenase A

药物设计策略可能需要从单一界面阻断转向利用蛋白构象动态变化进行更精细的干预, 例如, 通过分子动力学模拟和AI辅助设计, 识别可诱导变构的配体结合口袋以拓展成药位点, 并与PROTAC等靶向降解技术相结合[100]。此外, 将STAT3抑制剂与JAK抑制剂、免疫检查点抑制剂或代谢调节药物联用, 可通过多节点协同阻断关键适应性通路, 抑制旁路补偿和反馈再激活, 克服信号冗余及耐药问题[103]。总体而言, STAT3正逐步从传统认知中的"难以靶向"靶点, 逐步转变为"可精准调控"的转录因子, 其结构药理学研究为开发新一代肿瘤及免疫治疗策略提供了重要的理论支撑。

3.2 p53/MDM2 p53是由*TP53*基因编码的经典抑癌转录因子, 通过调控细胞周期、DNA修复、细胞凋亡及代谢应答等过程, 在维持基因组稳定和抑制肿瘤发生中发挥核心作用[104,105]。然而, p53功能失活在多种恶性肿瘤中普遍存在[106,107]。由于其含有较多柔性区域且缺乏稳定的小分子结合口袋, p53长期被认为是"难以靶向"的转录因子, 目前尚无直接靶向p53的药物获批上市。

当前p53靶向药物的开发主要围绕两类策略: 一是针对*TP53*野生型肿瘤, 通过抑制其负调控因子MDM2以恢复p53功能 (图4B); 二是针对*TP53*突变型肿瘤, 旨在稳定突变体构象或部分恢复其转录活性[108,109]。

在*TP53*野生型肿瘤中, p53的活性常被其关键负调控因子MDM2所抑制。MDM2作为E3泛素连接酶, 可识别p53 N端转录激活区中的关键疏水残基, 并介导其泛素化降解 (PDB: 1YCR)[110]。因此, 阻断p53-MDM2相互作用成为恢复p53功能的重要策略。早期nutlin类抑制剂通过模拟p53的关键疏水残基与MDM2结合 (PDB: 4HG7, 图4B)[111], 从而竞争性占据p53-MDM2互作界面, 维持内源p53转录激活活性。在此基础上, 多种小分子抑制剂进入临床开发。小分子药物idasanutlin (RG7388) III期临床研究未达到主要终点, 提示其临床转化仍受疗效与安全性平衡的限制。相比之下, navtemadlin (KRT-232/AMG 232) 已进入临床III期并在多个适应症中持续推进, 该药物通过优化给药模式、优先靶向*TP53*野生型患者及与JAK抑制剂或其他抗肿瘤药物联用的方式, 提高了该类药物的临床可行性。ALRN-6924 (sulanemadlin) 是首个进入临床阶段的订书肽 (stapled peptide) 类p53激动剂, 该化合物通过稳定的α-螺旋结构模拟p53 N端转录激活区, 与MDM2和MDMX结合, 从而同时阻断两种关键负调控蛋白对p53的抑制作用, 在早期临床中展现出一定潜力, 拓展了界面抑制剂的分子形式 (图4B)。

尽管p53/MDM2界面抑制剂已在结构层面和临床层面验证了其可成药性, 但其疗效高度依赖TP53野生型状态及MDM2通路。此外, p53激活可诱导MDM2表达上调, 形成负反馈回路, 也在一定程度上削弱单药疗效[112]。因此, 研究逐渐由单一的界面阻断策略拓展至降解MDM2的调控模式, 如PROTAC分子KT-253可通过直接降解MDM2蛋白实现对p53通路更长效的激活[113]。

对于*TP53*突变型肿瘤, 研究重点在于开发突变特异性的干预策略。其中, p53 Y220C突变在其DBD内形成一个独特的疏水空腔, 为药物设计提供了明确靶点[114,115]。针对该突变的小分子稳定剂rezatapopt (PC14586, 临床I/II期) 可选择性结合该疏水口袋并稳定突变体构象, 临床试验中已在部分携带Y220C突变的实体瘤患者中显示出抗肿瘤活性[114,115]。三氧化二砷 (arsenic trioxide, ATO) 是治疗急性早幼粒细胞白血病的上市药物, 近年来研究发现ATO可通过结合p53 DBD中的Cys124、Cys135和Cys141三个位点, 稳定p53结构并恢复p53突变体 (如G245S、R249S) 的部分功能 (PDB: 7DHY、7DHZ, 图4B)[116]。进一步研究表明, 通过MDM2靶向的纳米递送系统递送ATO, 不仅能实现肿瘤部位富集, 还能协同阻断MDM2介导的降解, 从而在多种实体瘤模型中显著增强抗肿瘤效果[117]。

总体而言, p53靶向药物研发正由通路调控向结构驱动的药物改造转变。p53-MDM2互作界面的结构解析推动了高亲和力界面抑制剂及降解剂的开发[118], 而特定突变 (如Y220C) 引起的蛋白构象改变则为"不可成药"蛋白提供了药物结合口袋和药物设计方向。未来, 通过整合高分辨率结构信息、动态构象分析与患者分子分型, 有望进一步提升p53/MDM2通路靶向治疗的有效性与选择性。

3.3 MYC/MAX (myelocytomatosis oncogene/MYC associated factor X) MYC/MAX蛋白属于bHLH-LZ (leucine zipper) 转录因子家族, 该蛋白形成异源二聚体后通过识别E-box序列 (5'-CANNTG-3') 调控细胞增殖、代谢重编程及核糖体生物发生等关键过程 (图4C)[119]。结构药理学研究表明, MYC蛋白构象以IDR为主, 仅在与MAX结合并接触DNA时形成相对稳定的构象[120]。由于MYC蛋白缺乏稳定的深结合口袋, 其与MAX及DNA的相互作用界面较为平坦且构象柔性高, 长期以来被认为"难以靶向", 但近年来的研究表明, 通过在转录、翻译、蛋白稳定性以及蛋白–蛋白相互作用等多个层面进行调控, MYC相关干预策略正逐步由间接调控向直接功能抑制和蛋白降解方向发展[121]。

在直接干预MYC/MAX功能的策略中, 基于蛋白或肽类分子的方式取得了更具代表性的进展。Omomyc是一种源自MYC bHLH-LZ结构域的工程化突变蛋白, 可竞争性结合MYC或MAX, Omomyc-MYC或Omomyc-MAX无法有效结合E-box序列, 从而阻断MYC/MAX下游基因的激活 (图4C)[122]。Omomyc衍生物OMO-103是一类可系统给药的迷你蛋白 (分子质量10 kDa), 在I期临床研究中显示出良好的安全性和初步抗实体瘤活性[123]。鉴于MYC在多数肿瘤中更偏向于信号整合节点而非单一驱动靶点, 其抑制效应具有明显的背景依赖性, 因此临床开发逐步聚焦于MYC依赖性更强的肿瘤类型, 如胰腺导管腺癌和骨肉瘤等 (NCT06059001), 以提高该化合物疗效。除OMO-103外, 订书肽类分子IDP-121也已进入临床I/II阶段 (NCT05908409) 用于治疗复发性难治性血液系统恶性肿瘤。该类分子通过稳定α螺旋构象增强其与MYC结构域的结合能力, 从而干扰MYC/MAX相互作用, 并可能伴随促进MYC蛋白降解的效应。

尽管MYC在肿瘤发生中具有核心驱动作用, 但目前仍缺乏有效的直接靶向手段, 相关研究已从直接干预其二聚化和DNA结合逐步转向调控MYC表达水平的间接策略, 包括通过BET (bromodomain and extraterminal)/HDAC (histone deacetylases) 等表观遗传因子抑制转录、靶向CDK9 (cyclin-dependent kinase 9) 等转录延伸机制、干预mRNA翻译及稳定性, 以及利用PROTAC降解其上游调控蛋白, 从多个层面实现对MYC信号的下调[121]。

总体来看, 靶向MYC/MAX异二聚体的药物开发已从早期体外概念验证进入人体临床探索阶段, 但整体仍处于起步期。一方面, 该类靶点缺乏经典小分子结合口袋, 导致传统结构导向药物设计方法受限; 另一方面, MYC在多种组织中具有广泛表达, 其系统性抑制可能带来安全性挑战。此外, MYC驱动肿瘤通常并非单一依赖型通路, 其抑制往往难以产生类似激酶抑制剂那样的深度应答, 这也限制了单药疗效的上限。未来研究需要在提高选择性、优化给药方式和探索联合治疗策略等方面进一步推进, 同时结合结构生物学与蛋白工程技术, 发展更具靶向性的MYC/MAX调控分子。

4 总结与展望

近年来, 结构药理学的快速发展显著推动了转录因子成靶性研究, 为部分长期被认为“难以靶向”的靶点提供了新的研究路径[124]。以核受体为代表的经典转录因子, 依托其相对稳定的配体结合结构域及明确的构象响应机制, 已成功实现从激动剂、拮抗剂到选择性调节剂的系统性药物开发, 构成转录因子靶向治疗中最为成熟的一类模式[12]。相关结构解析不仅阐明了配体依赖的构象调控机制, 也为理性药物设计提供了可靠依据。

在此基础上, 类核受体 (如AHR和HIF) 的结构与功能研究进一步拓展了转录因子可成靶性的边界。其PAS-B结构域中可诱导形成的配体结合腔体, 使得这类蛋白在保持转录调控特性的同时, 具备了通过小分子实现选择性调节的可能性。HIF-2α抑制剂贝组替凡和AHR激动剂本维莫得的成功, 充分证明了类核受体转录因子在药物开发方面具有很高的成药潜力[78,125,126]。

传统上被视为“难以靶向”的转录因子, 如p53、STAT3及MYC等, 近年来也通过多样化的药物设计策略逐步展现出可被靶向的潜力[108,123,127]。转录因子EWS-FLI1 (ewing sarcoma breakpoint region 1-friend leukemia integration 1) 可驱动异常的肿瘤相关转录程序, 该蛋白结构以IDR为主导, 且依赖动态相互作用网络发挥功能, 因而更难被靶向[128]。这类靶点通常缺乏稳定的配体结合口袋, 构象高度柔性, 且主要通过蛋白−蛋白相互作用发挥功能, 限制了经典小分子抑制策略的适用性。近年来, 通过对关键相互作用界面、变构调控位点及复合体装配方式的结构解析, 使得针对这些靶点的干预策略逐渐从单纯占位抑制转向构象调控与事件驱动调节, 为功能干预提供了新的可能。

与此同时, PROTAC及订书肽等肽类分子, 为绕开传统高亲和力结合需求、实现转录因子功能调控提供了补充手段[129-131]。结构药理学技术的进步, 尤其是冷冻电镜与人工智能辅助结构计算工具的结合, 使得动态复合体及多组分体系的构象解析成为可能, 为全面理解转录因子调控机制及药物作用模式提供了更加全面的结构基础[132]。

总体而言, 尽管转录因子靶向治疗仍面临构象异质性、选择性调控及体内递送等多方面挑战, 但随着结构解析、计算模拟及新型干预策略的持续发展, 转录因子正逐步从“难以靶向”的研究对象, 转变为在特定结构与生物学背景下可被精细调控的治疗靶点。未来, 结构药理学有望在转录因子靶向药物的机制阐释与策略优化中发挥持续而关键的支撑作用。

作者贡献: 陈晓宇负责收集综述资料及撰写文章; 庄静静和武大雷负责文章选题及论文指导、修改。

利益冲突: 无任何利益冲突。

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