



转录因子FoxM1在恶性肿瘤中的研究进展

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收稿日期: 2022-11-14; 接受日期: 2023-02-06; 网络版发表日期: 2023-05-25

摘要 叉头框转录因子(Forkhead box M1, FoxM1)是转录因子的一种, 被认为是多种癌症中肿瘤发展、细胞周期进展、侵袭和转移的主要调节因子, 与细胞增殖等过程密切相关. 近些年, 随着人们对FoxM1的关注, 科研人员做出了大量有价值的研究, 对FoxM1的调控和功能了解也逐步加深. 许多学者以其为靶点, 探索关于利用FoxM1的小分子抑制剂作为治疗癌症的新型药物. 本文回顾了有关文献, 系统阐述了FoxM1的基本结构、功能及在不同肿瘤中的作用, 以期对诊断肿瘤性质、评估肿瘤恶性程度、选择新的治疗靶点提供参考.

关键词 转录因子, FoxM1, 恶性肿瘤

叉头框转录因子(Forkhead box M1, FoxM1)是Forkhead超家族的成员之一, 是一种转录因子, 被认为是多种癌症中肿瘤发展、细胞周期进展、侵袭和转移的主要调节因子, 与细胞增殖、自我更新和肿瘤发生等过程密切相关. 多项研究表明, FoxM1的过表达与某些癌细胞中的有氧糖酵解有关^[1,2]. FoxM1通过在转录水平上调节靶基因的表达来维持癌症的某些特征, 在大多数人类癌症中, 其表达升高与不良预后相关^[3]. 有文献报道, 与FoxM1相关的恶性肿瘤包括肺癌^[4]、肝细胞癌^[5]、前列腺癌^[6]和卵巢癌^[7]等. 由于其在癌症治疗中作为分子靶点的潜在作用, FoxM1也被评为2010年的年度分子. 然而, FoxM1失调的机制仍不够

清楚^[8]. 本文对FoxM1的结构功能及在恶性肿瘤中的表达做一综述, 为恶性肿瘤的治疗及判断提供依据.

1 FoxM1结构

FoxM1曾被命名为HNF-3, HFH-11, MPP2, TGT3, INS1, PIG29, FKHL16, MPHOSPH2, LOC2305, 是Forkhead box蛋白超家族的一个转录因子, 该家族具备一个特有的有翼螺旋DNA结合域^[9]. 人类FoxM1蛋白是在海拉细胞系中被首次检测到的, FoxM1基因位于染色体带12p13.33上, 由10个外显子组成, 大小约为25 kb^[10]. 截至目前, 已经发现四种人类FoxM1的异构

引用格式: 李炎宸, 耿瑞璇, 赵珂, 等. 转录因子FoxM1在恶性肿瘤中的研究进展. 中国科学: 生命科学, 2023, 53: 1239–1246

Li Y C, Geng R X, Zhao K, et al. Research progress of transcription factor FoxM1 in malignant tumors (in Chinese). Sci Sin Vitae, 2023, 53: 1239–1246, doi: [10.1360/SSV-2022-0131](https://doi.org/10.1360/SSV-2022-0131)

体, 由外显子Va和VIIa的差异剪接产生. FoxM1a同时含有外显子Va和VIIa, 缺乏反式激活活性, 而FoxM1b(既不含外显子Va也不含VIIa)、FoxM1c(不含VIIa)和FoxM1d(不含Va)具有转录活性. FoxM1蛋白有三个明确的结构域: 一个保守的叉头DNA结合域(DNA-binding domain, DBD)、一个N端抑制域(N-terminal repressor domain, NRD)和一个C端反式激活域(C-terminal transactivation domain, TAD). TAD的反式激活活性可通过与NRD的直接相互作用被抑制^[11,12].

2 FoxM1功能及作用

FoxM1是许多生物过程和组织的重要调节因子, FoxM1失调可以显著促进肿瘤发生和癌症进展. 在静止期的细胞中, FoxM1几乎不表达; 而在某些恶性肿瘤进展过程中, FoxM1则可以刺激肿瘤细胞增殖, 并参与调节与细胞周期相关的多个基因的转录, 从而控制细胞DNA复制与有丝分裂过程^[13], 例如, 在胶质瘤中, FoxM1可通过与其下游靶基因*CEP55*的启动子区结合, 调控*CEP55*表达从而影响胶质瘤细胞增殖、迁移和侵袭能力^[14].

有学者利用蛋白免疫荧光聚焦染色证明了FoxM1的基因缺陷可以干扰RNA转录从而增加DNA损伤, 并可影响DNA双链断裂后的同源重组修复. 这些结果证实了FoxM1在DNA损伤后的转录反应中具有新作用, 并揭示了Chk2蛋白调节DNA修复酶表达的新机制^[15]. 由此可见, FoxM1同时也是DNA损伤修复信号转导过程中不可或缺的因子. 在细胞有丝分裂期间, FoxM1的诱导水平和其他一些细胞周期辅助蛋白类似^[16]. 一些研究表明, 分化的肝细胞可能通过上调FoxM1维持其细胞增殖能力, 也有研究发现FoxM1通过直接转录调控*Ccnb1*进而促进SCs增殖, 此外还发现, FoxM1可通过转录调控*Apc*进而抑制Wnt/ β -catenin信号, 最终维持SCs水平以修复受损骨骼肌^[17].

FoxM1在神经胚胎期的表达强烈上调, 在脊髓、视网膜和颧弓中也发现其表达, 证明FoxM1可能在神经系统发育过程中扮演着重要的角色^[18]. 不仅如此, 小鼠实验证明小鼠肺的发育也依赖于FoxM1转录因子, 该转录因子调控间充质细胞增殖、细胞外基质重塑和血管生成所必需的基因的表达, 这证实FoxM1在众多组织和细胞类型的增殖过程中具有共同的作用,

并且在器官形成过程中扮演着重要角色^[19], 还有实验证明FoxM1可能具有维持干细胞多能性的作用^[20].

3 FoxM1与恶性肿瘤

3.1 FoxM1与口腔及头颈部恶性肿瘤

FoxM1被认为是潜在的具有临床意义的免疫治疗靶点, 可以有效地预测口腔鳞癌患者的预后^[21]. FoxM1同时被认为是舌部鳞状上皮癌预后的标志物, 可以在临床上用于识别舌部鳞癌患者的不良预后和隐匿性淋巴结转移^[22]. 对于唾液腺恶性肿瘤, 其发生过程中重要的基因和途径还未完全明晰. 在确定其差异表达基因、关键中枢基因、转录因子、信号通路与原发唾液腺恶性肿瘤发病相关的生物学过程中, 发现FoxM1等可以显著调控相关基因, 因此它可能是治疗初级涎腺癌的合适靶点^[23].

FoxM1的持续表达是几乎所有人类癌症的标志, 包括头颈部鳞状细胞癌, 并且Waseem等人^[24]发现, 关键癌基因*FoxM1*在头颈部鳞状细胞癌中的上调. 头颈部鳞状细胞癌部分保留了上皮分化程序, 该程序概括了肿瘤起源组织的胎儿和成人特征, 但因基因改变和肿瘤支持途径而被解除调控. 实验证明, *FoxM1*基因的去除了会导致细胞增殖减少、侵袭减少和更具分化的表型, 证明了FoxM1在头颈部鳞癌异常分化调控中的作用^[25].

Huang等人^[26]发现, 在头颈部癌的患者样本中, Drp1的表达与FoxM1和MMP12的表达呈正相关. Drp1缺失通过下调糖酵解基因影响有氧糖酵解, 而MMP12在Drp1缺失细胞中的过表达有助于恢复葡萄糖消耗和乳酸产生. Drp1可以通过与其启动子结合来调控FoxM1表达, 从而促进MMP12转录, 提示靶向miR-575/Drp1/FoxM1/MMP12轴具有成为预防头颈部癌新疗法的潜力.

3.2 FoxM1与肺部恶性肿瘤

FoxM1亦可作为判断非小细胞肺癌预后的重要分子标志物. Zhang等人^[27]检测了128例非小细胞肺癌组织和细胞系中FoxM1的表达情况, 发现FoxM1在非小细胞肺癌组织和细胞系中高表达, 提示FoxM1的表达与淋巴结状况和TNM分期密切相关, 并对非小细胞肺癌细胞的增殖和侵袭有促进作用.

FoxM1在肿瘤增殖和耐药过程中均发挥重要作用。有学者发现, STAT3/FOXM1/ATG7信号诱导的自噬是一种新的耐药机制^[28]。Wang等人^[29]研究了c-FLIP对非小细胞肺癌细胞FoxM1表达和泛素化水平以及药物敏感性的影响, 并首次发现90例非小细胞肺癌组织中FoxM1和c-FLIP的表达水平均升高且呈正相关。预后分析的生存数据显示, FoxM1和c-FLIP联合检测可能比单独检测预后更准确, 且c-FLIP与FoxM1的高表达与非小细胞肺癌患者的预后不良有关。另外, 他们发现c-FLIP通过抑制FoxM1的泛素化, 从而在转录后水平上调FoxM1的表达。c-FLIP也通过上调FoxM1增加了非小细胞肺癌细胞对硫链丝菌素和奥西替尼的耐药性。这为靶向c-flip-FoxM1轴治疗肺癌的潜在益处提供了实验证据。

3.3 FoxM1与骨和软组织肉瘤

Fan等人^[30]的研究表明, FoxM1可能是骨肉瘤有价值的预后生物标志物。在骨肉瘤组织中, FoxM1的表达水平显著高于非癌骨组织, 因此FoxM1可能是骨肉瘤有价值的预后生物标志物。同时, 蛋白免疫印迹分析显示, 骨肉瘤组织中FoxM1的蛋白水平显著高于非癌骨组织。Kaplan-Meier分析显示, FoxM1高表达对总生存率亦有显著影响。王晓欣等人^[31]通过线性回归分析37例患者骨肉瘤组织中miR-370-3p与FoxM1的表达量变化, 发现骨肉瘤组织中miR-370-3p表达下降、FoxM1 mRNA表达升高。上调miR-370-3p表达及抑制FoxM1表达的MG63细胞的增殖、迁移、侵袭能力均降低。miR-370-3p可能通过靶向抑制MG63细胞FoxM1表达发挥肿瘤抑制作用。吴小军和谢小平^[32]采用免疫组化SP法分别检测FoxM1在96例骨肉瘤组织和30例骨软骨瘤组织中的表达, 也发现FoxM1在骨肉瘤组织中高表达, 这与患者的肺部转移及临床分期等病理特征有关, 且高表达与较差预后相关。在软组织肉瘤中, FoxM1是表达肉瘤驱动蛋白的重要转录因子^[33]。也有研究表明, FoxM1的过度表达可能是影响横纹肌肉瘤的一个预后因素, 并且FoxM1可能是抑制横纹肌肉瘤进展的一个有前景的治疗靶点^[34]。

3.4 FoxM1与肝脏恶性肿瘤

肝细胞癌预后差、复发率高。Egawa等人^[35]报道, FoxM1过表达与肝细胞癌患者临床结局恶化有关, 并

且FoxM1可能是一个预测肝癌预后的生物标志物和一个有前景的治疗靶点。Meng等人^[36]发现, FoxM1在肝细胞生长因子诱导的上皮间充质转化中起关键作用, FoxM1的过表达可以抑制E-钙黏蛋白的表达, 诱导上皮间充质转化的改变, 增加肝癌细胞的侵袭性。Shang等人^[2]的研究结果表明, SLC2A1-AS1通过与转酮醇酶和信号转导及转录激活剂3(signal transducer and activator of transcription 3, STAT3)竞争性结合对GLUT1起调节作用, 并通过STAT3抑制FoxM1的反式激活, 从而导致肝癌细胞FoxM1/GLUT1轴失活。

索拉非尼是治疗肝癌的一线药物, Yan等人^[37]的数据表明, 肝癌细胞的耐药性与AKT/FoxM1信号通路的激活有关, FoxM1在索拉非尼耐药的肝癌细胞中的mRNA和蛋白质水平上都有显著的过表达。FoxM1启动子上存在一个激活蛋白-1结合位点, 位于-608和-618之间。C-jun过度表达与FoxM1的上调有关, C-jun基因去除后, FoxM1水平显著降低, 肝癌细胞对索拉非尼的敏感性增强。此外, AKT的激活有助于C-jun和FoxM1的上调。BEZ-235抑制AKT可显著抑制C-jun和FoxM1的表达, 增强耐药细胞对索拉非尼的体内外敏感性。因此, 靶向FoxM1-KIF4A的治疗轴或许可用于治疗肝细胞癌。

3.5 FoxM1与泌尿系统恶性肿瘤

Kocarslan等人^[38]的免疫组化结果显示, 47例肾透明细胞癌组织中FoxM1蛋白的表达与肿瘤大小、分期、核分级、包膜侵犯、肾周脂肪侵犯和Ki-67表达均显著相关, 而与年龄、性别和有无淋巴结转移无关。在20例非肾透明细胞癌中, FoxM1的过表达与肿瘤大小密切相关。在非肾细胞癌中, FoxM1的表达与其他临床病理参数及Ki-67的表达均无相关性。因此, FoxM1在肿瘤组织中的高表达可以提示肾透明细胞癌的局部侵袭性行为和不良预后。此外, FoxM1还可以鉴别前列腺癌与良性前列腺增生症, 也可以用以评估前列腺癌的危重程度^[39]。

3.6 FoxM1与女性生殖系统恶性肿瘤

Zhang等人^[40]检测了94例卵巢高级别浆液性癌和20例正常输卵管组织中FoxM1和Gli-1的表达, 发现卵巢高级别浆液性癌中FoxM1和Gli-1的阳性表达率均显著高于正常对照组。FoxM1和Gli-1阳性组的5年总生

存率也显著低于FoxM1和Gli-1阴性组。FoxM1和Gli-1蛋白的过表达参与了卵巢高级别浆液性癌的发生发展, FoxM1蛋白表达也是影响卵巢高级别浆液性癌预后的独立因素。Lee等人^[41]发现, FoxM1在乳腺癌组织中呈高表达, 并在某些乳腺癌相关亚型的预后判断中有较大意义。而在宫颈癌中, MIR-216B可通过抑制FoxM1的表达来调节FoxM1相关的信号通路最终抑制癌细胞的增殖^[42]。有学者发现, 小分子抑制剂XST-20可与FoxM1-DNA结合结构域互相作用, 从而有效抑制FoxM1转录活性, 抑制卵巢癌细胞增殖^[43]。

Zhao等人^[44]研究发现, MFAP2在卵巢癌和卵巢细胞中表达上调, 并且与FoxM1和糖酵解相关基因呈正相关。此外, MFAP2还促进细胞增殖、葡萄糖摄取和乳酸生成, 提高卵巢癌细胞的ATP水平、胞外酸化率和氧耗率, 并增加糖酵解蛋白的表达。进一步的机制分析表明, MFAP2促进FoxM1/ β -连环蛋白介导的卵巢癌细胞糖酵解信号转导。MFAP2基因敲除可抑制小鼠卵巢癌移植瘤生长及Ki-67, MFAP2, FoxM1, GLUT1, HK2和 β -catenin的表达。因此, 结果表明MFAP2通过调控FoxM1/ β -连环蛋白信号通路促进卵巢癌细胞增殖和糖酵解, 为卵巢癌糖酵解途径的治疗提供了新的视角。

细胞因子信号转导抑制因子7(suppressors of cytokine signaling 7, SOCS7)可以调节细胞因子信号转导, 参与细胞周期停滞和细胞增殖调控, 可能也参与了肿瘤的发生。SOCS7在高级别浆液性卵巢癌组织中表达降低, 与患者的临床病理特征和总生存期相关, 并可以通过调节HUR和FoxM1抑制高级别浆液性卵巢癌的发生。这提示SOCS7有可能成为卵巢癌, 尤其是高级别浆液性卵巢癌临床治疗的生物标志物^[45]。

FoxM1在乳腺癌中的高表达与预后不良相关。在机制上, FoxM1与CBP结合激活转录, 与Rb结合抑制转录。Kopanjan等人^[46]的观察表明, FoxM1/Rb调控的转录组对乳腺癌侵袭性进展十分重要。Zhang等人^[47]的研究也揭示了USP39-FoxM1轴是乳腺癌细胞增殖的关键驱动因素, 并为靶向USP39-FoxM1轴治疗乳腺癌提供了理论基础。

3.7 FoxM1其他恶性肿瘤

除了上述提到的恶性肿瘤, Takata等人^[48]的研究表明在食管鳞癌中, FoxM1的表达是影响患者预后的

独立因素。在皮肤的鳞状细胞癌细胞中, FoxM1相关基因的去除可以降低高迁移率族AT-Hook的表达^[49]。FoxM1在黑色素肿瘤的化疗耐药中也起到重要作用, 抑制FoxM1的表达或许可以作为晚期黑色素瘤的一种治疗方案^[50]。

袁浩等人^[51]在抑制FoxM1基因表达对甲状腺乳头状癌TPC-1细胞糖酵解途径影响的研究中发现, 在TPC-1细胞中, 慢病毒rLv-hFoxM1转染可明显抑制TPC-1细胞中FoxM1基因mRNA及蛋白水平的表达, 且转染慢病毒rLv-hFoxM1后TPC-1细胞的活性明显下降($P<0.05$), 随着FoxM1基因表达降低, TPC-1细胞的葡萄糖摄取量及乳酸产量均明显下降($P<0.01$), 抑制FoxM1基因后, 其葡萄糖转运蛋白(glucose transporter 1, Glut1)、己糖激酶1(hexokinase isoform 1, HK1)和己糖激酶(hexokinase isoform 2, HK2)含量明显降低。表明抑制FoxM1基因表达能降低甲状腺乳头状癌细胞的糖酵解水平。

4 FoxM1与恶性肿瘤的治疗与展望

FoxM1可以参与细胞周期的调控, 促进细胞增殖, 延缓细胞衰老等过程, 并在众多肿瘤中有较高水平的表达, 在许多人类恶性肿瘤中既是一个促进因子, 也是一个预后指标。通常情况下, FoxM1通过其靶标的转录激活诱导癌症发生, 但FoxM1也可能成为激活其他致癌途径的辅因子^[52]。由于FoxM1的mRNA和蛋白在泛癌中的表达高度相关, FoxM1的过度表达与肿瘤的侵袭性、恶性程度以及对治疗目标的预后直接相关, 选择性调控FoxM1蛋白表达十分重要^[53]。

目前, FoxM1可以作为治疗癌症的潜在靶点, 如在肝癌中, TPX2是转录因子FoxM1的直接靶基因, FoxM1可以直接正向转录调控TPX2。Hh-FoxM1信号轴介导的肝癌细胞增殖依赖于TPX2的表达, 提示FoxM1和TPX2可作为肝细胞癌的潜在预后标志物及治疗靶点^[54]。虽然一些药物和抑制剂已经被证明能在体外有效地抑制FoxM1的活性, 但其还未成功进入临床应用^[55]。这可能是因为对FoxM1的机制了解得不够充分, 对于完整的FoxM1结构也存在一定争议^[56], 因此应对FoxM1的调控进行更加全面的研究。

由于FoxM1影响人类恶性肿瘤的不同病理生理学特征, 包括细胞增殖、迁移、转移、血管生成、化疗

耐药和辐射耐药等^[57], 抑制FoxM1表达的研究思路对新型靶向癌症治疗的发展具有重要影响. 近些年随着人们对FoxM1的关注, 科研人员已经做出了大量有价值的研究, 对FoxM1调控和功能的了解也逐步增加, 目前已知有许多化合物可以直接或间接地与FoxM1蛋白结合, 并阻碍其亲癌活性, 但这些化合物中的大多数仍不够理想^[58].

因此, 当前在FoxM1抑制剂进入临床试验之前, 对其抗肿瘤效果可能还需要进行更深入的临床前研究, 对药物的毒性进行更充分的评估, 目前也只有少数药物被批准用于临床实践^[59-61]. 例如, 硫链丝菌肽能够选择性地抑制增殖细胞中的转录激活因子FoxM1, 在癌症的许多生物学过程中可以调节FoxM1的表达, 是目前最具选择性和最有效的FoxM1化学抑制剂^[62]. 硫链丝菌肽具有很高的抗菌效力, 在恶性肿瘤的治疗中有着较大应用潜力, 但它从未被批准用于人类, 可能是由于其生物利用度非常有限, 而且很难生产和配制^[63]. Jang等人^[64]的研究明确了CDI作为一种抑制FoxM1-DNA相互作用的小分子, 可以抑制乳腺癌患者MDA-MB-231细胞的增殖并诱导其凋亡, 它不仅降低

了FoxM1的mRNA和蛋白表达, 而且还降低了*CDC25b*等下游靶基因的表达. 此外, MDA-MB-231细胞的RNA-Seq转录谱分析表明, CDI降低了FoxM1调节基因的表达. 分子对接和分子动力学模拟结果表明, CDI可能与FoxM1-DBD的DNA相互作用部位结合, 并抑制FoxM1-DBD的功能. 所以, CDI可能是FoxM1-DNA相互作用的有效抑制剂. 高梦圆等人^[65]证明, 小分子抑制剂1-3-51在胃癌细胞中可通过抑制FoxM1及其下游分子Cyclin D1和MMP9等的表达, 进而降低胃癌细胞的增殖、迁移、侵袭能力. Tabatabaei-Dakhili等人^[66]描述了FoxM1-DNA结合域中存在一个药物结合袋, 在这个结合袋中, 抑制剂会解离蛋白质-DNA复合体. 这项研究阐明了FoxM1抑制剂的作用机制, 并为设计新型FoxM1抑制剂提供了基本框架. 鉴于FoxM1在肿瘤发生和发展中的显著作用, 对FoxM1抑制剂的进一步探索或许将是未来几年的热点研究方向.

综上所述, 本文回顾相关研究, 分析FoxM1在不同肿瘤中的作用和表达情况, 可以为人们诊断肿瘤性质、评估肿瘤恶性程度提供理论依据, 也为选择新的治疗靶点、抗肿瘤药物的研制提供新思路.

参考文献

- 1 Cui J, Shi M, Xie D, et al. FOXM1 promotes the Warburg effect and pancreatic cancer progression via transactivation of LDHA expression. *Clin Cancer Res*, 2014, 20: 2595–2606
- 2 Shang R, Wang M, Dai B, et al. Long noncoding RNA *SLC2A1-AS1* regulates aerobic glycolysis and progression in hepatocellular carcinoma via inhibiting the STAT3/FOXM1/GLUT1 pathway. *Mol Oncol*, 2020, 14: 1381–1396
- 3 Li L, Wu D, Yu Q, et al. Prognostic value of FOXM1 in solid tumors: a systematic review and meta-analysis. *Oncotarget*, 2017, 8: 32298–32308
- 4 Wei P, Zhang N, Wang Y, et al. FOXM1 promotes lung adenocarcinoma invasion and metastasis by upregulating SNAIL. *Int J Biol Sci*, 2015, 11: 186–198
- 5 Hu G, Yan Z, Zhang C, et al. FOXM1 promotes hepatocellular carcinoma progression by regulating KIF4A expression. *J Exp Clin Cancer Res*, 2019, 38: 188
- 6 Lin J, Wang W, Hu T, et al. FOXM1 contributes to docetaxel resistance in castration-resistant prostate cancer by inducing AMPK/mTOR-mediated autophagy. *Cancer Lett*, 2020, 469: 481–489
- 7 Parashar D, Nair B, Geethadevi A, et al. Peritoneal spread of ovarian cancer harbors therapeutic vulnerabilities regulated by FOXM1 and EGFR/ERBB2 signaling. *Cancer Res*, 2020, 80: 5554–5568
- 8 Liao G B, Li X Z, Zeng S, et al. Regulation of the master regulator FOXM1 in cancer. *Cell Commun Signal*, 2018, 16: 57
- 9 Clark K L, Halay E D, Lai E, et al. Co-crystal structure of the HNF-3/fork head DNA-recognition motif resembles histone H5. *Nature*, 1993, 364: 412–420
- 10 Korver W, Roose J, Heinen K, et al. The Human *TRIDENT/HFH-11/FKHL16* Gene: structure, localization, and promoter characterization. *Genomics*, 1997, 46: 435–442
- 11 Park H J, Wang Z, Costa R H, et al. An N-terminal inhibitory domain modulates activity of FoxM1 during cell cycle. *Oncogene*, 2008, 27: 1696–1704

- 12 Anders L, Ke N, Hydbring P, et al. A systematic screen for CDK4/6 substrates links FOXM1 phosphorylation to senescence suppression in cancer cells. *Cancer Cell*, 2011, 20: 620–634
- 13 Kim I M, Ackerson T, Ramakrishna S, et al. The Forkhead Box m1 transcription factor stimulates the proliferation of tumor cells during development of lung cancer. *Cancer Res*, 2006, 66: 2153–2161
- 14 Wang Y J. The role and mechanism of FOXM1/CEP55 axis in the development of glioma (in Chinese). Dissertation for Doctoral Degree. Jinan: Shandong University, 2020 [王延俊. FOXM1调控CEP55在胶质瘤发生发展中的作用及其机制研究. 博士学位论文. 济南: 山东大学, 2020]
- 15 Tan Y, Raychaudhuri P, Costa R H. Chk2 mediates stabilization of the FoxM1 transcription factor to stimulate expression of DNA repair genes. *Mol Cell Biol*, 2007, 27: 1007–1016
- 16 Ledda-Columbano G M, Pibiri M, Cossu C, et al. Aging does not reduce the hepatocyte proliferative response of mice to the primary mitogen TCPOBOP. *Hepatology*, 2004, 40: 981–988
- 17 Li L. The role and mechanism of FoxM1 in skeletal muscle development and regeneration (in Chinese). Dissertation for Master's Degree. Chongqing: Southwest University, 2020 [李蕾. FoxM1在骨骼肌发育与再生中的作用及机制研究. 硕士学位论文. 重庆: 西南大学, 2020]
- 18 Pohl B S, Rossner A, Knochel W. The Fox gene family in *Xenopus laevis*: FoxI2, FoxM1 and FoxP1 in early development. *Int J Dev Biol*, 2005, 49: 53–58
- 19 Kim I M, Ramakrishna S, Gusarova G A, et al. The Forkhead Box M1 transcription factor is essential for embryonic development of pulmonary vasculature. *J Biol Chem*, 2005, 280: 22278–22286
- 20 Xie Z, Tan G, Ding M, et al. Foxm1 transcription factor is required for maintenance of pluripotency of P19 embryonal carcinoma cells. *Nucleic Acids Res*, 2010, 38: 8027–8038
- 21 Yang W, Zhou W, Zhao X, et al. Prognostic biomarkers and therapeutic targets in oral squamous cell carcinoma: a study based on cross-database analysis. *Hereditas*, 2021, 158: 15
- 22 Thangaraj S V, Shyamsundar V, Krishnamurthy A, et al. Dereglulation of extracellular matrix modeling with molecular prognostic markers revealed by transcriptome sequencing and validations in Oral Tongue squamous cell carcinoma. *Sci Rep*, 2021, 11: 250
- 23 Bayat Z, Ahmadi-Motamayel F, Parsa M S, et al. Potential biomarkers and signaling pathways associated with the pathogenesis of primary salivary gland carcinoma: a bioinformatics study. *Genomics Inform*, 2021, 19: e42
- 24 Waseem A, Ali M, Odell E W, et al. Downstream targets of FOXM1: CEP55 and HELLS are cancer progression markers of head and neck squamous cell carcinoma. *Oral Oncol*, 2010, 46: 536–542
- 25 Roh V, Hiou-Feige A, Misetic V, et al. The transcription factor FOXM1 regulates the balance between proliferation and aberrant differentiation in head and neck squamous cell carcinoma. *J Pathol*, 2020, 250: 107–119
- 26 Huang T L, Chang C R, Chien C Y, et al. DRP1 contributes to head and neck cancer progression and induces glycolysis through modulated FOXM1/MMP12 axis. *Mol Oncol*, 2022, 16: 2585–2606
- 27 Zhang Y, Qiao W, Shan L. Expression and functional characterization of FOXM1 in non-small cell lung cancer. *Onco Targets Ther*, 2018, Volume 11: 3385–3393
- 28 Lyu X, Zeng L, Shi J, et al. Essential role for STAT3/FOXM1/ATG7 signaling-dependent autophagy in resistance to Icotinib. *J Exp Clin Cancer Res*, 2022, 41: 200
- 29 Wang W, Shang Y, Wang C, et al. c-FLIP promotes drug resistance in non-small-cell lung cancer cells via upregulating FoxM1 expression. *Acta Pharmacol Sin*, 2022, 43: 2956–2966
- 30 Fan C L, Jiang J, Liu H C, et al. Forkhead box protein M1 predicts outcome in human osteosarcoma. *Int J Clin Exp Med*, 2015, 8: 15563–15568
- 31 Wang X X, Liu H Y, Zhu X. Effects of miR-370-3p and FOXM1 mRNA on proliferation, migration, and invasion of human osteosarcoma cells and verification of their targeting relationship (in Chinese). *Shandong Med J*, 2022, 62: 36–40 [王晓欣, 刘红艳, 朱兴. miR-370-3p和FOXM1 mRNA对人成骨肉瘤细胞增殖、迁移、侵袭的影响观察及其靶向关系验证. 山东医药, 2022, 62: 36–40]
- 32 Wu X J, Xie X P. The expression of forkhead box protein M1 in osteosarcoma and its correlation with prognosis (in Chinese). *J Mod Oncol*, 2020, 28: 3063–3066 [吴小军, 谢小平. 叉头框蛋白M1在骨肉瘤组织中的表达及其与预后的相关性. 现代肿瘤医学, 2020, 28: 3063–3066]
- 33 Ke X Y, Chen Y, Tham V Y Y, et al. MNK1 and MNK2 enforce expression of E2F1, FOXM1, and WEE1 to drive soft tissue sarcoma. *Oncogene*, 2021, 40: 1851–1867
- 34 Kuda M, Kohashi K, Yamada Y, et al. FOXM1 expression in rhabdomyosarcoma: a novel prognostic factor and therapeutic target. *Tumor Biol*, 2016, 37: 5213–5223

- 35 Egawa M, Yoshida Y, Ogura S, et al. Increased expression of Forkhead Box M1 transcription factor is associated with clinicopathological features and confers a poor prognosis in human hepatocellular carcinoma. *Hepatol Res*, 2017, 47: 1196–1205
- 36 Meng F D, Wei J C, Qu K, et al. FoxM1 overexpression promotes epithelial-mesenchymal transition and metastasis of hepatocellular carcinoma. *World J Gastroenterol*, 2015, 21: 196–213
- 37 Yan D, Yan X, Dai X, et al. Activation of AKT/API/FoxM1 signaling confers sorafenib resistance to liver cancer cells. *Oncol Rep*, 2019, 42: 785–796
- 38 Kocarslan S, Guldur M E, Ekinci T, et al. Comparison of clinicopathological parameters with FoxM1 expression in renal cell carcinoma. *J Can Res Ther*, 2014, 10: 1076–1081
- 39 Kim M Y, Jung A R, Kim G E, et al. High FOXM1 expression is a prognostic marker for poor clinical outcomes in prostate cancer. *J Cancer*, 2019, 10: 749–756
- 40 Zhang J, Li Z Y, Duan X J, et al. Clinical significance of FOXM1 and Gli-1 protein expression in high-grade ovarian serous carcinoma (in Chinese). *Chin J Oncol*, 2016, 38: 904–908 [张军, 李志艳, 段晓瑾, 等. 卵巢高级别浆液性腺癌组织中叉头框转录因子M1和Gli-1蛋白表达的临床意义. *中华肿瘤杂志*, 2016, 38: 904–908]
- 41 Lee J J, Lee H J, Son B H, et al. Expression of FOXM1 and related proteins in breast cancer molecular subtypes. *Int J Exp Path*, 2016, 97: 170–177
- 42 He S, Liao B, Deng Y, et al. MiR-216b inhibits cell proliferation by targeting FOXM1 in cervical cancer cells and is associated with better prognosis. *BMC Cancer*, 2017, 17: 673
- 43 Zhang Z, Xue S, Gao Y, et al. Small molecule targeting FOXM1 DNA binding domain exhibits anti-tumor activity in ovarian cancer. *Cell Death Discov*, 2022, 8: 280
- 44 Zhao L Q, Sun W, Zhang P, et al. MFAP2 aggravates tumor progression through activating FOXM1/ β -catenin-mediated glycolysis in ovarian cancer. *Kaohsiung J Med Scie*, 2022, 38: 772–780
- 45 Du Y, Xu X, Lv S, et al. SOCS7/HuR/FOXM1 signaling axis inhibited high-grade serous ovarian carcinoma progression. *J Exp Clin Cancer Res*, 2022, 41: 185
- 46 Kopanja D, Chand V, O'Brien E, et al. Transcriptional repression by FoxM1 suppresses tumor differentiation and promotes metastasis of breast cancer. *Cancer Res*, 2022, 82: 2458–2471
- 47 Zhang Z, Liu W, Bao X, et al. USP39 facilitates breast cancer cell proliferation through stabilization of FOXM1. *Am J Cancer Res*, 2022, 12: 3644–3661
- 48 Takata A, Takiguchi S, Okada K, et al. Clinicopathological and prognostic significance of FOXM1 expression in esophageal squamous cell carcinoma. *Anticancer Res*, 2014, 34: 2427–2432
- 49 Ha W, Hinde A, Xie L, et al. Biomarker function of HMGA2 in ultraviolet-induced skin cancer development. *Exp Dermatol*, 2020, 29: 1021–1026
- 50 Ito T, Kohashi K, Yamada Y, et al. Prognostic significance of Forkhead Box M1 (FoxM1) expression and antitumour effect of FoxM1 inhibition in melanoma. *Histopathology*, 2016, 69: 63–71
- 51 Yuan H, Li Y P, Jiang X F, et al. Effect of inhibiting *FoxM1* gene expression on glycolytic pathway in thyroid papillary carcinoma TPC-1 cells (in Chinese). *Cancer Res Prevent Treat*, 2019, 46: 289–293 [袁浩, 李永平, 蒋晓飞, 等. 抑制*FoxM1*基因表达对甲状腺乳头状癌TPC-1细胞糖酵解途径的影响. *肿瘤防治研究*, 2019, 46: 289–293]
- 52 Gartel A L. FOXM1 in cancer: interactions and vulnerabilities. *Cancer Res*, 2017, 77: 3135–3139
- 53 Barger C, Branick C, Chee L, et al. Pan-cancer analyses reveal genomic features of FOXM1 overexpression in cancer. *Cancers*, 2019, 11: 251
- 54 Wang Y T. The critical role of dysregulated Hh-FOXM1-TPX2 signaling in hepatocellular carcinoma cell proliferation (in Chinese). Dissertation for Doctoral Degree. Nanchang: Nanchang University, 2020 [王奕婷. 异常活化的Hh-FOXM1-TPX2信号轴促进肝癌细胞恶性增殖的分子机制. 博士学位论文. 南昌: 南昌大学, 2020]
- 55 Koo C Y, Muir K W, Lam E W F. FOXM1: from cancer initiation to progression and treatment. *Biochim Biophys Acta*, 2012, 1819: 28–37
- 56 Littler D R, Alvarez-Fernandez M, Stein A, et al. Structure of the FoxM1 DNA-recognition domain bound to a promoter sequence. *Nucleic Acids Res*, 2010, 38: 4527–4538
- 57 Halasi M, Gartel A L. Targeting FOXM1 in cancer. *Biochem Pharmacol*, 2013, 85: 644–652
- 58 Borhani S, Gartel A L. FOXM1: a potential therapeutic target in human solid cancers. *Expert Opin Ther Targets*, 2020, 24: 205–217

- 59 Khan I, Halasi M, Patel A, et al. FOXM1 contributes to treatment failure in acute myeloid leukemia. *JCI Insight*, 2018, 3
- 60 Halasi M, Hitchinson B, Shah B N, et al. Honokiol is a FOXM1 antagonist. *Cell Death Dis*, 2018, 9: 84
- 61 Ziegler Y, Laws M J, Sanabria Guillen V, et al. Suppression of FOXM1 activities and breast cancer growth *in vitro* and *in vivo* by a new class of compounds. *NPJ Breast Cancer*, 2019, 5: 45
- 62 Bailly C. The bacterial thiopeptide thiostrepton. An update of its mode of action, pharmacological properties and applications. *Eur J Pharmacol*, 2022, 914: 174661
- 63 Chan D C K, Burrows L L. Thiopeptides: antibiotics with unique chemical structures and diverse biological activities. *J Antibiot*, 2021, 74: 161–175
- 64 Jang W D, Lee M Y, Mun J, et al. CDI exerts anti-tumor effects by blocking the FoxM1-DNA interaction. *Biomedicines*, 2022, 10: 1671
- 65 Gao M Y, Gu J, Luo Y, et al. Anti-gastric cancer effect of a novel small molecule inhibitor 1-3-51 targeting FOXM1 *in vitro* (in Chinese). *J Army Med Univ*, 2021, 43: 798–805 [高梦圆, 古晶, 罗娅, 等. 通过下调FOXM1的新型小分子抑制剂1-3-51抗胃癌细胞的作用. 第三军医大学学报. 2021, 43: 798–805]
- 66 Tabatabaei-Dakhili S A, Aguayo-Ortiz R, Dominguez L, et al. Untying the knot of transcription factor druggability: molecular modeling study of FOXM1 inhibitors. *J Mol Graph Model*, 2018, 80: 197–210

Research progress of transcription factor FoxM1 in malignant tumors

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Forkhead box M1 (FoxM1), is a transcription factor closely related to cell proliferation, the main regulator of tumor development, cell cycle, invasion and metastasis in many cancers. In recent years, much research attention has been drawn to FoxM1, and the understanding of the regulation and function of FoxM1 is gradually increasing. Researchers have explored small molecular inhibitors of FoxM1 as a new type of drug for cancer treatment. This work reviews the relevant literature and systematically expounds on the basic structure and function of FoxM1 and its role in different tumors to provide a reference for diagnosing the nature of tumors, evaluating their malignancy of tumor, and selecting new therapeutic targets.

transcription factor, FoxM1, malignant tumor

doi: [10.1360/SSV-2022-0131](https://doi.org/10.1360/SSV-2022-0131)