·综述·

*HMGB1*基因调控胶质瘤恶性生物学行为研究进展

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【摘要】 胶质瘤因其复杂的生物学特性以及胶质瘤干细胞的干细胞特性,标准治疗后易复发。高迁移率族蛋白1(HMGB1)作为癌基因通过多种不同方式参与调控胶质瘤恶性进展。本文对*HMGB1*基因与胶质瘤预后、肿瘤病理分级、干细胞相关性以及*HMGB1*基因调控胶质瘤方式如非编码RNA途径、细胞自噬途径、肿瘤微环境等进行综述,为胶质瘤的治疗提供参考。

【关键词】 神经胶质瘤; HMGB1蛋白质; RNA,未翻译; 自噬; 肿瘤微环境; 综述

Progress on the regulation of malignant biological behavior of glioma by *HMGB1* gene

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【Abstract】 Glioma is often recurred after standard treatment due to its complex biological characteristics and the presence of glioma stem cells (GSCs). High-mobility group box 1 (HMGB1) can regulate the malignant progression of glioma through a variety of ways as an oncogene. This article reviews the relationship between *HMGB1* gene and the prognosis of glioma patients, tumor pathological grading, GSCs, and the ways including non coding RNA pathway, autophagy pathway, tumor microenvironment, etc., in which *HMGB1* gene regulates glioma, so as to provide the reference for the treatment of glioma.

【Key words】 Glioma; HMGB1 protein; RNA, untranslated; Autophagy; Tumor microenvironment; Review

This study was supported by Ningxia Hui Autonomous Region Natural Science Foundation (No. 2021AAC03313), The Sixth Batch of Young Scientists and Technological Talents Promotion Project in Ningxia Hui Autonomous Region in 2021, Scientific Research Foundation of Ningxia Medical University (No. XM2020087), and Pre-experiment Project of National Natural Science Foundation of People's Hospital of Ningxia Hui Autonomous Region (No. 2021GZRYSY017).

Conflicts of interest: none declared

胶质瘤是临床最常见且最致命的原发性脑肿瘤,予以手术、放疗和替莫唑胺化疗的标准治疗后仍不可避免复发,严重危及生命[1-3]。胶质瘤的确切发病机制尚未阐明,随着分子病理学的发展,其恶性进展除增殖、侵袭、耐药、胶质瘤干细胞(GSCs)及微血管生成外,还与肿瘤微环境(TME)中独特的信息传递和不同类型的表观遗传学征象密切相关,如组蛋白修饰、DNA甲基化、染色质重塑等[4-7],成为胶质瘤治疗的新靶点。高迁移率族蛋白1(HMGB1)是一种高度保守的染色质结合蛋白,可作为DNA伴侣发挥作用,亦是一种分泌蛋白,参与调控细胞损伤,在炎症反应和自身免疫性疾病的发生发展中发挥重要作用[8-10]。近年有研究显示,*HMGB1*基因在

doi:10.3969/j.issn.1672-6731.2024.05.014

基金项目:宁夏回族自治区自然科学基金项目(项目编号:2021AAC03313);2021年第六批宁夏回族自治区青年科技人才托举工程;宁夏医科大学科学研究基金资助项目(项目编号:XM2020087);宁夏回族自治区人民医院国家自然科学基金预实验项目(项目编号:2021GZRYSY017)

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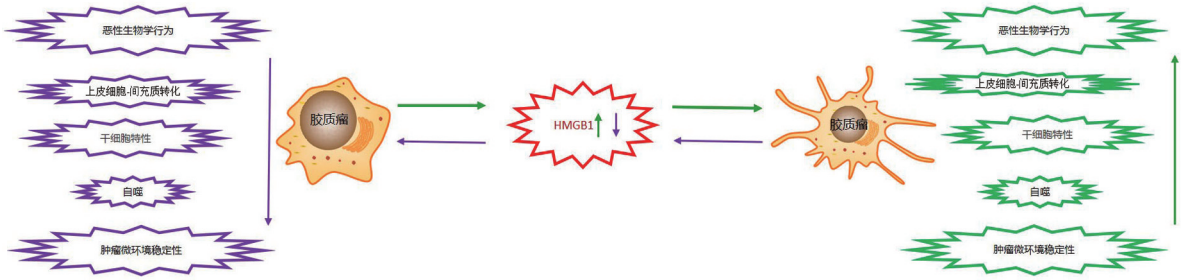

HMGB1，高迁移率族蛋白1

图1 *HMGB1*基因调控胶质瘤恶性生物学行为示意图

Figure 1 *HMGB1* regulates the malignant biological behavior of glioma cells through multiple molecular mechanisms.

多种肿瘤细胞增殖、浸润中起关键作用[11-14]，并经多种途径参与调控胶质瘤恶性生物学行为及进展（图1）[15-17]。本文拟综述*HMGB1*基因在胶质瘤恶性进展中的作用，以为胶质瘤的治疗提供参考。

一、*HMGB1*基因与胶质瘤预后

*HMGB1*基因表达变化与胶质母细胞瘤患者生存和预后呈负相关。Kluckova等[18]检测胶质母细胞瘤患者血清HMGB1、$CD14^+TREM-1^+$和$CD14^+TREM-2^+$细胞水平，Cox回归显示，$CD14^+TREM-2^+$细胞比例越高、患者生存率越高，血清HMGB1水平与$CD14^+TREM-1^+$细胞比例以及TREM-1/TREM-2比值呈负相关。杨如意等[19]对比分析87例胶质瘤患者术后肿瘤标本与20例颅内减压术后脑组织标本HMGB1及其受体Toll样受体4（TLR4）表达变化，发现胶质瘤标本HMGB1和TLR4阳性表达率均高于颅内减压脑组织，且HMGB1水平与TLR4水平呈正相关，二者均随肿瘤级别的增加而升高，而患者生存期则随肿瘤级别的增加而缩短，预后较差。郭丹等[20]的Meta分析亦得出上述结论。周少龙等[21]检测胶质瘤周围组织HMGB1和TLR4表达量，其表达水平越高、患者患癫痫并发症的风险越高、预后越差。然而，HMGB1与胶质瘤患者预后的相关性并未在胶质瘤标准诊断条件下进一步验证。

二、*HMGB1*基因与胶质瘤恶性行为

外源性干预*HMGB1*基因可以调控胶质瘤恶性进展[22-23]。李壮等[24]选取肿瘤基因组学图谱计划（TCGA）数据库中319例样本的*HMGB1*基因测序数据进行差异表达及生存分析，发现*HMGB1* mRNA在肿瘤组织中显著表达上调，且随肿瘤分级（WHO分级）的增加而升高，并与患者预后呈负相关；沉默*HMGB1*基因的胶质母细胞瘤细胞系增殖和侵袭能力下降，且对替莫唑胺的反应更敏感。黄俊强等[25]将*HMGB1*基因小干扰RNA（siRNA）质粒在脂质体介导下转染U373和U87胶质瘤细胞，显示位于S期的细胞比例明显减少，提示*HMGB1*基因表达下调后细胞周期发生S期阻滞，导致胶质瘤细胞增殖、侵袭受到抑制。Zhang等[26]通过糖尿病小鼠构建胶质瘤模型，无论肿瘤植入何部位，高血糖小鼠GL261胶质瘤细胞生长体积均增加，并发现其作用机制为通过上调晚期糖基化终末产物受体（RAGE）及其配体HMGB1表达以及抑制抗肿瘤免疫反应，促进胶质瘤生长。王新军等[27]的裸鼠成瘤实验采用RAGE抑制剂FPS-ZM1干预LN229胶质瘤细胞，发现肿瘤细胞HMGB1表达受到明显抑制，成瘤速度明显减慢。Li等[28]采用重组人HMGB1干预胶质母细胞瘤细胞系和原代细胞，发现HMGB1可通过糖原合成酶激酶-3β（GSK3β）/Snail信号转导通路促进细胞上皮间质转化（EMT），后者是胶质瘤恶性进展的重要因素，并通过激活TLR4/P38/核因子E2相关因子2（Nrf2）信号转导通路介导P62蛋白的过表达，*p62*基因敲低则反向抑制HMGB1诱导的上皮间质转化。李卫玲等[29]采用钾离子通道阻断剂4-氨基吡啶、四乙胺和ATP敏感性钾离子通道阻断剂格列苯脲干预U87和U251胶质瘤细胞，发现肿瘤细胞迁移、侵袭均受到抑制，且HMGB1水平降低。李文涛等[30]构建胶质瘤大鼠模型并进行体外研究，通过感染外源性病毒上调促凋亡基因*TRAIL*的表达，大鼠肿瘤细胞和原代肿瘤细胞HMGB1释放增加，他们还发现，即将凋亡的胶质瘤细胞诱发巨噬细胞释放HMGB1，并通过TLR4刺激成熟树突状细胞（DC）免疫应答肿瘤抗原，形成一定的自我保护，而下调HMGB1表达可诱

发抗肿瘤免疫反应，使大鼠存活期缩短。早期生长反应蛋白1（EGR1）作为胶质母细胞瘤预后的生物标志物，与HMGB1协同作用可以更准确地预测预后，亦可通过诱导HMGB1表达以促进肿瘤细胞侵袭[31]。肿瘤浸润中性粒细胞（TINs）产生的中性粒细胞胞外诱捕网（NETs）通过调节HMGB1/RAGE/白细胞介素-8（IL-8）信号转导通路以介导胶质瘤细胞与肿瘤微环境间的信号转导，靶向抑制NETs生成或IL-8分泌可能是阻止胶质瘤进展的有效途径[32]。HMGB1亦可通过甲基化下调*SASH1*基因的表达，降低整合素β8水平，从而抑制胶质瘤细胞黏附，促进细胞迁移[33]。

三、*HMGB1*基因与胶质瘤干细胞

GSCs的干细胞特性可导致胶质瘤手术后易复发[34]。缺氧环境下，HMGB1在GSCs表达上调，沉默*HMGB1*基因可导致GSCs标志物丢失和自我更新能力减弱；此外，*HMGB1*基因敲除还可抑制RAGE依赖性细胞外信号调节激酶1/2（ERK1/2）信号转导通路激活，抑制GSCs细胞周期改变[35]。GSCs被认为是胶质瘤对替莫唑胺耐药的主要原因之一，即替莫唑胺可以促进GSCs生成，同时HMGB1通过TLR2/NEAT1/Wnt信号转导通路促GSCs生成，HMGB1表达下调时替莫唑胺使GSCs生成受限[36]。Zhang等[37]对比分析放疗后GSCs和胶质瘤细胞凋亡率以及γ-H2AX阳性细胞率，结果发现，经6 Gy放疗后GSCs仍有良好的成球能力，肿瘤细胞凋亡率和γ-H2AX阳性细胞率均较低，而PCAT1在GSCs中表达水平升高，敲低*PCAT1*基因可抑制GSCs成球，加速肿瘤细胞凋亡和DNA损伤；此外，沉默*PCAT1*基因还可通过上调微小RNA-129-5p（miRNA-129-5p）、下调HMGB1抑制肿瘤细胞增殖。Zang等[38]通过腺病毒感染A172和T98G胶质瘤细胞和人原代胶质瘤细胞，结果显示，腺病毒感染使干细胞性标志物水平升高，使被感染肿瘤球的自我更新能力和多谱系分化能力增强；腺病毒感染的肿瘤球在免疫缺陷小鼠中具有更强的异种移植瘤形成潜力；腺病毒通过诱导*TLR9*基因表达上调促进GSCs生成，*TLR9*基因表达下调则使GSCs成球能力下降；此外，髓样分化因子88（MyD88）、总信号转导与转录激活因子3（STAT3）、磷酸化STAT3和长链非编码RNA（lncRNA）NEAT1在腺病毒诱导的GSCs中亦表达上调，敲除*MYD88*基因或抑制*STAT3*、*NEAT1*基因可以减弱腺病毒诱导的GSCs干细胞特性。

四、*HMGB1*基因与胶质瘤非编码RNA

非编码RNA（ncRNA）是不参与蛋白质编码的RNA，主要以癌基因或抑癌基因方式在转录、RNA加工、翻译、表观遗传修饰和翻译后修饰中作为关键调控因子发挥作用[39-40]。目前，胶质瘤领域研究最广泛的有lncRNA、miRNA和环状RNA（circRNA），其中lncRNA占比最高（> 80%），较miRNA具有更大的变异性，且二者之间存在双向调控机制；circRNA高度保守，表达模式具有组织特异性和肿瘤分期依赖性，通常经海绵化miRNA调节基因转录和蛋白质合成[41-42]。

1. 长链非编码RNA　lncRNA异常表达与胶质瘤发生发展密切相关。Chen等[43]发现，*LINC00665*基因在胶质瘤中表达上调，其表达变化与肿瘤直径、WHO病理分级、MRI信号强化、瘤周水肿呈正相关，通过吸附miRNA-129-5p间接升高HMGB1的表达水平，促进胶质瘤恶性进展。Wu等[44]发现*LINC00662*基因可直接与*miRNA-107*基因相互作用，而*HMGB1*基因又是*miRNA-107*基因的已知作用靶点；*LINC00662*基因在胶质瘤中过表达与晚期恶病质和不良预后相关，沉默*LINC00662*基因可抑制胶质瘤细胞增殖、侵袭及其在裸鼠体内的生长，*HMGB1*基因过表达（或*miRNA-107*基因抑制）可以逆转敲低*LINC00662*基因所引起的胶质瘤生长抑制。Tian等[45]在U251和LN229胶质瘤细胞中敲除或过表达*HMGB1*基因，采用逆转录-聚合酶链反应（RT-PCR）和lncRNA芯片筛选发现，*LINC00320*基因变化 > 10倍提示*LINC00320*受HMGB1的调控；细胞核定位的*LINC00320*在体内外均可抑制胶质瘤细胞增殖，新鲜胶质瘤组织中*LINC00320*表达下调提示预后不良。Zhang等[46]发现，lncRNA TP73-AS1（又称TP73-AS1）在胶质瘤及其细胞系中特异性表达上调，而miRNA-142表达下调且与预后不良相关，他们还通过体外研究证实HMGB1/RAGE信号转导通路参与TP73-AS1/miRNA-142对胶质瘤细胞增殖、侵袭的调控，这一过程中TP73-AS1与HMGB1竞争miRNA-142的结合位点，即TP73-AS1通过海绵化miRNA-142上调HMGB1的表达，从而促进胶质瘤细胞的增殖和侵袭。

2. 微小RNA　Zheng等[47]采用RT-PCR法对胶质母细胞瘤和瘤旁组织进行检测发现，肿瘤组织miRNA-339-5p表达量低于瘤旁组织，而瘤旁组织PTP4A1表达量升高；体外培养U251胶质瘤细胞，外

源性上调miRNA-339-5p表达，肿瘤细胞PTP4A1和HMGB1降低，血管样结构减少，提示miRNA-339-5p可通过抑制PTP4A1/HMGB1信号转导通路以抑制U251细胞的血管生成、迁移和侵袭。Cheng等[48]认为，miRNA-505-3p低表达与胶质母细胞瘤患者预后不良相关，过表达则可抑制胶质瘤细胞增殖、迁移和侵袭；体外研究证实，HMGB1是miRNA-505-3p的直接靶点，后者通过靶向抑制HMGB1和蛋白激酶B（PKB）以阻止胶质母细胞瘤进展。Li等[49]报告，miRNA-10b在胶质瘤组织和U87、U251细胞中特异性表达上调，转染miRNA-10b-5p抑制剂可使细胞划痕愈合能力和侵袭性下降，转染miRNA-10b-5p拟似物则呈相反效果，肿瘤细胞侵袭相关蛋白HMGB1、RhoC和基质金属蛋白酶2（MMP-2）水平升高。体外研究结果显示，miRNA-218-5p通过与*HMGB1* mRNA 3'非翻译区（3′UTR）的位点结合下调HMGB1在胶质瘤细胞中的表达，从而抑制胶质瘤细胞增殖、侵袭和迁移，并诱导其凋亡[50]。动物实验显示，miRNA-218-5p通过下调HMGB1表达抑制裸鼠胶质瘤生长；miRNA-142-3p通过与HMGB1 3′UTR结合抑制Wnt/β-catenin信号转导通路关键分子，激活Caspase-3，从而抑制胶质瘤细胞增殖，并诱导其凋亡[51]。Gu等[52]发现，miRNA-218在U251和U87胶质瘤细胞中表达下调，而HMGB1表达上调；转染miRNA-218拟似物可以显著降低肿瘤细胞活性和集落形成，促进细胞凋亡，减少细胞侵袭和迁移，并将细胞阻滞在G0/G1期；miRNA-218可下调HMGB1、RAGE、细胞周期蛋白D1和MMP-9表达，上调Caspase-9表达，沉默*HMGB1*基因后肿瘤细胞RAGE、细胞周期蛋白D1和MMP-9水平升高，而Caspase-9水平下降；HMGB1和miRNA-218共同过表达时胶质瘤生长抑制明显改善，但细胞凋亡增加，而HMGB1和miRNA-218共同抑制时上述作用消除，HMGB1过表达而miRNA-218抑制时肿瘤细胞侵袭性增强。Yang等[53]发现，miRNA-129-2在胶质瘤中表达下调，其主要通过靶向抑制HMGB1而发挥抑制肿瘤生长作用。

3. 环状RNA　circRNA在胶质瘤领域的研究较少，但其功能不可忽视。Tao等[54]采用RT-PCR法检测胶质瘤circFANCL、miRNA-337-3p和HMGB1的表达变化，结果显示，circFANCL在胶质瘤组织和细胞中显著升高，且与预后呈负相关，下调其表达可抑制肿瘤细胞增殖、诱导细胞周期阻滞、促进细胞凋亡，进而抑制胶质瘤生长；同时，circFANCL还可作为miRNA-337-3p的海绵对其进行调控，HMGB1又是miRNA-337-3p的作用靶点，即circFANCL通过调控miRNA-337-3p/HMGB1信号转导通路促进胶质瘤恶性进展。

4. *HMGB1*基因与胶质瘤细胞自噬　自噬是细胞基于细胞质内容物的循环和通过溶酶体降解清除受损分子，从而面对各种刺激维持内环境稳态的关键过程[55]。Lei等[56]采用碳离子束照射U251胶质瘤细胞发现其可诱导细胞凋亡，1 Gy照射24小时后自噬显著增强，随后呈时间和剂量依赖性下降，HMGB1则以时间和剂量依赖性方式释放至细胞外，提高自噬和细胞外HMGB1水平，从而在一定程度上保护自身免受程序性死亡的调控。释放入细胞质的HMGB1定位于内质网或线粒体，与Beclin1或P53结合，内质网蛋白Sigma1-R可调控HMGB1表达，与线粒体结合的HMGB1使线粒体变长，导致"巨型"线粒体形成、线粒体DNA（mtDNA）耗竭和线粒体蛋白质破坏，进而调控自噬[57]。由于胶质母细胞瘤微环境氧含量和营养缺乏，故其具有较高的自噬活性，自噬在胶质母细胞瘤的进展中发挥重要作用[58]。YAP在胶质瘤中过表达，并与HMGB1水平呈正相关，体外研究显示，YAP过表达可增强基础和诱导条件下U251和U87胶质瘤细胞的自噬，以氯喹阻断自噬可消除YAP的促肿瘤生长作用，下调HMGB1表达亦可消除YAP对自噬和胶质瘤生长的促进作用，提示YAP通过增强HMGB1介导的自噬以促进胶质瘤进展，抑制YAP/HMGB1信号转导通路是胶质母细胞瘤可行治疗靶点[59]。

5. *HMGB1*基因与胶质瘤微环境　胶质瘤细胞间通讯依赖肿瘤微环境的稳态，不同的信息传递方式表现出不同功能[60-61]。外泌体是一种源自细胞并介导细胞间通讯的细胞外囊泡，不同类型细胞各有其独特的外泌体进行信息传递[62-63]。Ma等[64]发现，星形胶质细胞外泌体*HMGB1*表达量高于C6胶质瘤细胞外泌体，且从星形胶质细胞中提取的外泌体可升高C6细胞SASH1水平，而自*HMGB1*耗尽的星形胶质细胞中提取的外泌体则无此功能，但在细胞外直接加入重组HMGB1后，SASH1水平下降，提示HMGB1作为细胞外蛋白可下调SASH1的表达，但作为外泌体则可上调SASH1的表达，从而在不同条件下使胶质瘤细胞的病理活动向相反方向发展。Hong等[65]以溶瘤病毒感染胶质瘤小鼠模型和体外

培养的U87胶质瘤细胞，结果发现，感染后肿瘤微环境HMGB1分泌增多，小鼠瘤周脑组织血管渗出和水肿增加，抑制HMGB1表达可提高小鼠存活率。

综上所述，*HMGB1*基因参与基因复制、表达、DNA损伤修复，并积极维持基因组稳定性，通过促进并维持细胞免疫应答在非感染性疾病、炎症、自身免疫性疾病、缺血再灌注、肿瘤微环境免疫调控中发挥重要作用，特别是在胶质瘤中作为癌基因以不同方式参与调控肿瘤恶性进展[66-68]。深入探讨*HMGB1*基因在胶质瘤中的异质性以及研发其特异性药物进行抗肿瘤研究可能是未来研究方向。

利益冲突　无

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（收稿日期:2024-02-15）
（本文编辑:彭一帆）

·小词典·

中英文对照名词词汇(六)

中性粒细胞/淋巴细胞比值
neutrophil-to-lymphocyte ratio(NLR)

肿瘤基因组学图谱计划
The Cancer Genome Atlas(TCGA)

肿瘤浸润中性粒细胞 tumor-infiltrating neutrophils(TINs)

肿瘤微环境 tumor microenvironment(TME)

重症肌无力 myasthenia gravis(MG)

重症肌无力定量评分
Quantitative Myasthenia Gravis Score(QMGS)

周期性肢体运动障碍
periodic limb movement disorder(PLMD)

周围神经过度兴奋综合征
peripheral nerve hyperexcitability syndromes(PNHS)

主要组织相容性复合物
major histocompatibility complex(MHC)

转化生长因子-β transforming growth factor-β(TGF-β)

自然杀伤细胞 natural killer lymphocyte(NK)

自身免疫性脑炎 autoimmune encephalitis(AE)

Miller Fisher综合征 Miller Fisher syndrome(MFS)

阻塞性睡眠呼吸暂停 obstructive sleep apnea(OSA)

阻塞性睡眠呼吸暂停综合征
obstructive sleep apnea syndrome(OSAS)

最小临床表现 minimal manifestation(MM)