·REVIEWS· ·综 述·

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高迁移率族蛋白B1在肿瘤中的作用

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[摘 要] 高迁移率族蛋白B1(high-mobility group box 1，HMGB1)是一种普遍存在于真核细胞中的非组核蛋白。在细胞核内的HMGB1主要参与DNA修复、转录、维持端粒酶的活性以及染色体稳定。释放至细胞核外的HMGB1在细胞的增殖、炎症、血管生成、免疫耐受、免疫逃逸中发挥促肿瘤作用；但又能活化和募集免疫细胞至肿瘤微环境中，诱导肿瘤细胞发生免疫原性细胞死亡，从而发挥抗肿瘤作用。HMGB1在多种肿瘤中异常表达，参与了肿瘤的发生、发展和转移，故推测它可能同时发挥促肿瘤和抗肿瘤的双重作用。

[关键词] 高迁移率族蛋白B1；肿瘤；双重作用

Role of high-mobility group box 1 in cancer

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ABSTRACT High-mobility group box 1 (HMGB1) is a non-histone nuclear protein in most eukaryocytes. Inside the nucleus, HMGB1 plays an important role in several DNA events such as DNA repair, transcription, telomere maintenance, and genome stability. While outside the nucleus, it fulfils more complicated functions, including promoting cell proliferation, inflammation, angiogenesis, immune tolerance and immune escape, which may play a pro-tumoral role. Meanwhile, HMGB1 acts as an anti-tumoral protein by regulating immune cell recruitment and inducing immunogenic cell death (ICD) during the carcinogenesis process. Therefore, abnormal expression of HMGB1 is associated with

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oncogenesis, development, and metastasis of cancer, which may play a dual role of pro-tumor and anti-tumor.

KEY WORDS high-mobility group box 1; tumor; dual role

高迁移率族蛋白B1(high-mobility group box 1，HMGB1)作为真核细胞中高度保守的非组核蛋白参与了肿瘤的发生和发展，其生物学功能与其表达水平及亚细胞分布密切相关。在细胞核中HMGB1可作为DNA分子伴侣参与DNA复制、结合及损伤修复，维持核稳态，同时可通过一系列调节转录途径发挥抗肿瘤作用；释放至细胞外的HMGB1作为一种细胞因子可直接或间接作用于Toll样受体(Toll-like receptors，TLRs)及晚期糖基化终末产物受体(receptor for advanced glycation end products，RAGE)，从而调控肿瘤微环境中的免疫细胞及特定的信号转导通路，包括炎症、增殖、转移、自噬、新陈代谢、细胞凋亡等[1-4]转导通路，提示异常表达的HMGB1可作为一把双刃剑，在肿瘤发生、发展进程中同时发挥促肿瘤和抗肿瘤的双重作用。

1 HMGB1的结构与分布

1.1 HMGB1的结构

HMGB1作为一种高度保守的非组核蛋白由215个氨基酸组成，包含了DNA结合区A盒(1~79氨基酸序列)、B盒(89~163氨基酸序列)及羟基末端结构域(C-tail)(186~215氨基酸序列)。在细胞中C-tail缺失的HMGB1过表达可影响下游基因的转录、翻译和表达。细胞外的结合区B盒具有促炎作用，而A盒则发挥抗炎作用。同时，不同区域的氨基酸序列发挥不同的生物学功能，如7~74氨基酸序列主要与抑癌基因*P53*结合调控靶向基因转录；89~108氨基酸序列与Toll样受体4(Toll-like receptor 4，TLR4)结合促进机体发生炎性反应；150~183氨基酸序列结合RAGE受体引起细胞迁移等[5]。

1.2 HMGB1的分布与功能

HMGB1的不同分布表现出不同的生物学功能，在细胞核中可作为DNA分子伴侣参与DNA复制、结合及损伤修复，维持核稳态[6]，参与调节和维持端粒酶的功能和活性[7-8]，以及一系列靶向基因的转录作用[3]；HMGB1还可通过转录来调节细胞的自噬与凋亡[9]。在细胞质中，HMGB1可作为传感器参与氧化还原反应[10]，调节细胞自噬，并参与免疫逃逸或免疫耐受[9]，此外，它还可通过出胞的方式释放HMGB1[11]。细胞外的HMGB1可调节肿瘤微环境中特定的信号转导通路[12]：1)与RAGE受体结合，诱导细胞凋亡及发生苄氯素1(Beclin-1)依赖的自噬，并能促进肿瘤细胞的侵袭、迁移和生长；2)参与调控树突状细胞(dendritic cells，DCs)诱导的免疫耐受，如与DCs的T细胞免疫球蛋白黏蛋白分子-3(T cell immunoglobulin domain and mucin domain protein-3，TIM-3)结合，降低抗肿瘤免疫，促进肿瘤的发生[13]；3)具有趋药活性，可募集白细胞，增加药物毒性，促进细胞死亡；4)促进自然杀伤细胞(natural killer cell，NK)释放γ干扰素(interferon-gamma，IFN-γ)[14]，从而与其他细胞因子一起发挥协同作用[15]。

2 HMGB1作用的双面性

2.1 HMGB1的抗肿瘤作用

HMGB1的抗肿瘤作用主要表现如下：1)通过影响肿瘤发生、发展中的一系列转录因子发挥作用，如HMGB1能够直接与*P53*作用，从而提高其基因结合力[3, 16]；同时，通过维持染色质结构与稳定来抑制编码肿瘤抗原的癌基因突变，从而阻止针对肿瘤浸润性淋巴细胞(tumor infiltrating lymphocytes，TILs)识别的免疫逃逸的发生[17-18]。2)从死亡细胞中释放的HMGB1，能通过TLR4受体刺激成熟树突状细胞(mature dendritic cells，mDCs)进行抗原提呈，从而促进抗肿瘤免疫反应的发生，同时，胞内HMGB1通过维持基因组稳定来调控自噬，因而可作为抗肿瘤蛋白发挥作用[3]。3)免疫原性细胞死亡(immunogenic cell death，ICD)是来自于肿瘤细胞释放出的死亡细胞抗原刺激机体产生抗肿瘤免疫反应导致的一种细胞死亡方式[19]。有研究[20]证实释放至细胞外的HMGB1与ICD的免疫原性密切相关；不伴随ATP分泌及HMGB1释放的细胞死亡，不能被免疫系统所感知，故可导致局部或者整体的免疫应激反应丧失[21]。化学药物治疗刺激产生的急性ICD可激活免疫系统，从而发生抗肿瘤效应[18,22-25]。4)HMGB1在肿瘤微环境中能够与多种炎性细胞接触，从而产生不同的生物学效应。如HMGB1能够促进基质细胞释放趋化因子配体12(C-X-C motif chemokine ligand 12，CXCL12)进

而引起大量中性粒细胞及DCs趋化至肿瘤微环境中，从而清除浸润的肿瘤细胞[26]。

2.1.1 在肺癌中的抗肿瘤作用

HMGB1在肺癌中具有的抗肿瘤作用如下：1)肺癌发生时HMGB1能够促进DCs的成熟，上调IFN-γ在$CD8^+$ T细胞中的表达；同时HMGB1能够促进趋化因子受体5(C-C motif chemokine receptor 5，CCR5)及趋化因子受体3(C-X-C motif chemokine receptor 3，CXCR3)的表达，从而诱导DCs在肿瘤微环境中的聚集，并且上调IFN-γ，能够提高肿瘤细胞中HMGB1和DCs相关趋化因子(C-C基元)配体5(C-C motif chemokine ligand 5，CCL5)、趋化因子(C-X-C基元)配体10(C-X-C motif chemokine ligand 10，CXCL10)及趋化因子(C-X-C基元)配体11(C-X-C motif chemokine ligand 11，CXCL11)的表达水平。因此，HMGB1-IFN-γ信号通路在DCs介导的抗肿瘤免疫反应中发挥了关键的作用[27]。同时，有研究[28]指出在肺腺癌患者中，HMGB1亦能趋化和增加与TILs有关的DCs至肿瘤微环境，促进肿瘤-DCs-T淋巴细胞的交互作用，从而能够提高非小细胞肺癌患者的生存期及生存质量。2)在使用多西他赛治疗肺癌患者的研究[24]中发现：在肿瘤微环境中HMGB1与CXCL11表达均上调，从而提高了$CD8^+$ T细胞的募集。该研究证实在使用多西他赛治疗非小细胞肺癌患者时通过促进HMGB1与CXCL11的分泌，从而趋化$CD8^+$ T细胞至肿瘤微环境中，可发挥抗肿瘤效应。3)有研究[29]证实在敲除HMGB1后，人肺癌A549细胞的迁移和侵袭能力显著增加，而使用重组人HMGB1对敲除细胞进行治疗时，肿瘤细胞的迁移与侵袭能力明显受到抑制。这项结果也提示HMGB1可通过限制肿瘤细胞的迁移与侵袭能力而发挥抗肿瘤作用。

2.1.2 HMGB1在乳腺癌中的抗肿瘤作用

有研究[30]表明HMGB1能够促进宿主DCs参与肿瘤抗原的提呈作用，HMGB1可作用于DCs的TLR4，因而参与了体内的抗肿瘤T淋巴细胞的交叉致敏。在小鼠和人体中都能观察到坏死的肿瘤细胞释放HMGB1，它能作用于DCs表面的TLR4，从而参与肿瘤抗原特异性T细胞的活化[20]；在乳腺癌中，HMGB1亦可作为肿瘤抑制剂和放射增敏剂。HMGB1与成视网膜细胞瘤基因(retinoblastoma gene，*RB*)的相互作用在HMGB1介导的转录阻抑、细胞生长限制、G_1细胞周期停滞、催生凋亡以及肿瘤生长抑制中发挥作用[31]。研究[32]证实细胞质中HMGB1在三阴乳腺癌以及原癌基因人类表皮生长因子受体2(human epidermal growth factor receptor-2，HER2)阳性乳腺癌中呈高表达，并且在三阴乳腺癌人群中，细胞质中HMGB1的高表达与高组织学分级、大量肿瘤浸润性淋巴细胞以及大量的$CD8^+$细胞浸润具有明显的相关性，提示细胞质中HMGB1参与调控肿瘤浸润性淋巴细胞，发挥抑癌作用。

2.1.3 在结肠癌中的抗肿瘤作用

HMGB1在结肠癌中的抗肿瘤作用报道较少。NK细胞来源的HMGB1可通过诱导代谢性细胞死亡来清除肿瘤细胞，HMGB1可结构性地限制M2型丙酮酸激酶四聚体的形成，可阻断葡萄糖驱动的有氧呼吸，从而导致细胞快速地改变为依赖糖酵解来维持能量[33]。作为NK细胞中表达的一种蛋白，HMGB1通过结合与限制M2型丙酮酸激酶(pyruvate kinase isozyme typeM2，PKM2)而阻断有氧糖酵解的进程，最终引起肿瘤细胞的死亡[33]。

2.2 HMGB1的促肿瘤作用

HMGB1的促肿瘤作用主要表现如下：1)HMGB1和RAGE受体活化后会激活核转录因子κB(NF-kappa B，NF-κB)，从而上调白细胞黏附分子的表达，促进促炎因子和促血管生成因子的生成，从而发挥促癌作用[3]。2)HMGB1参与了肿瘤组织的侵袭与转移，阻断RAGE-HMGB1结合能够限制肿瘤的生长与转移[34]。3)HMGB1参与调节细胞增殖，当其高表达时，调节细胞增殖的癌基因蛋白表达上调，而抑癌基因蛋白表达下调[35]。4)癌细胞释放的HMGB1能够促进抑制性免疫细胞的聚集，从而促进肿瘤的发生、侵袭、转移。例如趋化因子CXCL12在趋化因子(C-X-C基元)受体4(C-X-C motif chemokine receptor 4，CXCR4)的作用下与HMGB1形成复合物，从而趋化肿瘤相关性巨噬细胞(tumor-associated macrophages，TAMs)在肿瘤微环境中发挥促肿瘤作用[16]，而且肿瘤来源的外泌体HMGB1可通过诱导程序性细胞死亡蛋白1的肿瘤相关性巨噬细胞(programmed cell death protein 1 positive tumor-associated macrophages，$PD1^+$TAMs)扩增，从而促进食管鳞癌的进展[36]。5)HMGB1可以促进肿瘤浸润性T细胞表达淋巴细胞毒素α1/β2(lymphotoxin α1/β2，LTα1/β2)，趋化巨噬细胞$CD11b^+F4/80^+$亚群至肿瘤微环境中，分泌生长因子及血管生成因子，从而促进肿瘤生长[37]。6)肿瘤细胞来源的HMGB1还可以通过刺激调节性T细胞(regulatory T cells，Tregs)分泌IL-10来抑制$CD8^+$ T细胞依赖的抗肿瘤免疫，从而形成Tregs介导的免疫耐受[38]。7)HMGB1可调控骨髓来源的抑制性细胞(myeloid-derived suppressor cells，MDSCs)，在不同类型肿瘤中发挥促肿瘤作用[39-45]。MDSCs主要通过产生IL-10抑制$CD4^+$和$CD8^+$ T细胞的抗肿瘤免疫反

应，另一方面还能够降低未活化T细胞归巢受体(L-选择素)的表达，从而加强T细胞从肿瘤微环境中排除，导致免疫治疗的失败[46]。8)HMGB1可诱导肿瘤细胞发生自噬，从而促进肿瘤细胞通过自噬维持自身的存活[41, 47-48]。9)HMGB1亦可通过作用于TIM-3降低抗肿瘤免疫[13]。也有研究[11]指出：HMGB1与肿瘤微环境中浸润的DCs上表达的TIM-3的相互作用能够增强免疫抑制性细胞的作用。10)通过调节性B细胞(regulatory B cells，Bregs)诱导免疫耐受[49]。目前肿瘤微环境中浸润的Bregs已被多个研究[50-51]所证实。

2.2.1 *在肺癌中的促肿瘤作用*

HMGB1在非小细胞肺癌中的阳性表达明显高于正常组织[52]，且体外HMGB1可降低非小细胞肺癌对顺铂的敏感性[53]。研究[54]表明：HMGB1能够促进肺癌细胞在体外的增殖和转移，提示HMGB1的表达与肺癌的进展有明显的相关性；也有研究[55-57]显示：HMGB1能够通过依赖NF-κB途径上调基质金属蛋白酶-2(matrix metalloproteinase-2，MMP-2)的表达和活化，促进肺癌细胞的侵袭与转移，同时HMGB1亦能够通过TLR4/NF-κB信号活化整合素αvβ3/局部黏着斑激酶(focal adhesion kinase，FAK)通路而提高肿瘤细胞的迁移性，导致非小细胞肺癌发生转移；HMGB1调控的自噬参与了肺腺癌对多西他赛抵抗，抑制或者限制HMGB1的细胞质异位能够下调自噬和降低肺腺癌细胞对多西他赛的抵抗；HMGB1的高表达与较晚的临床分期(III~IV期)以及基质金属蛋白酶-9(matrix metalloproteinase-9，MMP-9)的表达存在相关性。患者存在较高水平的HMGB1表达往往预示着较差的临床预后，同时体外实验[58]证实：在高表达HMGB1的人非小细胞肺癌细胞系(A549与H23)中可观察到较高的MMP-9的表达与较强的癌细胞迁移能力有关。在使用小干扰RNA进行干预时能明显降低MMP-9的表达水平及肿瘤细胞的迁移能力。

2.2.2 *在乳腺癌中的促肿瘤作用*

HMGB1被认为参与了乳腺癌的发生、发展过程，并且能够作为乳腺癌诊断的生物标志物[59]。已有研究[60]证实：HMGB1能够促进MDSCs从骨髓中的分化，抑制NK细胞和$CD4^+$及$CD8^+$细胞的活性，从而促进乳腺癌的发生、发展。乳腺癌细胞分泌的HMGB1能够通过RAGE受体活化成纤维细胞，活化的成纤维细胞可促进乳腺癌细胞的转移[61]。HMGB1通过调节缺氧诱导因子1(hypoxia-inducible factor-1α，HIF-1α)促进血管的形成，从而上调血管上皮生长因子(vascular endothelial growth factor，VEGF)的表达。使用短发夹RNA(short hairpin RNA，shRNA)抑制乳腺癌细胞HMGB1的表达时，可明显限制血管的生成，限制肿瘤细胞的侵袭能力，并且能下调VEGF及HIF-1α的表达，抑制蛋白激酶B(protein kinase B，Akt)的磷酸化，从而可消除HMGB1在乳腺癌中对血管生成及侵袭能力的调控能力[62]。

2.2.3 *在结肠癌中的促肿瘤作用*

磷酸化的HMGB1转移至细胞质，再从细胞中分泌出来，它可通过活化与肿瘤细胞转移有关的基因而参与肿瘤的进展[63]。结肠癌细胞产生的HMGB1能够通过抑制DCs而影响宿主的抗肿瘤免疫[64]。HMGB1不同的氧化还原状态可以调控肿瘤细胞的自噬或者凋亡。还原状态的HMGB1通过作用于RAGE受体来诱导Beclin 1依赖的自噬，从而促进结肠癌细胞对放射治疗和化学药物治疗的抵抗。相反，氧化状态的HMGB1能够增加药物的细胞毒性，从而通过线粒体途径诱导凋亡的发生[65]。也有研究[44]指出：腹部手术损伤会导致大量HMGB1释放至腹腔，从而趋化大量的MDSCs至腹腔，促进结肠癌在术后发生腹腔转移。

4 结 语

HMGB1作为真核细胞中高度保守的非组核蛋白参与了肿瘤的发生、发展，并且在多种肿瘤中可检测到其高表达，提示HMGB1与肿瘤的进展密切相关。HMGB1的生物学功能与其表达水平和亚细胞分布密切相关，体现在其不同的分布表现的功能不同，如HMGB1在细胞核中可作为DNA分子伴侣参与DNA复制、结合及损伤修复，维持核稳态，同时HMGB1能维持端粒酶的功能与活性，且能通过转录调节细胞的自噬与凋亡，提示HMGB1在细胞核中可通过一系列调节转录途径发挥抗肿瘤作用。而释放至细胞外的HMGB1一方面能够促进细胞的增殖、炎症反应、血管生成、诱导免疫耐受和免疫逃逸，从而发挥促肿瘤作用；另一方面，释放至细胞外的HMGB1可活化和募集免疫细胞至肿瘤微环境中，发挥抗肿瘤作用，并诱导肿瘤细胞发生ICD，同时刺激机体在放射治疗和化学药物治疗过程中发生抗肿瘤免疫反应。因此，HMGB1在肿瘤中的调控作用是多方面的，其发挥抗肿瘤作用还是促肿瘤作用与其结构、来源、分布、氧化还原状态等密切相关。

目前大多数研究主要关注于释放至细胞外的HMGB1作为细胞因子参与肿瘤微环境中特定信号转导通路的功能研究，而HMGB1在细胞核中作为非组核蛋白对肿瘤的调控作用没有进一步阐明，这不利于为肿瘤治疗策略提供多层次的理论依据；并且，现有研究更多地关注HMGB1在肿瘤微环境中的促肿

瘤作用，而对其抗肿瘤作用的进一步阐明更有助于深入理解HMGB1在肿瘤进展中功能的复杂性和多面性。

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