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# HMGB1和NF-κB在癌症中的研究进展

**潘志昂，成红军，白兆兆，白鹏伟，达明绪**

甘肃省人民医院肿瘤外科，甘肃 兰州

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## 摘　要

**癌症已成为影响人类健康的重大威胁，癌症患者逐年上升，这也刺激着癌症的研究越发深入。近些年的研究说明癌症与炎症的关系是毋庸置疑的，然而验证的促癌机制仍是众说纷纭。本文从促炎因子高迁移率族蛋白1出发，论述其与经典炎症因子NF-κB共同作用下与癌症的进展、治疗及预后的关系。**

## 关键词

**胃癌，HMGB1，NF-κB，信号通路**

# Research Progress of HMGB1 and NF-κB in Cancer

**Zhiang Pan, Hongjun Cheng, Zhaozhao Bai, Pengwei Bai, Mingxu Da**

Surgical Oncology Department, Gansu Provincial People's Hospital, Lanzhou Gansu

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## Abstract

**Cancer has become a major threat to human health, and the number of cancer patients is increasing year by year, which also stimulates the further research of cancer. Recent studies have shown that the relationship between cancer and inflammation is beyond doubt, but the proven mechanisms that promote cancer remain controversial. Based on the high mobility group protein 1 of proinflammatory factor, the relationship between proinflammatory factor NF-κB and cancer progression, treatment and prognosis was discussed in this paper.**

## Keywords

**Gastric Cancer, HMGB1, NF-κB, Signaling Pathway**

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## 1. 引言

胃癌，常见的消化道恶性肿瘤之一，2020 年全球新发病例显示，全年新发胃癌病例近 109 万，新增死亡病例超 77 万，发病率和死亡率分别位于全球第五和第四。我国作为胃癌大国，2020 全年胃癌新发约 48 万人，死亡约 37 万[1]。胃癌的治疗是以手术为主的综合治疗，且胃癌的预后与诊治时机密切相关，约有 90%早期胃癌患者可通过内镜下或手术切除将生存率延长至 5 年以上，而进展期胃癌即使经过治疗后 5 年生存率也不足 30% [2]，尽管化疗和放疗等其他治疗上有所发展，但众多的胃癌患者仍然面临着预后差、5 年生存率低的情况。研究表明胃癌的复发与转移与其预后密不可分[3] [4]。胃癌的机制是一个多基因参与和多阶段的复杂过程[5]，因此，针对胃癌转移机制的研究一直是一个重点。

## 2. HMGB1 和 NF-κB 的分子结构和生理作用

高迁移率族蛋白 1 (High Mobility Group Box 1, HMGB1)是一种染色体结合蛋白，同时也是一种损伤相关的模式分子。1973 年，Ernest Johns 及其同事 Graham Goodwin 和 Clive Sanders 首次通过 0.35 M NaCl 萃取从小牛胸腺染色质中分离出两组蛋白质[6] [7]，依据其在聚丙烯酰胺凝胶电泳体系中快速迁移速率，分别命名为高迁移率族和低迁移率族。其中高迁移率族即为 HMG 蛋白，通过凝胶进一步的分离 HMG 蛋白可知至少含有两种蛋白，即 HMG-1 和 HMG-2，其中 HMG-1 在 2001 年由 HMG 染色体蛋白命名委员会将其更名为 HMGB1 [8]。HMGB1 由 216 个氨基酸残基构成，形成 2 个 N 端结构域和 1 个 C 端酸性结构域(186~215 aa)，N 端分别由 HMG A 盒(9~79 aa)和 HMG B 盒(95~163 aa)组成。据报道，HMGB1 的促炎活性区域主要定位于 B 盒，而 A 盒具有抗炎的作用，可作为 HMGB1 拮抗剂[9]。HMGB1 在炎症反应中的作用[10]主要可以分为以下几点：① 刺激细胞迁移，促进免疫细胞定位损伤部位；② 促进固有免疫细胞对细菌及其产物的识别；③ 激活固有免疫细胞，产生促炎因子、细胞因子等加重炎症反应；④ 抑制中性粒细胞凋亡，使凋亡的中性粒细胞累积随后再次释放细胞因子。

核因子 κB (nuclear factor kappa-B, NF-κB)由 Rel 同源家族的二聚体蛋白组成[11]，参与了炎症反应、细胞凋亡、生长和增殖、细胞间通讯等诸多功能，是一种功能全面的炎症因子[12]。其中 p65 是 NF-κB 家族中重要的成员之一，相对分子量 65 KD，组成的 P50/P65 异源二聚体是最常见的 NF-κB/Rel 复合体，其含量常常最高，并几乎存在于体内所有细胞中[11]。NF-κB 自 David Baltimore 在 B 细胞肿瘤提取物中被发现以来，众多的研究逐渐的充实了 NF-κB 的生理作用。NF-κB 是 NF-κB/Rel 蛋白家族成员之一，目前在哺乳动物中已发现有 5 种 NF-κB/Rel 蛋白，包括 p50 (又称为 NF-κB1，由前体蛋白 p105 产生)、p52 (又称为 NF-κB2，由前体蛋白 p100 产生)、RelA (p65)，RelB 和 c-Rel。每一个 NF-κB/Rel 蛋白家族成员的 N 端都含有 Rel 同源结构域，包括核定位信号序列、二聚化区域、DNA 结合区和 IκB 结合位点。p65，RelB 和 Rel 的 C 端含有转录激活域，其中富含丝氨酸、酸性氨基酸和疏水性氨基酸，能直接作用于转录元件并激活转录过程。除了 p52 和 p50 外，这些蛋白两两结合成具有 NF-κB 活性的不同转录因子复合物，其中 p65/p50 是存在最广泛且是目前研究最多的二聚体复合物[13]。

## 3. HMGB1 和 NF-κB 与肿瘤

HMGB1 有强大的促炎作用，是器官损伤的关键介质之一[14]和炎症控制的靶点[15]。HMGB1 参与

包括癌症在内的某些生理和病理过程，有研究发现其在前列腺癌和卵巢癌中差异表达[16] [17]。HMGB1在不同分化水平的恶性肿瘤中均有表达[18]，在淋巴瘤[19]和头颈部鳞状细胞癌中表达上调[20]，并有助于头颈部鳞状细胞癌的恶性进展[21]。另有研究指出HMGB1与结直肠癌进展和不良预后相关[22]。

NF-κB的激活途径主要包含经典途径和旁路途径[23] [24]。NF-κB二聚体由两个信号通路激活[25]。其中经典的通路被多种刺激激活，如白细胞介素-1β (IL-1β)、肿瘤坏死因子(TNF)及细菌等[26]。研究指出，NF-κB因子与脓毒血症[27]、克罗恩病[28]、溃疡性结肠炎[29]等炎症过程有关。同时，NF-κB及其信号通路中的大部分激活因子被认为在肿瘤的发生发展中有重要作用[30]。我国一项包含187例卵巢上皮性癌和221例健康志愿者的研究中发现，NF-κB基因与卵巢上皮性癌症的易感性相关[31]。Zhao的研究指出NF-κB信号通路抑制结直肠癌的细胞生长的作用[32]。Arisawa的研究指出在一项包含479例胃癌和880例对照的研究中发现，NF-κB与胃癌易感性有关[33]。Zhang等人的研究发现胃癌中的NF-κB受到C12orf59和CDH11的双向调节，进一步阐述了NF-κB介导的胃癌发生发展信号通路[34]。

## 4. HMGB/NF-κB信号通路与肿瘤

HMGB1作为警报蛋白触发机体的固有防御，NF-κB作为炎症通路修复机体损伤，二者介导的HMGB1/NF-κB信号通路参与了体内多种恶性肿瘤的发生和发展。Xu等发现骨髓间充质来源外泌体可抑制HMGB1/NF-κB信号通路的激活进而降低烟雾性肺损伤的程度[35]。Wang等的研究证实骨肉瘤EMT过程中HMGB1/NF-κB信号通路起关键作用，厚朴碱可抑制其活性并增加骨肉瘤对顺铂化疗的敏感性[36]。另有研究提示，HMGB1/NF-κB信号通路参与了前列腺癌[37]、肝细胞肝癌的EMT过程[38]及线粒体DNA损伤修复[39]。

HMGB1/NF-κB信号通路在多种炎症相关的信号通路中发挥着重要作用，越来越多的研究者意识到HMGB1/NF-κB信号通路在多个癌肿的发生及发展中起关键作用，并通过相关的研究证明了这些作用，HMGB1/NF-κB信号通路有望成为治疗肿瘤的新的靶点，但仍需进一步的研究去完善和证明。

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