Oncological role of HMGA2 (Review)

SHIZHEN ZHANG[1,2], QIUPING MO[2] and XIAOCHEN WANG[1]

[1]Department of Breast Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, Zhejiang 310014; [2]Department of Surgical Oncology and Cancer Institute, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, P.R. China

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Abstract. The high mobility group A2 (HMGA2) protein is a non-histone architectural transcription factor that modulates the transcription of several genes by binding to AT-rich sequences in the minor groove of B-form DNA and alters the chromatin structure. As a result, HMGA2 influences a variety of biological processes, including the cell cycle process, DNA damage repair process, apoptosis, senescence, epithelial-mesenchymal transition and telomere restoration. In addition, the overexpression of HMGA2 is a feature of malignancy, and its elevated expression in human cancer predicts the efficacy of certain chemotherapeutic agents. Accumulating evidence has suggested that the detection of HMGA2 can be used as a routine procedure in clinical tumour analysis.

Contents

Correspondence to: Dr Xiaochen Wang, Department of Breast Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, 158 Shangtang Road, Hangzhou, Zhejiang 310009, P.R. China
E-mail: wangxiaochen@zju.edu.cn

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1. Introduction

The high mobility group (HMG) proteins, which are present in only ~3% of the histone content by weight (1), are novel abundant, heterogeneous, non-histone components of chromatin that were first identified in 1973 (2). The HMG protein family has been classified into three subfamilies: HMGA, HMGB and HMGN, previously known as HMGI/Y, HMG1-2 and HMG14/17, respectively (3). Each of these subfamilies has a unique protein signature and a characteristic functional sequence motif: The 'AT-hook' for the HMGA subfamily, the 'HMG-box' for the HMGB family and the 'nucleosomal binding domain' for the HMGN family. Through their respective functional motifs, each can bind to specific structures in DNA or chromatin in a sequence-independent manner. The HMGA subfamily consists of four proteins: HMGA1a, HMGA1b, HMGA1c and HMGA2. The first three members are encoded by the HMGA1 gene through alternative splicing. The latter is encoded by the separate HMGA2 gene. Although HMGA1 and HMGA2 have overlapping structures and functions (1,4), a number of genes are specifically regulated by only one of these, resulting in different roles in cancer (5,6). The distinct functions of the HMGA1 and HMGA2 proteins in human neoplastic diseases have been reviewed previously (7). The human *HMGA2* gene is located at chromosomal band 12q14-15, which contains at least five exons dispersed over a genomic region of ≥140 kb (Fig. 1). The HMGA2 protein encodes 108 amino acid residues, and although this small, non-histone chromatin-associated protein has no intrinsic transcriptional activity, it can modulate gene transcription by altering chromatin architecture (8). The AT-hook motif of HMGA2 is a positively charged stretch of nine amino acids containing the invariant repeat Arg-Gly-Arg-Pro(R-G-R-P) (9), which can bind to B-form DNA and undergo a disordered-to-ordered conformational change during the regulation of gene transcription. Depending on the number and spacing of the AT-rich binding sites in DNA, HMGA2 influences the conformation of combinative DNA substrates in different ways, thereby enhancing or suppressing the transcriptional activity of several human genes, subsequently influencing a variety of biological processes (10).

2. Regulation of the expression of HMGA2

Strict regulation of the expression of HMGA2 is critical for embryonic stem cell development. The dysregulation

of HMGA2 in adult somatic cells renders them prone to tumourigenesis, and mutation of the HMGA2-encoding gene is widely observed in a large array of tumours (11). The basal regulation of the HMGA2 gene promoter is controlled by a polypyrimidine/polypurine element, which can be positively or negatively bound by several regulatory elements (12,13). It is suggested that transforming growth factor (TGF)β induces the transcription of HMGA2, and it is TGFβ-induced Smad4 that directly binds to the HMGA2 promoter during-the regulation of HMGA2 (14). In addition, β-catenin directly binds to the HMGA2 promoter and leads to upregulation of the expression of HMGA2 (15). Runt-related transcription factor 1 binds to the HMGA2 promoter and regulates HMGA2 promoter activity in a cell-type-dependent manner (16). MicroRNAs (miRNAs) are small, 21-25 nucleotide lengths of non-coding RNAs, which post-transcriptionally repress specified messenger RNAs by binding to the 3' untranslated region (UTR) of their targets (17). Let-7 is one of the founding members of the miRNA family that can directly bind to the 3'-UTR of the human HMGA2 gene, resulting in the repressive expression of HMGA2 (18). Inhibition of the expression of HMGA2 by exogenous Let-7 impairs tumour cell proliferation, and Let-7 can be packaged and released via exosomes by tumours cells, thereby inducing a high expression of HMGA2 in tumour cells (19). By contrast, a decrease in the expression of Let-7 by oncostatin M treatment has been shown to cause the expression of HMGA2 to be rapidly elevated, resulting in enhancement of the invasiveness and metastasis of breast cancer (20). Therefore, Let-7 is accepted as an upstream inhibiting factor targeting HMGA2. In addition, Lin-28, an embryonic stem cell-specific protein, serves as a competitor RNA that can mimic the binding site of Let-7 and prevent the Let-7 precursor from being processed to mature miRNAs by inducing terminal uridylation and degradation of Let-7 precursors. Therefore, the overexpression of Lin-28 impairs Let-7 function and derepresses the expression of HMGA2 (21). The Lin28-Let-7-HMGA2 axis is a critical regulatory system for maintaining an undifferentiated state in cancer cells (18,22,23). Raf-1 kinase inhibitory protein (RKIP) is a member of the evolutionarily conserved phosphatidylethanolamine-binding protein family that is poorly expressed in tumour cells. It has been shown that RKIP negatively modulated Raf-1/MEK/ERK1/2 cascade activity and subsequently impaired the Lin28/Let-7/HMGA2 axis, thereby inhibiting the transcription of HMGA2 (24,25). Several other miRNAs, including miRNA (miR)-33b, miR-145, miR-9, miR-93 and miR539, have also been reported to be involved in the regulation of HMGA2 (26-30). Furthermore, long non-coding RNAs (IncRNAs) are also likely to affect the expression of HMGA2 (31). RPSAP52 is an antisense lncRNA transcribed from the HMGA2 locus, and it can form an R-loop at the promoter of HMGA2, thereby improving accessibility to the transcription machinery (31,32).

3. Expression of HMGA2 in cancer

Notably, HMGA2 is expressed in pluripotent embryonic stem cells during embryogenesis, but is absent or present only at low levels in adult tissue cells (33). However, HMGA2 is re-expressed in human malignancies, indicating that HMGA2 may be essential in development and carcinogenesis. Heterozygous $HMGA2^{-/+}$ mice and homozygous $HMGA2^{-/-}$ mice exhibit a pygmy phenotype, with a body size of 80 and 40% of wild-type littermates, respectively, due to a reduction in cell growth (33). A common variant of HMGA2 is associated with human growth height (34), and HMGA2 disruption may lead to foetal growth restriction (35). Several experimental models have shown the potent neoplastic transforming ability of HMGA2. Full-length HMGA2 transgenic mice and truncated HMGA2 transgenic mice produce a similar benign mesenchymal neoplastic phenotype, including fibroadenomas of the breast and salivary gland adenomas (36). Transgenic mice carrying wild-type HMGA2 genes develop pituitary adenomas (8). When fibroblast cells with ectopic overexpression of HMGA2 are injected into athymic nude mice, fibrosarcomas are formed and develop distant metastases (4). Transgenic mice bearing the human HMGA2 gene under the control of the VH promoter/Eμ enhancer suffer from precursor T-cell lymphoblastic leukaemia (37). Therefore, the dysregulation of HMGA2 may be an important step in the pathogenesis of malignancies. Furthermore, the dysregulation of HMGA2 in different human tumour tissues suggests the role of carcinogenesis. Non-random chromosomal translocations (38) lead to the overexpression of HMGA2 in several types of mesenchymal tumour, including conventional and intramuscular lipomas, well-differentiated and dedifferentiated liposarcoma, benign fibrous histiocytomas, nodular fasciitis and aggressive angiomyxoma (39). In addition, it has been suggested that the overexpression of HMGA2 in human epithelial malignancies is correlated with a highly malignant phenotype and poorer survival rates (Table I). The same phenomenon is seen in acute myeloid leukaemia (40). To illustrate, HMGA2 immunoreactivity is observed in primary colorectal cancer cells and metastatic colon cancer to liver, but not in the adjacent normal colorectal epithelium. HMGA2 also correlates positively and significantly with distant metastasis and poor survival rates, which support the use of HMGA2 as a potential diagnostic and prognostic tumour marker (41).

4. HMGA2 influences the cell cycle of cancer cells

Cell proliferation requires precise progression of the cell cycle, and an uncontrolled cell cycle gives rise to malignant behaviour, which is responsible for neoplastic transformation. As the overexpression of HMGA2 promotes cancer cell proliferation, HMGA2 is considered to affect cancer cell cycle progression (Fig. 2). The knockdown of HMGA2 causes G1 arrest in ovarian cancer cells (42) and G2/M arrest in leukaemia cells (43). HMGA2 directly binds to the cyclic AMP-responsive element of cyclin A2, which displaces $p120^{E4F}$-containing complexes from cyclin A2, thus inducing the expression of cyclin A2 and contributing to cell cycle progression (44,45). The transcription factor activator protein-1 (AP1) complexes, composed of members of Jun proteins (JUN, JUNB and JUND), FOS proteins (FOS, FOSB and FRA1) and FRA2, are critical in the regulation of cell proliferation (46). In HMGA2-deficient cells, the expression of JUNB and FRA1 are completely inhibited (47). By contrast, these genes are upregulated correspondingly when HMGA2 is ectopically overexpressed (47). HMGA2 also enhances the expression of cyclin A2 by promoting AP1

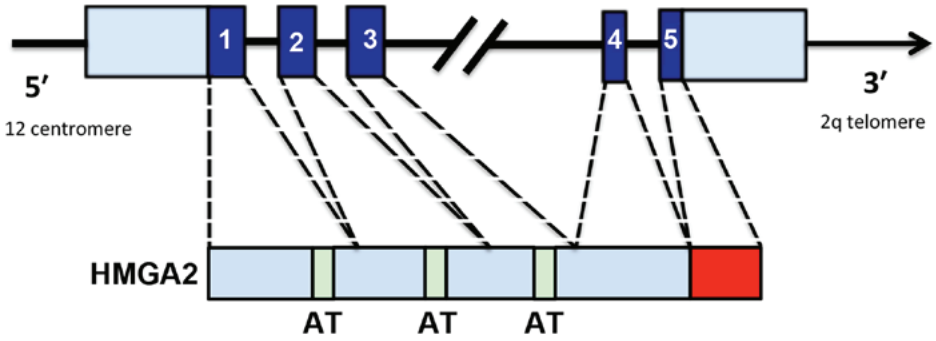

Figure 1. General characteristics of HMGA2 genes and proteins. The HMGA2 protein is composed of 108 amino acid residues. This protein contains three basic domains of AT-hooks, which can bind DNA in the minor groove, and an acidic carboxy-terminal region, the function of which remains unclear. The human HMGA2 gene is located at the chromosome band 12q13-15, spans >140 kb and consists of five exons, all of which encode the HMGA2 protein. Each of the first three exons codes for an AT-hook domain, whereas the fifth exon codes for the acidic C-terminal tail (red box). HMGA2, high mobility group A2.

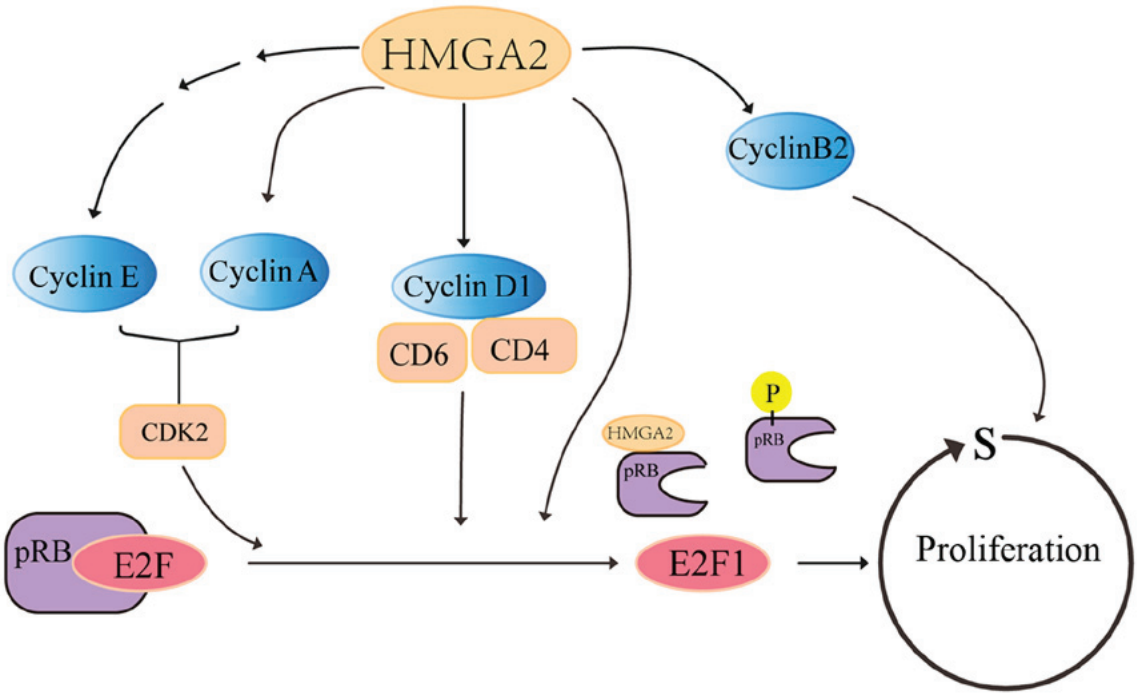

Figure 2. Overexpression of HMGA2 promotes cancer cell proliferation. The activation of cyclin A, cyclin D1 and cyclin E enhanced by HMGA2 initiates the phosphorylation of pRB, leading to the release of E2F transcription. HMGA2 directly promotes the activation of E2F1 by displacing histone deacetylase 1 from pRB. HMGA2 also enhances the expression of cyclin B2. HMGA2, high mobility group A2; pRB, retinoblastoma protein; S, synthesis phase).

transcriptional induction (47). As a tumour suppressor protein, retinoblastoma protein (pRB) strictly controls cell cycle entry into the S phase through its interactions with the E2F1 transcription factors (48). Before cells enter the S phase, pRB is phosphorylated and inactivated to release E2F1, resulting in cell cycle progression (49). It is suggested that HMGA2 displaces histone deacetylase 1 from phosphorylation of the pRB or to act directly on the E2F-responsive DNA elements, thereby promoting the activation of E2F1 and resulting in cell cycle progression (50). $P16^{INK4A}$ and $p21^{CIP1/WAF1}$ are two cyclin-dependent kinase inhibitors that are important in restricting cell cycle progression by inhibiting the release of E2F1. The overexpression of HMGA2 directly activates the phosphatidylinositide 3-kinase (PI3K)/AKT/mTOR/p70S6K signalling pathway, and subsequently facilitates cyclin E and suppresses the activity of $p16^{INK4A}$ and $p21^{CIP1/WAF1}$, resulting in cell proliferation (51). The activation of cyclin D1/CDK4/CDK6 is responsible for the phosphorylation of RB. HMGA2 knockout markedly decreases the synthesis of cyclin D1, whereas the ectopic expression of HMGA2 has the opposite effect, suggesting that HMGA2 also regulates cell cycle progression by influencing the cyclin D1/CDK4/CDK6/pRB-E2F1 axis (52,53). In addition, cyclin B2 protein, coded by the ccnb2 gene, is a cell-cycle-dependent protein controlling the G2-M transition (54). The HMGA2 protein is capable of binding to the ccnb2 promoter and enhancing the expression of cyclin B2 to increase cell growth (55).

5. HMGA2 and the DNA damage response

The complete replication of chromosomal DNA is required for maintaining genome stability. However, DNA damage

Table I. Prognostic values of HMGA2 in human cancer.

Author, year	Type	High HMGA2 expression, n (%)	Stage grade correlation	Hazard ratio (95% CI)	Refs.
Zhang *et al*, 2018	Glioma	NG	Positive	DFS 1.40 (1.30-1.42) OS 1.29 (1.23-1.34)	(170)
Qian *et al*, 2009	Pituitary adenoma	39/98 (39)	NG	NG	(168)
Xia *et al*, 2015	Nasopharyngeal carcinoma	54/124 (43.55)	Positive	OS 3.60 (2.16-8.15)	(159)
Belge *et al*, 2008	Thyroid carcinoma	64/64 (100)	NG	NG	(169)
Mito *et al*, 2017	Oesophageal adenocarcinoma	25/91 (27.4)	Positive	NG	(173)
Gunther *et al*, 2017	Laryngeal squamous cell carcinoma	NG	Positive	OS 4.00 (1.18-13.62)	(172)
Gunther *et al*, 2017	Oral squamous cell carcinoma	NG	Positive	TFS 2.88 (1.06-7.84)	(172)
Wend *et al*, 2013	Triple-negative breast carcinoma	47/59 (80)	Positive	OS 2.0	(15)
Wu *et al*, 2016	Breast cancer	135/273 (49.45)	Positive	5-year-OS 1.84 (1.02-3.33)	(133)
Rogalla *et al*, 1997	Breast carcinoma	20/44 (45.5)	Positive	NG	(161)
Di Cello *et al*, 2008	Lung cancer	37/89 (41.6)	Positive	NG	(175)
Sarhadi *et al*, 2006	Lung adenocarcinoma	41/51 (80.4)	NG	NG	(174)
Wang *et al*, 2011	Colorectal carcinoma	102/280 (36.4)	Positive	OS 2.52 (1.37-4.58)	(41)
Lee *et al*, 2014	Intrahepatic cholangiocarcinoma	18/55 (33)	Positive	OS 2.20 (1.12-4.33)	(162)
Zuo *et al*, 2012	Gallbladder adenocarcinoma	64/108 (59.3)	Positive	OS 3.02 (1.58-5.78)	(165)
Lee *et al*, 2013	Hepatoblastoma	15/15 (100)	NG	NG	(166)
Watanabe *et al*, 2009	Pancreatic adenocarcinoma	11/14 (78.6)	Positive	NG	(135)
Hristov *et al*, 2009	Pancreatic ductal adenocarcinoma	55/124 (44.4)	Positive	NG	(163)
Strell *et al*, 2017	Pancreatic ductal adenocarcinoma	253 (56.6)	Positive	1.74 (1.33-2.29)	(176)
Strell *et al*, 2017	Pancreatic ampullary adenocarcinoma	155 (32.7)	Positive	3.12 (2.07-4.70)	(176)
Dong *et al*, 2017	Gastric cancer	180/249 (72.28)	Positive	NG	(145)
Motoyama *et al*, 2008	Gastric cancer	83/110 (75.4)	Not significant	2.00 (1.32-3.15)	(177)
Yang *et al*, 2011	Bladder carcinoma	77/148 (52)	Positive	RFS 3.83 (2.19-6.71) PFS 3.47 (1.43-8.45)	(164)
Na *et al*, 2016	Clear cell renal cell carcinoma	146/162 (90.1)	Not significant	OS 3.12 (1.64-5.90)	(171)
Davidson *et al*, 2015	Ovarian carcinoma	71/100 (71)	Positive	NG	(160)
Baskin *et al*, 2013	Melanoma metas-tases	6/7 (85.7)	Positive	DFS 6.3 (1.8-22.3) DMFS 6.4 (1.4-29.7)	(167)
Marquis *et al*, 2018	Acute myeloid leu-kaemia	80/358 (23.35)	Positive	OS 2.03 (1.36-3.04)	(40)

NG, not given; CI, confidence interval; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; DFS, disease-free survival DMFS, distant metastases-free sur-vival; TSF, tumour-specific survival.

frequently occurs by endogenous and exogenous stimuli and induces a fraction of replication fork arrest in every cell cycle (56). The complex of triple-stranded RecA then forms on the nascent DNA to stabilise forks until the replication is resumed (57,58). HMGA2 can serve as a complement of the RecA complex and create a protective scaffold with branched DNA at arrest forks to reduce replication recovery times (59). In response to the DNA damage response (DDR), an array of DNA repair pathways, such as non-homologous end-joining (NHEJ), base excision repair (BER) and nucleotide excision repair (NER), occur in a multiple-step process (60). HMGA2, as a transcriptional regulation factor, is responsible for the regulation of several DNA repair-related proteins and influences the DNA repair process (Fig. 3). It is reasonable to hypothesise that, during the early stage of carcinogenesis, HMGA2 inhibits DDR, resulting in increased DNA mutation and promoting tumour development. In tumour treatment, HMGA2 protects tumour cells from chemoradiotherapy damage by facilitating the DNA repair process.

6. Dual role of HMGA2 in the regulation of non-homologous end-joining

DNA double-strand breaks (DSBs) are among the most deleterious forms of DNA damage caused by genotoxic agents (61). There are two main repair pathways, the homologous recombination (HR) and the NHEJ pathways, in response to DSBs (62). The NHEJ pathway is the major DSB repair system in homologue absence during the S/G2 phase of the cell cycle (63,64). When DSBs occur in vertebrates, Ku protein binds to the damaged DNA end to form a Ku:DNA complex, serving as a scaffold that not only recruits kinases to the sites of DNA damage but also serves a major role in activating, other PI3K-related kinase family kinases, including ataxia-telangiectasia-mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), respectively (65). Subsequently, the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) associates with Ku in a DNA-dependent manner to form an active DNA-PK holoenzyme (66). The phosphorylation of H2AX is a sensor of DSBs, facilitating the DNA repair process by altering chromatin structure surrounding the DNA lesion and allowing DNA repair proteins to access the damaged regions (67). Finally, DNA ligase IV, X-ray repair cross-complementing 4 (XRCC4) and XRCC4-like factor are recruited for the final joining of the DNA strands (68). As a tumour promotor, HMGA2 causes more spontaneous chromosome aberrations in eukaryotes (69). Li *et al* observed that there were considerably more DNA lesions in cells overexpressing HMGA2 (69). Cells with tetraploidy (4n DNA), a phenotype of NHEJ-impaired cells, are frequently observed in HMGA2-overexpressing cells (70), suggesting that HMGA2 is associated with the NHEJ process. Notably, HMGA2 has been suggested to interact with NHEJ-related proteins and serve as a negative regulator of the DNA-PK pathway, thereby impairing the NHEJ process and rendering cells more susceptible to DNA damage (71). The prolonged presence of DNA-PKcs phosphorylation at Ser-2056 and Thr-2609, and accumulation of γ-H2AX before and after laser damage have been observed in HMGA2-overexpressing cancer cells. The release of DNA-PKcs from DSB sites and the steady-state of the Ku80 complex in the nuclear and DNA ends were significantly decreased when cells ectopically overexpressed HMGA2, indicating that an appropriate NHEJ repair mechanism did not occur in time in the HMGA2-overexpressing cells (72). Additionally, ATM is difficult to activate effectively following doxorubicin treatment in HMGA2-overexpressing cancer cells, which renders cells more susceptible to doxorubicin-induced genotoxicity (73). These observations suggest that HMGA2 has a negative effect in the regulation of NHEJ process, which may specifically render precancerous cells more susceptible to harmful stimuli, but may render cancer cells more sensitive to chemotherapeutics. By contrast, HMGA2 may also promote the NHEJ pathway. A positive feedback loop of ATM activation during the DNA repair process is dependent on the presence of HMGA2, and the phosphorylation of ATM at serine 1981 is reduced in HMGA2-knockout cells in response to DSB, causing cells to be more sensitive to infrared exposure (74). Furthermore, HMGA2 promotes the DNA repair pathway by sustaining the phosphorylation of ATR, also rendering cells more resistant to the genotoxic agent hydroxyurea (75).

7. HMGA2 promotes base excision repair

The base excision repair (BER) system serves a critical role in removing the lesions and mutations of single bases. During the BER process, damaged DNA bases are recognised and removed by DNA glycosylases, such that apyrimidinic/apurinic (AP) sites are formed. These AP sites are then incised by AP endonuclease 1 (APE1) to create 5'-dRP and 3'-OH strand break products. Finally, the single nucleotide gaps are filled by Polβ and the XRCC1/LIG3α complex (76). Of note, HMGA2 possesses intrinsic dRP site cleavage activity residing within the AT-hook 3, and the lysine at the N-terminus of the hook of HMGA2 is responsible for recognizing and cleaving DNA containing AP sites. In addition, HMGA2 can physically interact with APE1 and enhance the BER process, thereby reducing the number of genomic DNA strand breaks and conferring resistance to AP site-inducing genotoxicants (77). Poly(ADP-ribose) polymerase 1 (PARP-1) is a eukaryotic nucleus enzyme that can bind to DNA damage AP sites and DNA strand breaks by zinc-finger of binding of the PARP-1 N-terminal DNA-binding domain, and the C-terminal catalytic domain of PARP-1 is involved in the poly ADP-ribosylation (PARylation) of DNA binding proteins, thus contributing to the DNA damage repair process. HMGA2 has been reported to function as an antagonist of PARP1 inhibitors in human cancer cells (78). Specifically, HMGA2 colocalises and interacts with PARP1 to increase the activity of PARP1. The AT-hooks of HMGA2 are required for PARylation upon DNA damage during BER. As a result, HMGA2 increases cell survival and reduces sensitivity to PARP inhibitors in cancer cells, and targeting HMGA2 in combination with a PARP inhibitor may be a promising therapeutic approach (78).

8. HMGA2 promotes nucleotide excision repair

Nucleotide excision repair (NER) is a main DNA repair pathway when cells confront broad helix-distorting adducts as a result of UV-light or chemical mutagens (79). During NER, the complex

of xeroderma-pigmentosum C (XPC)-RAD23B-centrin 2 initially recognise DNA lesions, following which the TFIIH complex, helicases XPB and XPD, and endonucleases XPG and excision repair cross complementing group 1 (ERCC1)-XPF complex are recruited to lesions in an orderly manner, thus opening the DNA double helix and performing cleavage to remove the aberrant bases (80). Therefore, ERCC1 serves a critical role in the NER pathway, and the high expression of ERCC1 is considered a marker for NER activity (81). A microarray experiment revealed that the ERCC1 gene was transcriptionally regulated by HMGA2. Furthermore, the HMGA2 protein has a high affinity to the ERCC1 promoter, which enhances its expression (82). Luciferase promoter assays showed that the wild-type HMGA2 formed 1:1 stoichiometry binding to the ERCC1 promoter, while the truncated HMGA2 formed 2:1 complexes with ERCC1 but without transcriptional activity (82). Together, HMGA2 may promote the NER pathway by increasing the transcription of ERCC1, resulting in the resistance of cancer cells to chemotherapeutic treatment.

9. Apoptosis

Apoptosis is a crucial process in multicellular organisms, where it eliminates unnecessary and abnormal cells, thereby preventing unwanted immune responses, to maintain a healthy balance between cell survival and cell death (83,84). Tumours deficient in apoptosis are prone to progression and lead to a poor prognosis (85). Inducing the apoptosis of tumour cells is considered an effective way to prevent tumour progression (86). As the 'guardian of the genome', p53 protein is essential for the maintenance of genome stability. This protein induces growth arrest and promotes DNA repair following the appearance of soft DNA damage. Extensive DNA damage induces prolonged activated p53, thereby initiating cellular apoptosis (87). There are two major pathways, the extrinsic pathway and the intrinsic pathway, contributing to apoptosis (88). The interaction between HMGA2 and these two pathways is described in Fig. 4.

10. Dual role of HMGA2 in apoptosis

Considering the malignant property of HMGA2, it is suggested that HMGA2 can prevent tumour cells from undergoing apoptosis and contribute to tumour growth. Accumulating evidence supports that tumour cells with a low expression of HMGA2 present with more apoptosis and growth inhibition compared with HMGA2-overexpressing cells (89-91). However, the mechanism of how HMGA2 regulates cellular apoptosis remains to be fully elucidated to date. The Bcl-2 protein serves as an anti-apoptotic factor that negatively regulates the apoptotic pathway. The knockdown of HMGA2 in epithelial ovarian carcinoma cells enhances cellular apoptosis with decreased expression of Bcl-2 (92). In addition, HMGA2 derepresses the expression of Bcl-2 by inhibiting miR-34a, thereby promoting an anti-apoptotic pathway (91). In thyroid cells overexpressing Bcl-2 by infection with a Bcl-2 retroviral vector, the expression of HMGA2 was correspondingly increased and apoptosis was inversely decreased (93). The PI3K/Akt signalling pathway is always hyperactivated in human cancer, which is a key contributor to resistance to apoptosis (94). Activated Akt is sufficient to inhibit the activation of caspase-9 and Bad, leading to the inhibition of cellular apoptosis (95,96). Notably, HMGA2 can initiate activation of the PI3K/Akt pathway and impair the activation of caspase-9 and Bad, thus suppressing apoptosis (97). Taken together, the above evidence supports that HMGA2 is able to protect cancer cells from apoptosis. However, variations also indicate that the overexpression of HMGA2 may lead to cellular apoptosis. Caspase-2 contributes to the leakage of cytochrome *c* from mitochondria, which is an essential step in apoptosis (98). The ectopic expression of HMGA2 in WI38 cells was shown to significantly induce apoptosis, accompanied by the activation of caspase-2 (99). The HMGA2 protein also promotes apoptosis triggered by O6-methylguanine-induced DNA damage (100). In the process of apoptosis, the phosphorylation of ATR/CHK1 is significantly reduced, and the activation of caspase-9 is repressed by inhibiting HMGA2, which results in the inhibition of apoptosis (101). Otherwise, interrupting the apoptotic pathway by the knockdown of TNF-related apoptosis-inducing ligand-R2 significantly increased the level of let-7 and decreased the expression of HMGA2 (102). Taken together, these findings indicate that HMGA2 serves multifactorial roles in apoptosis, and the anti-apoptotic effect of HMGA2 exacerbates tumour growth and enhances resistance to chemotherapy. However, HMGA2 can also promote apoptosis, and the contradictory results may be associated with the different expression levels of HMGA2 in cells (99).

11. HMGA2 impairs or enhances cellular senescence

Cellular senescence was originally defined as the state of proliferative arrest accompanied by replicative exhaustion of cultured human cells due to the shorter telomere (103). Generally, it is well known that diverse stress-induced senescence is the outcome of DDR (104,105). Developmental senescence is initiated without DDR during embryonic development (106,107). The senescence response serves a pivotal role in maintaining genome integrity and stability, protecting cells with dysfunctional telomeres from malignant transformation (108). From a certain point of view, cellular senescence can be equated to cellular apoptosis, acting as a tumour-suppressive mechanism to remove cells with a mutation (109,110). There are two mainly primary pathways that are governed by proteins p53 and pRB, contributing to the senescence process (111). $p14^{AFR}$ causes premature senescence by neutralizing the ability of MDM2, resulting in p53 stabilization and activation (112,113). The overexpression of $p16^{INK4a}$ induces an allosteric change of CDK4/6, which dephosphorylates the Rb protein (114), leading to cellular senescence (115,116). Notably, HMGA2 is reported to directly bind to the $p14^{AFR}$/$p16^{INK4a}$ locus and negatively regulate the expression of $p14^{AFR}$ and $p16I^{NK4a}$ (117,118), thus restraining the cellular senescence process. $p14^{AFR}$ also acts as an upstream repressor of HMGA2; $p14^{AFR}$ reduces the expression of HMGA2 and results in senescence (119). In addition, miRNA profiling and microarray analysis have revealed that miR-10A and miR-21 are two critical miRNAs that can regulate senescence. The inhibition of miR-10A and miR-21

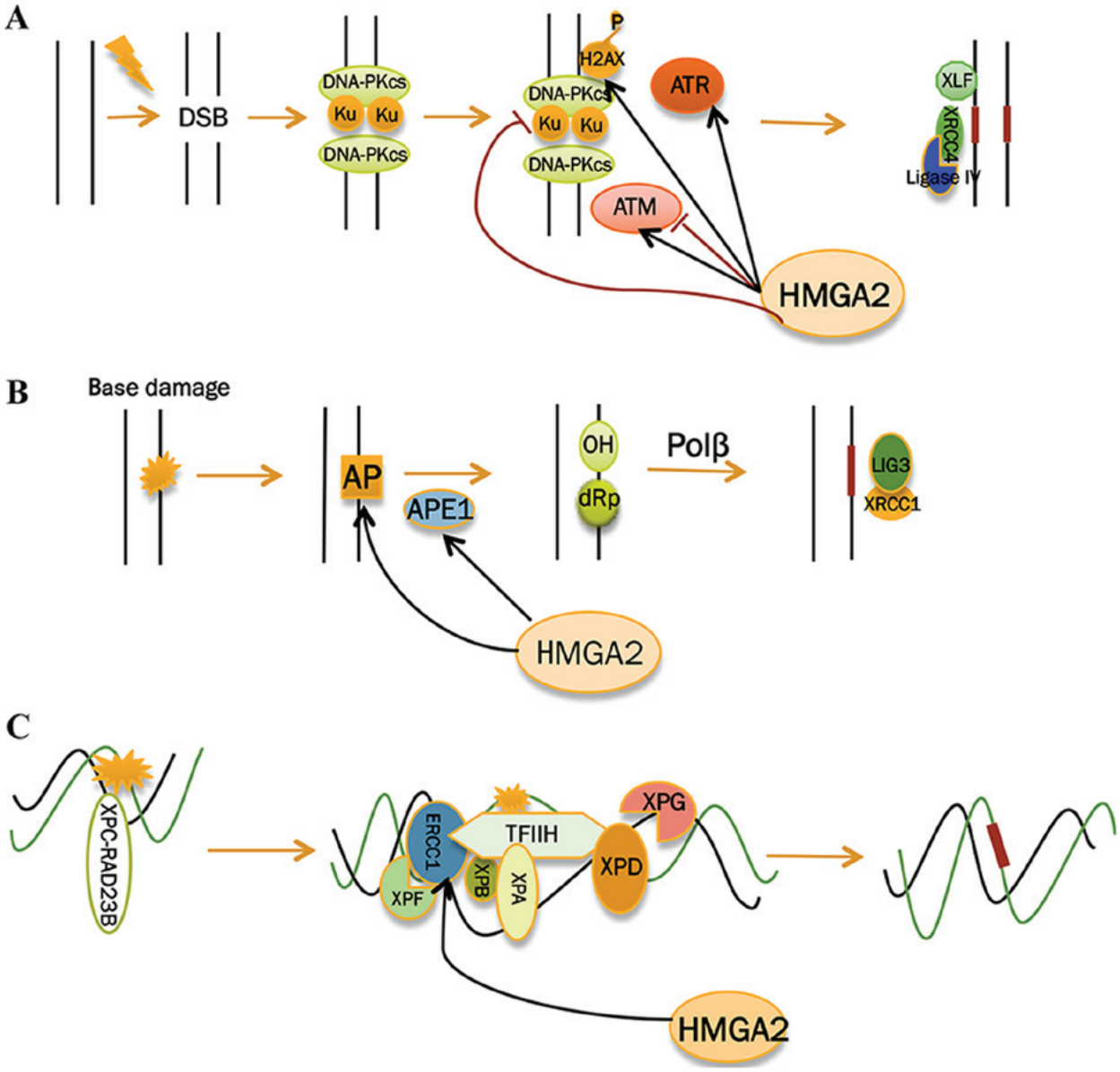

Figure 3. (A) HMGA2 impairs NHEJ via decreasing the Ku80 complex or impeding the activation of ATM, and the persistence of γ-H2AX caused by HMGA2 may represent the ineffective NHEJ. HMGA2 also enhances NHEJ by activating ATM. (B) HMGA2 possesses intrinsic AP site cleavage activity to recognise and cleave DNA containing AP sites. HMGA2 also physically interacts with APE1 to enhance the base excision repair process. (C) HMGA2 has a higher affinity to specifically bind to the ERCC1 promoter and enhance its expression, promoting the NER. HMGA2, high mobility group A2; DSB, double-strand break; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; NHEJ, non-homologous end-joining; ATM, ataxia-telangiectasia-mutated; ATR, ataxia telangiectasia and Rad3-related; APE1, AP endonuclease 1; ERCC1, excision repair cross complementing group 1; XRCC4, X-ray repair cross-complementing 4; XRCC4-like factor; XPC-RAD23BC2, xeroderma-pigmentosum C-RAD23B-centrin 2.

induced the expression of HMGA2, which subsequently led to the downregulation of $p16^{INK4a}$ and senescence-associated β-galactosidase (SA-β-gal), thus rejuvenating senescence (120). In a transgenic mouse model, mouse embryonic fibroblasts (MEFs) from HMGA1/HMGA2-null mice were more susceptible to senescence than MEFs from HMGA1-null mice and wild-type mice, on account of SA-β-gal activity and increased levels of $p16^{INK4a}$ (121). By contrast, HMGA2 has been shown to induced the formation of senescence-associated heterochromatin foci (SAHF) in the nuclei and repress proliferation-associated genes (122,123). The HMGA2 protein colocalises with SAHF by binding to the minor groove of AT-rich DNA, serving as an essential component of SAHF. If the expression of HMGA2 is depleted, SAHF may be dissolved. However, $p16^{INK4}$-knockout did not affect the morphology of HMGA2-induced SAHF, suggesting that HMGA2 is indispensable for senescence establishment and maintenance (123). Furthermore, emerging evidence has indicated that the PI3K/Akt pathway serves a critical role in endothelial senescence (124). AKT protects against stressed-induced premature senescence (125), and suppression of the PI3K/Akt pathway by an Akt inhibitor triggers cellular senescence efficiently (126). Further mechanistic studies have revealed that senescence-induced Akt inhibition is mediated by HMGA2, the colocalization of which to the nucleus into SAHF is required for senescence. The knockdown of HMGA2 significantly decreases the formation of SAHF bodies in response to an Akt inhibitor (127).

12. HMGA2 promotes epithelial-mesenchymal transition

Epithelial-mesenchymal transition (EMT), a process that comprises the transdifferentiation of epithelial cells into motile mesenchymal cells, is important in embryonic development, wound healing, stem cell behaviour and cancer progression (128). The changes in gene expression contributing to repression of the epithelial phenotype and activation of the mesenchymal phenotype involve several master regulators, including Snail1, Snail2, Twist, E47, E2 and zinc-finger E-box-binding transcription factors. During EMT, epithelial proteins, including E-cadherin and zonula 1, are downregulated, whereas mesenchymal proteins, including vitamin and fibronectin, are upregulated (129). The detailed molecular mechanisms of EMT have been reviewed previously (130,131). Accumulating studies have shown that the decrease in epithelial characteristics and enhanced expression of mesenchymal markers accompanied by the overexpression of HMGA2 are present in several cancer cells (132-137), which suggests that HMGA2 is involved in the regulation of EMT. Morishita *et al* suggested that HMGA2 was upstream of the TGFβ/Smads pathway, and the expression of TGFβRII and phosphorylation of Smad3 were significantly increased by HMGA2, which activated the TGFβ pathway and subsequently induced EMT (137). TGFβ signalling in the regulation of EMT also includes non-SMAD pathways, such as the PI3K/Akt signalling pathway. The depletion of HMGA2 represses activation of the PI3K/AKT pathway by attenuating high glucose-induced EMT in HK2 cells (138). Endogenous HMGA2 is essential, but not indispensable, for TGFβ-induced EMT, as the depletion of HMGA2 by RNA interference is not sufficient to completely prevent EMT (14). HMGA2 can form a complex with Smads or directly bind to the critical element of endogenous Twist1 and Snail promoters to induce target protein expression (135,136,139), resulting in EMT (140). Aberrant HMGA2 directly binds to the proximal E-cadherin gene (Cdh1) promoter, together with DNA methyltransferase 3A, which leads to silencing of the expression of E-cadherin, contributing to EMT (141). RAS/RAF/MEK/ERK signalling is another pathway contributing to EMT (142). Treating tumour cells with the MEK1/2 inhibitor U0126, reverses the HMGA2-induced expression of Snail and impairs HMGA2-induced EMT (135). The interaction between HMGA2 and the canonical Wnt signalling is presented at different stages during lung development (143). Upon activation of the canonical Wnt pathway, a β-catenin-T-cell factor transcriptional complex is formed to trigger the EMT, depending on the Axin2-GSK3β-Snail1 axis (139). The Wnt/β-catenin pathway serves an epistatic role in the regulation of HMGA2 (15). The upregulation of HMGA2 and downregulation of WIF1 in HMGA2/WIF1 fusion transcript-expressing cells activates the Wnt/β-catenin pathway (144), suggesting that HMGA2 contributes to EMT via interaction with the Wnt/β-catenin pathway (139). It has been demonstrated that HMGA2 interacts with pRb and enhances E2F1 to bind with the forkhead box protein L2 (FOXL2) promoter, resulting in enhanced transcription of FOXL2 and contributing to EMT (145). Taken together, these data support the function of HMGA2 as a tumour promoter, which can directly or indirectly enhance the formation of EMT (Fig. 5).

13. HMGA2 maintains telomere length

Telomeres are the non-coding DNA sequences located at the ends of the linear chromosomes. The DNA sequence of telomeres is similar in all vertebrates, which is usually a repeat of six bases (TTAGGG) (146). The loss of the coding sequences observed as a result of DNA replication occurring in a semiconservative manner can be prevented from degradation by telomeres. Without telomere restoration, cell senescence and apoptosis are initiated when the limit of the short telomeres is reached (147). Telomerase enzyme, a critical complex for telomere restoration, contains several components, including a catalytic protein subunit telomerase reverse transcriptase (hTERT), human telomerase RNA (hTR), human telomerase-associated protein 1 (hTP1), HSP90, P23 and dyskerin. Almost 90% of cancer cases exhibit of telomerase hyperactivation, which is a critical step in carcinogenesis (148). HMGA2 knockdown in HepG2 cells results in telomere erosion, reducing the tumourigenic ability (149). Furthermore, HMGA2 can directly localise at telomeres and maintain telomere stability (150). The expression of HMGA2 and hTERT are at lower levels in adipose-derived stem cells, and at higher levels in lipoma-derived mesenchymal stem cells (151). However, the mechanism underlying how HMGA2 regulates the expression of hTERT is elusive. It is suggested that HMGA2 derepress H3-K9 hyperacetylation in a protein-to-protein manner, which can subsequently stimulate hTERT activation and promote telomere restoration. TRF2 is a key regulator in telomere protection, it can directly bind to the tandem array of duplex TTAGGG repeats of telomeres, executing its functions in chromosomal end-protection via a two-step mechanism (152). Natarajan *et al* revealed that HMGA2 directly binds to the TRF2 promoter via its AT-hooks and protects telomeres from damage (151).

14. HMGA2 predicts the efficacy of chemotherapy

Chemotherapeutic resistance is one of the main causes of treatment failure in human cancer. In response to chemotherapeutic stimuli, cancer cells initiate a series of mechanisms to protect themselves from death and cause chemoresistance. Tumours with DSB-repair-deficiency exhibit more sensitive to chemotherapies, whereas cancer cells with enhanced DNA repair potential show resistance to chemotherapy agents (153). To the best of our knowledge, HMGA2 can promote DNA repair processes, thereby contributing to cancer chemoresistance (74,75,82). By contrast, HMGA2 can impair the DNA repair system and also cause tumour cells to be more sensitive to chemotherapy (73). Cellular senescence serves a critical role in regulating antitumour effects (110), and tumour defects in cellular senescence result in drug resistance (154). Therefore, HMGA2 causes chemoresistance by inducing cancer cell senescence. The process of EMT can be hijacked by cancer cells, thus contributing to therapeutic resistance. Sunitinib, a tyrosine kinase inhibitor, is widely used in the treatment of renal cell carcinoma, gastrointestinal stromal tumour and lung cancer. It has been reported that cancer cells with a high expression of HMGA2 exhibit increased resistance to sunitinib, partly due to the HMGA2-induced EMT (155). In addition, the collagen-rich microenvironment in human pancreatic ductal adenocarcinoma

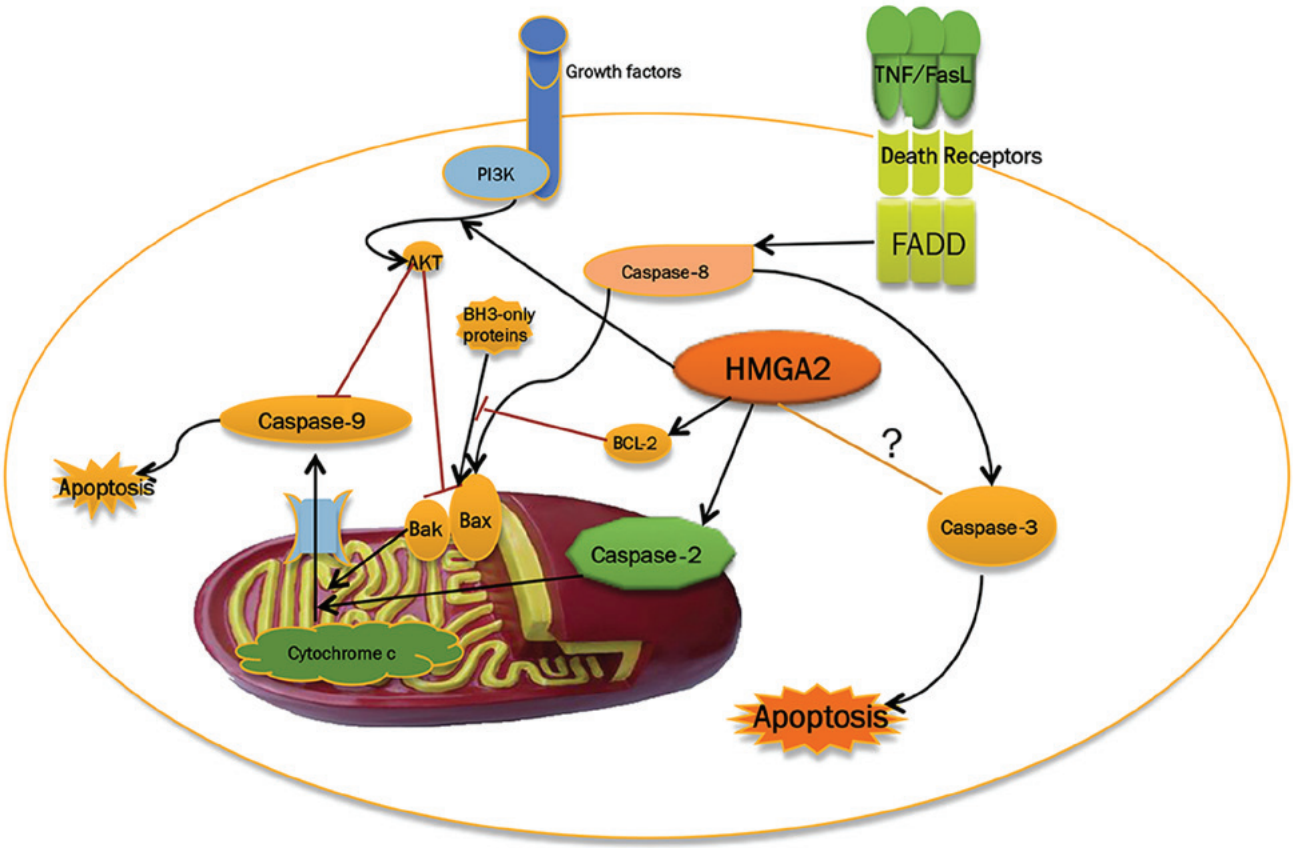

Figure 4. Illustration showing that HMGA2 is engaged in interfering with apoptosis. HMGA2 induces the activation of caspase-2, and causes mitochondrial outer membrane permeabilization to facilitate apoptosis. However, HMGA2 can also activate the PI3K/Akt pathway or promote the expression of Bcl-2, exerting an anti-apoptotic effect. HMGA2, high mobility group A2; PI3K, phosphatidylinositide 3-kinase.

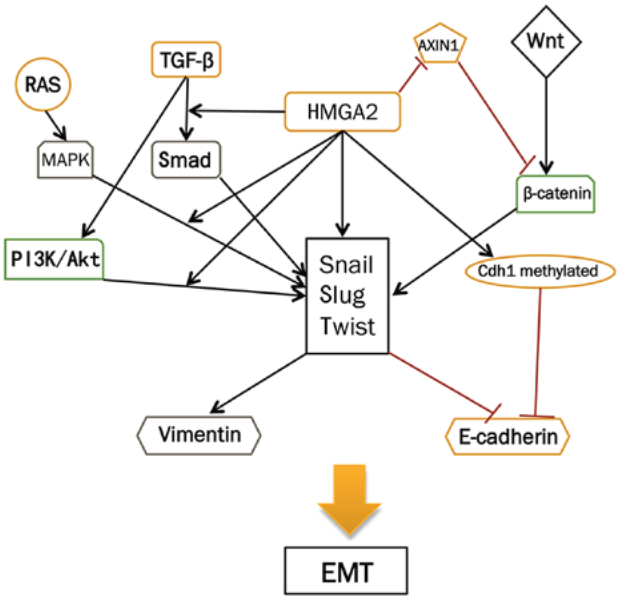

Figure 5. HMGA2 is critical in the promotion of EMT. HMGA2 is involved in promoting EMT by directly or indirectly inducing mesenchymal protein expression and inhibiting epithelial protein expression. HMGA2, high mobility group A2; EMT, epithelial-mesenchymal transition.

increases the expression of HMGA2 through the MT1-MMP pathway (156), and HMGA2 upregulates the expression of HATs to limit the effectiveness of gemcitabine (157). Retinoic acid (RA) is a potent inducer of neuroblastoma (NB) cell differentiation and inhibits NB cell growth, however, the exogenous expression of HMGA2 is associated with a phenotype that is resistant to RA (158). With increasing understanding of the association between the expression of HMGA2 and the efficacy of chemotherapy, detecting the expression of HMGA2 in cancer patients may help to guide rational clinical therapy.

15. Considerations and perspectives

HMGA2 serves a key role in the process of embryogenesis, however, it becomes an oncoprotein when expressed in adult cells. HMGA2 is highly expressed in a various types of human cancer and serves as a prognostic marker (15,40,41,133,135,145,159-177) (Table I). Almost a decade ago, Fusco and Fedele reviewed the functions of HMGA proteins, including HMGA1 and HMGA2, in human neoplastic diseases, and suggested that the detection of HMGA be introduced as a routine procedure in clinical tumour analysis (7). Increasingly, evidence has suggested that HMGA2 is an independent prognostic factor of several malignant tumours, and that the expression level of HMGA2 is associated with the therapeutic efficacy of certain chemotherapeutic agents. Therefore, the detection of HMGA2 in cancer may provide important prognostic data or other information for clinicians. However, questions remain that warrant further investigation, including what standard experimental method to use to detect the expression

of HMGA2, how to make the positive standard, and how the expression of HMGA2 affects the prognosis of cancer patients. Although HMGA2-targeting drugs have not been developed, preclinical experimental studies have demonstrated that inhibiting HMGA2 protein synthesis via an antisense methodology can inhibit cancer cell growth and prevent neoplastic transformation (89,178). Therefore, targeting of the expression of HMGA2 may be a promising approach for cancer treatment in the future.

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Authors' contributions

SZ, QM and XW were involved in the conception of the study. SZ and QM were involved in writing the article. XW critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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