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Research Progress on MAZ in Malignant Tumors

Yunxiao Zhang[1*], Yan Qin[1*], Feng Gao[2], Huihuang Shen[3], Siyuan Hou[1,4], Mingxue Zhang[1,4], Hongmei Wu[1,4,5#], Linfeng Mo[1,4,5#]

[1]Department of Basic Medicine, Guangzhou Huashang Vocational College, Guangzhou, China
[2]Department of Medical Records, Shandong Province Hospital of Occupational Diseases, Jinan, China
[3]Department of Hospital Management, Hangzhou Children's Hospital, Hangzhou, China
[4]Department of Health Management, Guangzhou Huashang Vocational College, Guangzhou, China
[5]Department of Epidemiology and Health Statistics, Guilin Medical University, Guilin, China
Email: [#]1579796669@qq.com, [#]13077558919@163.com

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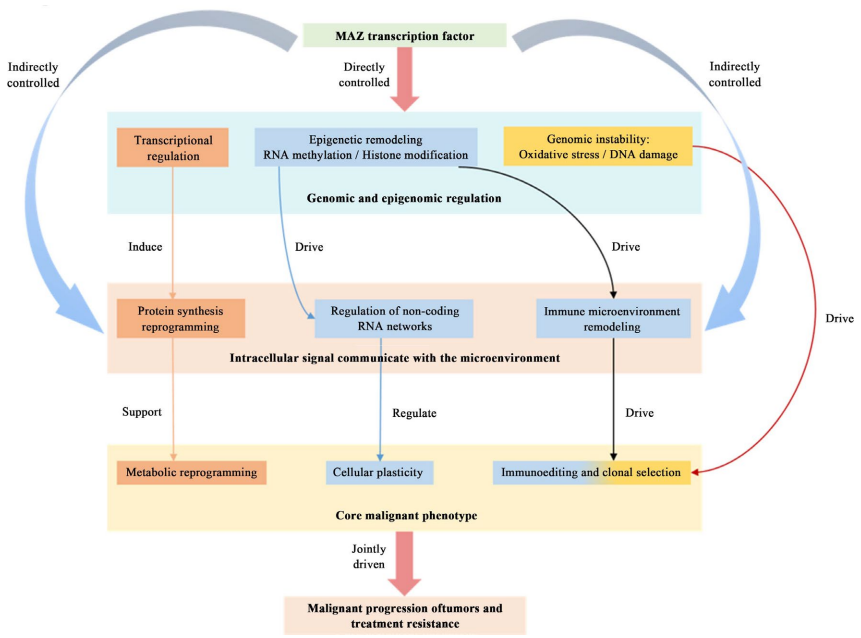
Abstract

Transcription factors play a critical regulatory role in the occurrence and development of malignant tumors. MAZ (MYC-Associated Zinc finger protein), as an important transcriptional regulator, exhibits a multi-layered molecular regulatory network in tumorigenesis and progression. Through the integration and analysis of existing research, we have elucidated the multiple mechanisms through which MAZ participates in the pathogenesis and progression of various malignant tumors: it directly regulates nuclear gene transcription, epigenetic remodeling, and genomic stability, while coordinately mediating cytoplasmic protein synthesis and non-coding RNA networks. These coordinated actions drive the acquisition of malignant phenotypes in tumor cells—including uncontrolled proliferation, metabolic reprogramming, and immunosuppressive microenvironment remodeling—ultimately promoting tumor progression and conferring therapy resistance. Its distinctive capability for bidirectional transcriptional regulation—mediating transcription initiation complex assembly at promoters while also guiding termination at specific gene loci—establishes MAZ as a pivotal regulator of gene expression programs. This mechanistic insight solidifies MAZ's central role in tumor progression. Based on its specific expression patterns across various malignancies, this research provides a theoretical foundation for developing novel MAZ-based liquid biopsy technologies, which are expected to advance early tumor diagnosis towards non-invasive and precise directions.

*These authors have contributed equally to this work and shared first authorship.
[#]Corresponding authors.



Keywords

MAZ, Transcription Factor, Malignant Tumors, Liquid Biopsy, Biomarker

1. Introduction

Malignant tumors have become a major global public health issue that seriously threatens human health. According to the latest statistical data from the World Health Organization's International Agency for Research on Cancer (IARC), there are over 19 million new cancer cases and nearly 10 million cancer-related deaths worldwide each year. Cancers such as lung cancer, Colorectal Cancer (CRC), Hepatocellular Carcinoma (HCC), and prostate cancer rank among the most prevalent in terms of both incidence and mortality rates [1]. Due to the complex pathogenesis and poor prognosis of malignant tumors, identifying reliable prognostic markers across various cancer types is a crucial approach to achieving effective prevention and treatment. Among the numerous molecules closely associated with tumorigenesis and progression, the MYC-Associated Zinc finger protein (MAZ), a key transcription factor, has garnered increasing attention. MAZ recognizes GC-rich regions in target genes through its C2H2-type zinc finger domain, thereby extensively regulating gene transcription [2] [3]. Studies have revealed that MAZ is aberrantly overexpressed in various highly prevalent malignant tumors—such as colorectal, lung, prostate, and liver cancers—and is significantly associated with poor patient prognosis, indicating its critical role in the progression of malignancies [4]-[6]. Further experiments have revealed the cancer-specific mechanisms of MAZ. For instance, in lung cancer, knockdown of MAZ significantly inhibits tumor cell proliferation and migration [6]; in prostate

cancer, MAZ has been shown to promote bone metastasis [7]; while in colon cancer, MAZ can mediate the STAT3 signaling pathway to regulate inflammatory responses and tumor progression [8]. Importantly, MAZ can also form a complex interaction network with other key oncoproteins such as MYC, collectively regulating tumorigenesis and development [9]. These findings demonstrate that MAZ may serve as a molecular target with significant research value and potential therapeutic promise.

However, although numerous studies have confirmed the central role of MAZ in the pathogenesis and progression of various malignant tumors, the complex regulatory networks underlying its function and its translational value remain underexplored. Moreover, in contrast to its well-established prognostic value, studies targeting MAZ itself are scarce, making its translation into an effective interventional target a primary challenge in the field. This review systematically analyzes the role of MAZ in tumor development, integrating recent advances in molecular mechanisms and clinical translation. The analysis provides an important reference for a deeper understanding of the role of MAZ in tumors and offers new ideas for developing novel anti-tumor strategies based on MAZ.

2. Biological Characteristics and Functions of MAZ

MAZ, a transcription factor ubiquitously expressed across major human tissues and organ systems, has a biological function that is intricately tied to its distinct molecular structure [10] [11]. The most prominent structural feature of this protein is the presence of multiple canonical C2H2-type zinc finger domains at its carboxyl terminus. These domains enable specific recognition and binding to GC-rich cis-regulatory elements (such as the 5'-GGGAGGG-3' sequence) in the promoter regions of target genes. Consequently, the protein plays a dual role in transcriptional regulation—it can both facilitate transcription initiation and mediate transcription termination [10] [12]. MAZ exhibits context-dependent regulatory functions in tumors, and the mechanisms underlying its dual roles primarily stem from the following factors. First, MAZ interacts with different protein cofactors to exert distinct functions. For instance, MAZ not only assembles a transcriptional activation complex with C-MYC to drive proliferation-related gene expression [9], but also recruits HDAC1/RBBP7/CUL4B to form a repression complex [13]. This complex facilitates histone deacetylation, resulting in chromatin conformational changes and subsequent transcriptional repression. Second, the different isoforms generated by alternative splicing of the MAZ gene (e.g., MAZ-1, MAZ-2, and MAZ-3) exhibit varying expression levels in the tumor microenvironment. These isoforms may possess distinct DNA-binding properties or protein interaction interfaces, ultimately leading to completely opposite biological effects [14]. Due to its structural and target-binding diversity, MAZ can extensively participate in multiple malignant biological processes of tumor cells—including proliferation, migration, invasion, apoptosis, and drug resistance—by regulating key cellular processes such as replication, repair, transcription, and translation (**Figure**

1) [6] [15] [16]. In tumorigenesis and development, MAZ plays a central role by regulating the expression of multiple key oncogenes. Studies have shown that it can not only directly bind to the promoter region of the c-Myc gene to maintain its basal transcription level, but also regulate the expression of Ras gene family members, thereby activating key signaling pathways such as MAPK [17] [18]. Adding another layer of complexity, a single MAZ molecule can simultaneously activate pro-cancer genes such as Vascular Endothelial Growth Factor (VEGF) [19] and Recombination Activation Gene 2 (RAG-2) [20], while also suppressing the expression of genes like Endothelial Nitric Oxide Synthase (eNOS) [21] and the proto-oncogene C-MYB [22]. This dual regulatory capability not only establishes MAZ as a critical focus in cancer research but also provides a theoretical foundation for its potential as a therapeutic target.

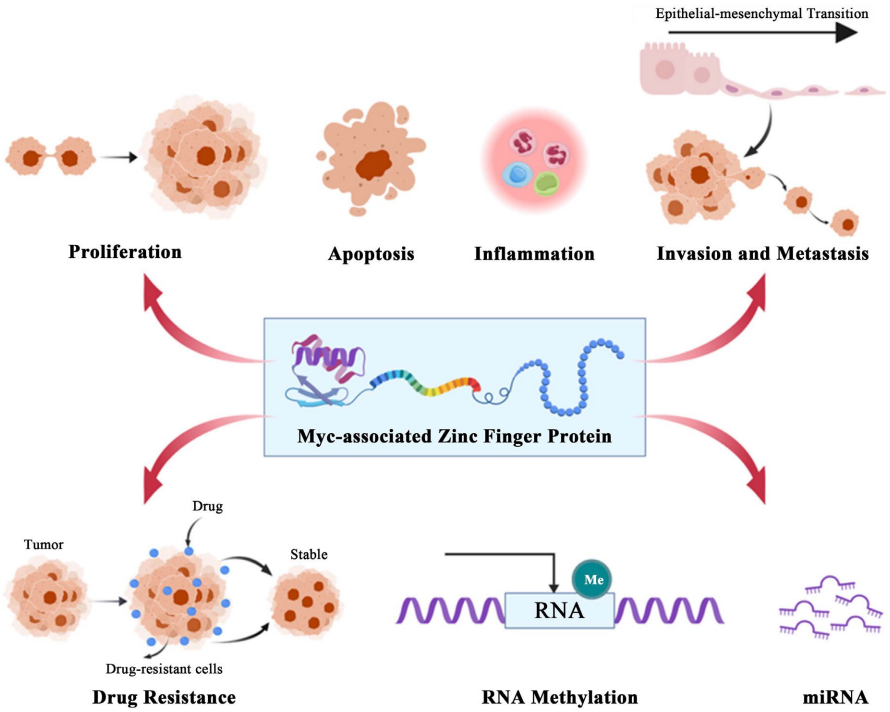


Figure 1. Various biological functions of Myc-associated zinc finger proteins in malignancies.

3. Research Progress on MAZ in Various Malignant Tumors

3.1. MAZ and Breast Cancer

Breast Cancer (BC) is the most common cancer among women worldwide and a leading cause of cancer-related deaths [23]. Its incidence exceeds 2 million cases annually, with over 680,000 fatalities [24]. Triple-Negative Breast Cancer (TNBC), a highly heterogeneous and clinically aggressive subtype lacking effective targeted therapies, exhibits a high incidence among Black women and is often diagnosed at later stages. This contributes significantly to racial disparities in BC mortality rates [25] [26]. Moreover, it is noteworthy that these clinical disparities are un-

derpinned by specific molecular mechanisms, among which dysregulation of MAZ plays a particularly crucial role. Substantial evidence indicates that MAZ contributes to the development and progression of BC through multi-dimensional molecular pathways. At the transcriptional level, MAZ has dual roles. It binds to the PPARγ1 promoter, forming the MAZ-PPARγ1 oncogenic axis that promotes tumor cell proliferation and survival [27] [28]; in contrast, it also forms a p53 heterodimer that activates miR-34a transcription to suppress tumors [29]. Additionally, in basal-like BC, MAZ demonstrates dual functions by regulating FOXF2, inhibiting tumor invasion while promoting tumor proliferation [12]. In terms of signaling pathway regulation, MAZ directly activates Ras gene transcription and forms a positive feedback loop with SAF-1 to amplify MEK/MAPK signaling, thereby promoting tumor angiogenesis and metastasis [18]. Concurrently, it drives TNBC progression by activating the SIPL1/AKT/NF-κB signaling axis [30]. In metabolic reprogramming, MAZ coordinates mitochondrial function-related gene networks to regulate energy metabolism [31]. Furthermore, lactate-activated MAZ forms a "lactate-SHH-MAZ-TMEM105" positive feedback loop that enhances glycolysis [32]. In TNBC, MAZ directly upregulates BCKDK expression, activating the BCKDK/G6PD signaling axis to drive pentose phosphate pathway reprogramming, thereby promoting tumor proliferation and oxidative stress resistance [33]. Notably, MAZ expression is closely associated with molecular subtypes of BC. Particularly in TNBC, it demonstrates low expression levels and exhibits a significant negative correlation with immune cell infiltration [34]. This pattern indicates a potential role for MAZ in regulating the tumor immune microenvironment. These findings systematically reveal the multi-layered regulatory network of MAZ in BC, providing an important theoretical foundation for developing targeted therapeutic strategies tailored to different molecular subtypes.

3.2. MAZ and Lung Cancer

Lung cancer has the highest incidence and mortality rates among malignancies worldwide and is classified into small-cell lung cancer and Non-Small Cell Lung Cancer (NSCLC). NSCLC includes Lung Squamous Cell carcinoma (LUSC), Lung Adenocarcinoma (LUAD), and Large Cell Undifferentiated Carcinoma (LCAC), accounting for approximately 90% of all lung cancer cases [35]. According to cancer incidence data, the five-year survival rate for NSCLC patients is approximately 15% due to atypical early symptoms and limited treatment options [36] [37]. LUAD is the most common histological subtype of lung cancer. In recent years, the oncogenic role of the transcription factor MAZ in LUAD has been gradually uncovered, and its high expression has been confirmed as an independent indicator of poor prognosis. Multiple studies have demonstrated that MAZ drives the malignant progression of LUAD through various mechanisms [38]-[40]. By directly binding to the promoter regions of downstream target genes, MAZ governs several oncogenic signaling pathways. It transcriptionally upregulates Thymidine Kinase 1 (TK1), thereby activating the GDF15 signaling axis to promote tumor growth

and metastasis [41]. Simultaneously, it enhances DNA damage repair capacity and facilitates cancer cell migration and invasion by activating NEIL3 expression [39]. Furthermore, MAZ promotes the activation of the PI3K-AKT pathway through transcriptional regulation of NSUN2, further accelerating tumor progression [40]. At the epigenetic level, MAZ suppresses GATA4 transcription by binding to its promoter. Conversely, MYC can competitively displace MAZ, alleviating the suppression of GATA4 through histone modification reprogramming and specific demethylation, thereby driving tumor metastasis [42]. In terms of treatment resistance, on the one hand, MAZ contributes to chemotherapy resistance via the MAZ/NEIL3 axis, which enhances DNA damage repair [39]. On the other hand, it reduces radiosensitivity by regulating Phrenolog-Interacting Factor 1 (PIF1), affecting telomere maintenance and the DNA damage response [43]. Notably, MAZ induces immune checkpoint molecules like Galectin-9, fostering an immunosuppressive microenvironment and potential immunotherapy resistance [6] [44]. MAZ itself is finely regulated by non-coding RNAs. For instance, miR-149-3p directly targets and suppresses MAZ, a mechanism through which the Chinese medicine compound "Jin Formula" inhibits lung cancer [45]. Simultaneously, MAZ regulates hsa-miR-424-3p to form the MAZ-miR-424-3p-EIF5A axis, which drives LUAD proliferation and suppresses apoptosis by modulating the cell cycle [46]. This finding not only confirms the key transcriptional regulatory role of MAZ in LUAD progression but also expands its novel regulatory mechanisms at the non-coding RNA level. Studies have also revealed that MAZ promotes tumor proliferation by directly activating KRAS signaling and driving SLC25A1-mediated metabolic reprogramming [6] [44]. The multi-layered regulatory capacity of MAZ in LUAD positions it as a highly promising therapeutic target. Developing specific MAZ inhibitors could achieve synergistic therapeutic effects. This approach simultaneously targets tumor cell autonomous proliferation, DNA damage repair, metabolic reprogramming, and tumor microenvironment remodeling. It thus offers a new strategy for LUAD precision therapy.

3.3. MAZ and Prostate Cancer

Prostate cancer, with over 1.2 million new cases annually and approximately 350,000 deaths, is one of the major malignant tumors threatening men's health [47]. The development and progression of this disease involve complex interactions among multiple factors, including genetics, environmental exposures, and dietary habits. Recent studies have shown that MAZ plays a critical role in the progression of prostate cancer. Mechanistically, MAZ directly binds to and activates the c-MYC promoter region while also regulating the transcriptional activity of members of the Ras gene family. Notably, transcriptional upregulation—not mutation—drives Ras pathway activation in 20% - 30% of human tumors [48]. As a key transcriptional regulator, MAZ may sustain high transcriptional levels of Ras genes, leading to continuous MAPK/ERK signaling pathway activation. This sustained signaling ultimately drives the abnormal proliferation and malignant transformation of tumor cells [4] [49]. Particularly in prostate cancer bone metastasis, MAZ expres-

sion levels are closely associated with the clinical characteristics and biological behavior of the disease. The upregulation of MAZ from primary tumors to bone metastases significantly correlates with shorter overall and progression-free survival in prostate cancer patients [3] [36]. From a functional perspective, MAZ overexpression enhances prostate cancer cells' invasion and migration, whereas its silencing suppresses bone metastasis [7]. This effect achieved through techniques such as RNA interference has been demonstrated in both *in vitro* and *in vivo* models. These findings establish MAZ as a key driver of bone metastasis in prostate cancer, highlighting its relevance for both prognosis and therapy. Future research focusing on developing specific MAZ inhibitors and combining them with existing therapies offers promising prospects for advancing treatment strategies in advanced prostate cancer.

3.4. MAZ and Hepatocellular Carcinoma

HCC, one of the most aggressive malignant tumors, causes approximately 830,000 deaths worldwide annually and accounts for the vast majority of primary liver cancer cases [1] [50]. HCC, characterized by its insidious progression and high malignancy, presents severe clinical challenges such as high metastasis, frequent recurrence, and poor short-term survival. Recent studies have revealed that MAZ is commonly overexpressed in various malignancies, including HCC, and is deeply involved in tumor progression [15]. MAZ exerts its function by specifically recognizing and binding to promoter regions of downstream target genes. This binding enables direct regulation of transcriptional activity for genes controlling cell proliferation, invasion and metastasis. Consequently, this transcriptional regulation drives malignant tumor progression. This discovery provides important directions for understanding the pathogenesis of HCC and developing new therapeutic strategies. Li *et al.* demonstrated that MAZ is significantly overexpressed in HCC, and this dysregulation is closely associated with the m6A methylation regulatory network [51]. Further mechanistic studies revealed that MAZ participates in HCC epigenetic reprogramming by transcriptionally regulating key m6A methyltransferases like METTL3. Findings from Zhang *et al.* also uncovered the central regulatory role of MAZ in metabolic reprogramming in HCC [52]. As a key transcription factor, MAZ directly activates NOP2 transcription. The upregulated NOP2 then stabilizes c-MYC via m5C methylation, ultimately driving the expression of glycolysis-related genes (e.g., LDHA, TPI1) and promoting tumor metabolic reprogramming. This discovery of the MAZ/NOP2/c-MYC signaling axis elucidates MAZ's upstream regulatory role in HCC metabolic dysfunction while establishing its potential as a novel therapeutic target for HCC. Furthermore, MAZ and HDAC1 form a complex that dually promotes HCC cell proliferation and metastasis. This is achieved through two coordinated mechanisms: HDAC1 catalyzes histone deacetylation to modify chromatin accessibility, while the complex concurrently represses the expression of the tumor suppressor CSK [13]. MAZ promotes metastasis in HCC by inducing the Epithelial-Mesenchymal Transition (EMT) program. EMT is a critical process in which epithelial cells reduce E-cad-

herin expression and increase vimentin levels, thereby acquiring invasive and migratory capabilities [53] [54]. This MAZ-driven EMT activation enhances the invasive and metastatic capabilities of tumor cells [55]. These findings reveal the complexity of MAZ's function in tumor progression and its potential multi-pathway regulatory roles. Data from The Cancer Genome Atlas (TCGA) further confirm that high MAZ expression is significantly associated with poor prognosis in HCC patients ($p < 0.05$). More importantly, MAZ expression correlates with both immune-related gene levels (e.g., HLA-DQB2, HLA-H) and chemotherapy sensitivity [15]. These discoveries demonstrate that MAZ holds a critical position in HCC pathogenesis and progression. Furthermore, they suggest its potential as both a prognostic biomarker and therapeutic target. This word provides a key theoretical foundation for developing novel HCC treatment strategies.

3.5. MAZ and Other Tumors

MAZ also demonstrates aberrant expression in various other malignant tumors. In colon cancer, MAZ shows high expression levels and is associated with poor patient prognosis [8]. The molecular mechanism involves driving the development of inflammation-associated tumors through activation of the STAT3 signaling pathway. This evidence identifies MAZ as a potential therapeutic target in colon cancer. Targeting the MAZ-STAT3 axis may offer novel treatments, though clinical translation requires further validation. In gastric cancer, multiple lines of evidence collectively reveal MAZ's central role as a key oncogenic factor. Research by Wang *et al.* linked the acidic microenvironment to suppressed FOXK1. This suppression downregulates MAZ, inducing autophagy in gastric cancer cells, which ultimately inhibits tumor metastasis and reverses EMT [56]. The conclusions of Zhao *et al.* corroborate this finding. They showed that miR-29b-3p directly targets MAZ. Consequently, it suppresses proliferation and migration, and induces apoptosis, in gastric cancer cells [57]. The aforementioned studies demonstrate MAZ's multifaceted role in gastric cancer pathogenesis, encompassing the regulation of cellular autophagy, EMT progression, and the critical balance between proliferation and apoptosis. This provides a solid theoretical foundation for developing MAZ-targeted therapeutic strategies in gastric cancer. Research in skin cutaneous melanoma shows that MAZ drives tumor metabolic reprogramming [5]. It directly transcribes NDUFS3, a core subunit of mitochondrial complex I. The resulting enhancement of oxidative phosphorylation efficiency promotes melanoma malignancy. In pancreatic ductal adenocarcinoma, MAZ overexpression, particularly enriched in cancer stem cells, promotes invasive capacity, as its deficiency significantly suppresses this phenotype [58], indicating MAZ's crucial role in the malignant progression of pancreatic cancer. In Glioblastoma (GBM), MAZ drives malignant progression through two pathways: regulating PDPN to promote tumor proliferation/invasion, while activating VEGF signaling to mediate angiogenesis [19] [59]. These findings collectively reveal MAZ's value as a key therapeutic target in GBM. In papillary renal cell carcinoma, Polycomb Group RING Finger protein 6 (PCGF6) epigenetically activates MAZ through

H3K4 demethylation, mediated by a promoter-recruited ternary complex with MAX and KDM5D [60]. In intrahepatic cholangiocarcinoma, MAZ acts as a core transcription factor in the MNX1-AS1 pathway by activating the MNX1/Ajuba/Hippo signaling axis to drive progression [61]. This provides a novel theoretical basis for targeted cancer therapy. Furthermore, MAZ exhibits aberrant expression in various other malignancies including thyroid carcinoma and clear cell renal cell carcinoma, where it correlates with tumor malignancy and patient prognosis [4] [62] [63]. The abnormal expression of MAZ across multiple cancer types provides important directions for developing novel MAZ-based anti-tumor strategies.

4. New Applications of MAZ in Tumor Diagnosis: Feasibility as a Liquid Biopsy Biomarker

MAZ's central role in tumorigenesis and its characteristic persistent overexpression endow it with dual value as both a therapeutic target and a diagnostic biomarker. Consequently, exploring the clinical application of MAZ as a liquid biopsy marker holds significant translational medical importance. Cancer remains a leading cause of mortality worldwide. Tissue biopsy has long been regarded as the gold standard in tumor diagnosis due to its accuracy, high standardization, and reliability. However, its invasive nature and limited ability to comprehensively reflect tumor heterogeneity pose significant challenges in clinical practice. In this context, Liquid biopsy is a minimally invasive technique that analyzes circulating tumor components in blood and other bodily fluids for non-invasive, dynamic tumor monitoring. This approach provides new opportunities for early cancer screening, treatment efficacy assessment, and prognosis evaluation [64] [65]. The core of this technology lies in the integrated analysis of two key biomarkers: circulating tumor DNA (ctDNA) and circulating tumor RNA (ctRNA). CtDNA, a component of cell-free DNA (cfDNA) released by tumor cells into the circulatory system, carries genetic and epigenetic modifications that may reflect the genomic or epigenomic characteristics of their cells of origin. This underpins its significant value in prognostic assessment, minimal residual disease detection, treatment strategy selection, and early warning of recurrence risk [66]. Beyond ctDNA, ctRNA also constitutes a crucial component of liquid biopsy testing systems. ctRNA, a subset of cell-free RNA (cfRNA) released into bodily fluids via apoptosis, necrosis, or active secretion from cancer cells, includes molecules such as microRNA (miRNA) and long non-coding RNA (lncRNA). It can be isolated from multiple biofluid sources, including blood and urine [67]. ctDNA and ctRNA serve as dual biomarkers in liquid biopsy, capturing tumor-specific genetic alterations at the genomic and transcriptional levels respectively. Together, they enhance tumor diagnosis, prognosis assessment, and heterogeneity analysis. Particularly, ctDNA has been extensively validated as an excellent tumor biomarker due to the characteristic that all tumor sites release cfDNA into the bloodstream [64] [65] [68] [69]. Consequently, compared to tissue biopsy, liquid biopsy provides a more comprehensive representation of tumor heterogeneity.

Liquid biopsy technology has enabled screening for various cancers such as lung cancer, BC, and CRC through the detection of circulating tumor markers in body fluids [70]-[73]. Against this backdrop, the transcription factor MAZ, with its characteristic high expression specific to multiple malignant tumors, demonstrates significant potential as a novel liquid biopsy biomarker. It should be specifically noted that the use of MAZ as a liquid biopsy biomarker remains a conceptual proposal at present. No studies have yet specifically detected MAZ expression levels through ctDNA or ctRNA analysis or validated its clinical application value. Current research indicates that cfDNA-based liquid biopsy exhibits excellent performance in early screening for different cancer types. In lung cancer, machine learning models incorporating multidimensional features of cfDNA achieved detection sensitivities of 95.1% for stage I lung cancer and 96.2% for minimally invasive adenocarcinoma [74]. Plasma ctDNA detection demonstrated 90% sensitivity in distinguishing lung cancer patients from healthy individuals [75], while maintaining a 50% detection rate even in stage I patients [76]. Regarding CRC screening, SEPT9 gene methylation testing has received FDA clinical approval [77] [78]. Recently developed models utilizing 11 cfDNA methylation biomarkers have shown both high sensitivity and strong specificity in detecting early-stage CRC and advanced adenomas [79] [80]. Notably, ctDNA has demonstrated unique value in dynamic monitoring. Studies have revealed that ctDNA levels significantly correlate with tumor volume and can reflect treatment response earlier than radiographic imaging [81] [82]. In glioma research, tumor-derived DNA in cerebrospinal fluid showed significant correlation with tumor progression and patient survival [38], further confirming that ctDNA analysis can provide critical information on tumor progression. However, despite its considerable potential, liquid biopsy faces major challenges in standardization. Uniform protocols are urgently needed for sample collection procedures, biomarker isolation methods, and result interpretation criteria [83] [84]. Moreover, the release of biological materials (e.g., urine and blood) can be influenced by microenvironmental factors [85]. Additionally, not all clinically relevant cancer biomarkers are detectable through liquid biopsy [86], and many detection methods still require further research and clinical validation. Despite these challenges, liquid biopsy is expected to become an important complement to tissue biopsy. This prospect depends on continuous improvements in monitoring efficiency and a deeper understanding of biomarker mechanisms. Ultimately, the technology will provide more comprehensive information support for tumor immunotherapy. In this developmental trajectory, MAZ—as a novel biomarker highly expressed across multiple tumors—warrants further validation of its clinical utility through large-scale clinical studies.

5. Conclusions

MAZ, a transcription factor characterized by its distinctive C2H2 zinc finger structure, serves as a transcriptional regulatory hub in multiple malignant tumors. It not only drives malignant tumor progression by regulating multiple pathways such

as TK1-GDF15 and NEIL3-DNA damage repair, but also participates in key processes including chemotherapy resistance and immune regulation. These findings provide a solid theoretical foundation for the clinical application of MAZ. Based on current research advances, future studies could consider focusing on the following directions: Firstly, it is necessary to conduct a thorough analysis of the core role of MAZ in malignant tumors, and determine whether it plays a dominant role in the regulatory network of oncogenes. Secondly, it is essential to systematically clarify MAZ's functional network in normal physiological processes to assess potential adverse effects associated with targeting it therapeutically. Finally, it is essential to explore specific therapeutic strategies targeting MAZ. Herein, we propose two strategic therapeutic approaches for targeting MAZ. The first strategy involves developing small-molecule inhibitors designed to specifically disrupt its DNA-binding domain. Alternatively, targeted protein degradation technologies, particularly PROTACs, could be employed to achieve precise control of MAZ protein levels. Although transcription factors have traditionally presented formidable challenges for drug development, these innovative strategies offer promising avenues to overcome the inherent "undruggable" nature of such targets. The pursuit of these approaches represents a paradigm shift in therapeutic development for transcription factor-related malignancies.

To address key challenges in clinical translation—including functional heterogeneity of MAZ across cancer types, disparities between animal models and human studies, and balancing targeting specificity with toxicity—these issues can be addressed by advancing through three stages: The first phase focuses on the development of diagnostic markers, establishing standardized MAZ detection protocols in liquid biopsy through multicenter clinical studies. The second phase aims to validate MAZ as a therapeutic target by utilizing organoid models and gene-editing technologies to elucidate its regulatory networks and develop specific inhibitors. The third phase involves systematic preclinical evaluation, verifying the safety and efficacy of MAZ-targeted therapies in advanced animal models. Through this stepwise research strategy, MAZ is expected to become an important target in the field of precision oncology, thereby providing new diagnostic and therapeutic options for cancer patients.

Author Contributions

Yunxiao Zhang: Conceptualization, Writing—original draft. Yan Qin: Formal Analysis, Writing—original draft. Feng Gao: Formal Analysis, Writing—review & editing. Huihuang Shen, Siyuan Hou and Mingxue Zhang: Supervision, Writing—review & editing. Hongmei Wu and Linfeng Mo: Conceptualization, Project administration, Writing—review & editing.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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