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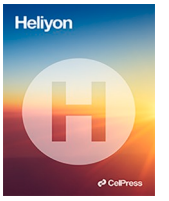

Review article

UNC-45A: A potential therapeutic target for malignant tumors

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ABSTRACT

Uncoordinated mutant number-45 myosin chaperone A (UNC-45A), a protein highly conserved throughout evolution, is ubiquitously expressed in somatic cells. It is correlated with tumorigenesis, proliferation, metastasis, and invasion of multiple malignant tumors. The current understanding of the role of UNC-45A in tumor progression is mainly related to the regulation of non-muscle myosin II (NM-II). However, many studies have suggested that the mechanisms by which UNC-45A is involved in tumor progression are far greater than those of NM-II regulation. UNC-45A can also promote tumor cell proliferation by regulating checkpoint kinase 1 (ChK1) phosphorylation or the transcriptional activity of nuclear receptors, and induces chemoresistance to paclitaxel in tumor cells by destabilizing microtubule activity. In this review, we discuss the recent advances illuminating the role of UNC-45A in tumor progression. We also put forward therapeutic strategies targeting UNC-45A, in the hope of paving the way the development of UNC-45A-targeted therapies for patients with malignant tumors.

1. Introduction

The *unc-45* (uncoordinated mutant number 45) gene was initially identified through a temperature-sensitive mutation affecting myofilament assembly in *Caenorhabditis elegans* [1,2]. The *C. elegans* UNC-45 protein was subsequently demonstrated to be a tetratricopeptide repeat (TPR) and UNC-45/Cro1/She4p (UCS) domain-containing protein that was proposed to be muscle-specific [3,4].

Model organisms, such as the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*, are well-developed for the study of muscle development and function [4,5]. Knowledge gained in these organisms should apply to vertebrate muscles, as the structure of the contractile mechanism of muscle is widely conserved across metazoan evolution [4,6]. The *C. elegans* UNC-45 protein has been shown to be necessary for thick filament assembly which can be explained by the fact that UNC-45 functions both as a molecular chaperone and as an Hsp90 co-chaperone for myosin [2,3,7]. Specifically, the UCS domain of UNC-45 bounds and exerts chaperone activity on the myosin head, and the TPR domain bounds the molecular chaperone heat shock protein 90 (Hsp90) to facilitate myosin folding [7]. As with *C. elegans*, *Drosophila* UNC-45 is essential for its skeletal muscle myosin stability and function [8,9]. Moreover, the effect of UNC-45A on heart development and function was further assessed in *Drosophila*. It was demonstrated that UNC-45 was particularly crutial during metamorphosis when the heart was remodeled to ensure normal sarcomeric structures and contractility [10]. Furthermore, heart-specific over-expression of UNC-45 could, to some extent, reverse Huntington's disease-induced cardiac amyloidosis as well as ceramide-associated lipotoxic cardiomyopathy in the *Drosophila* heart [11,12].

Most invertebrates express a single isoform of UNC-45 [13]. However, in humans, there are two UNC-45 isoforms with a sequence

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identity of ~55 % [14]. One is the general cell (GC) isoform designated as UNC-45A (GC UNC-45/SMAP-1) and the other is the striated muscle (SM)-specific isoform designated as UNC-45B (SM UNC-45) [14,15]. UNC-45A is ubiquitously expressed in different tissues and plays an important role in regulating cytoskeleton-associated functions in mammalian cells, including cytokinesis, exocytosis, cell motility, and neuronal development [5,14,16,17]; while UNC-45B is restricted in cardiac and skeletal muscle and responsible for muscle-specific function [14].

In particular, cumulative evidence suggests that the functions of UNC-45A are not specific to myosin. For example, UNC-45A has been shown to bind and destabilize microtubules [18,19]. However, still little is known about its functions in mammalian non-muscle cells. In recent years, UNC-45A has been reported to contribute to tumorigenesis, proliferation, metastasis, invasion, and drug resistance in multiple malignant tumors, and its overexpression may be associated with poor prognosis [5,16,17]. Nevertheless, the molecular mechanisms underlying the involvement of UNC-45A in tumor progression are not fully understood. This review aims to pave the way for further studies by elucidating the role of UNC-45A in tumor progression (Fig. 1) as well as possible targeted therapeutic strategies.

2. Gene and protein structures

The human *unc-45a* gene is located on chromosome 15 (15q26.1) [19]. Chromosome 15 is one of the seven human chromosomes with a high rate of segmental duplications, which may facilitate cancer-associated copy number transitions and rearrangements [20–22]. The length of *unc-45a* is 23,914 bp, containing 24 exons and seven transcripts [23,24].

Alternative splicing of UNC-45A pre-mRNA generates five distinct UNC-45A protein isoforms, including protein unc-45 homolog A isoform X1 (UNC45A-X1), protein unc-45 homolog A isoform X2 (UNC45A-X2), protein unc-45 homolog A isoform 2 (UNC45A-2), protein unc-45 homolog A isoform 3 (UNC45A-3), and protein unc-45 homolog A isoform 4 (UNC45A-4) [24]. The protein isoforms consist of 944, 506, 944, 929 and 799 amino acids, respectively [24].

Structurally, the three domains, namely an NH2-terminal TPR domain, a central region, and a COOH-terminal UCS domain, are conserved in UNC-45A (Fig. 2) [7,25]. As noted, the TPR domain of UNC-45A preferentially binds to Hsp90 [7]. Moreover, the TPR domain interacts not only with the N-terminal ATP-binding domain of Hsp90 but also with the C-terminal pentapeptide (MEEVD)

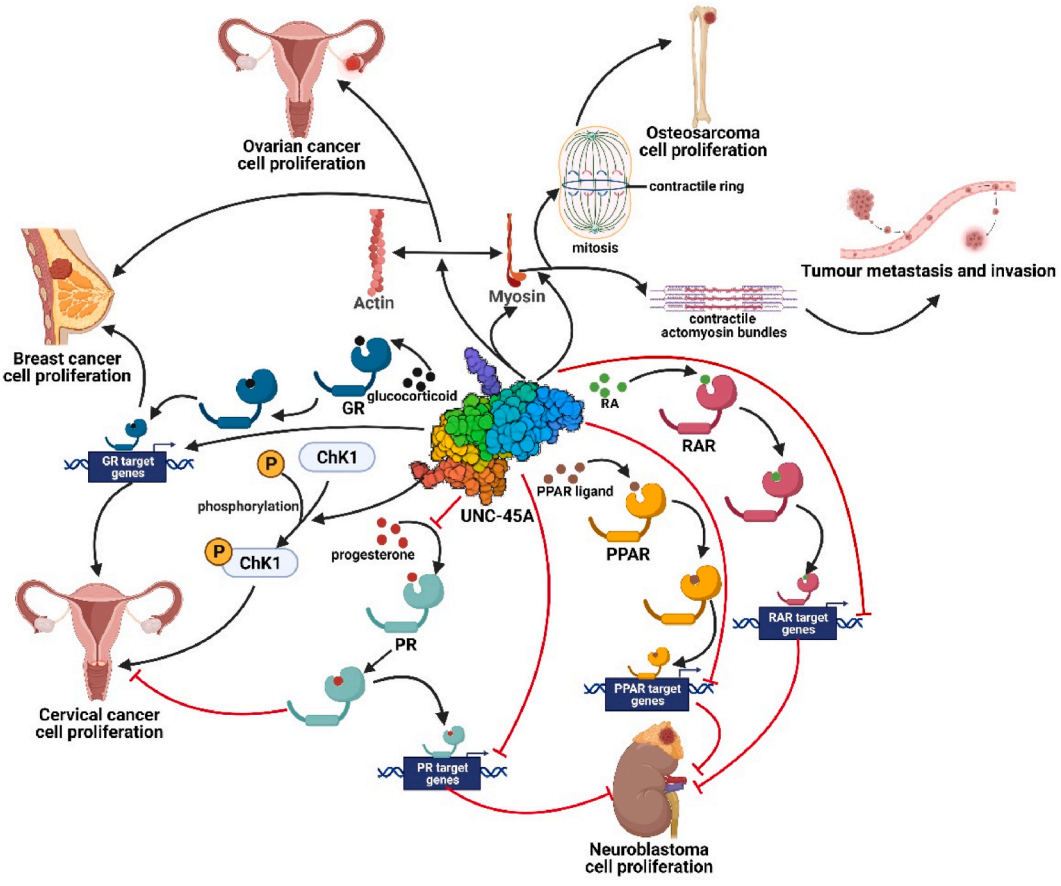

Fig. 1. The role of UNC-45A in tumor progression. ChK1, checkpoint kinase 1; GR, glucocorticoid receptor; NM-II, non-muscle myosin II; P, phosphorylation; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; RA, retinoic acid; RAR, retinoic acid receptor.

sequence of Hsp90 [7,26,27]. When its TPR domain interacts with the N-terminal domain of Hsp90, UNC-45A is involved in coordinating the chaperoning of client proteins (e.g. steroid receptors) [27]. On the other hand, UNC-45A serves as a co-chaperone assisting Hsp90-mediated myosin folding when the TPR domain binds to the C-terminal of Hsp90 [27]. Further, the TPR domain contributes to the assembly of contractile non-muscle myosin II (NM–II)–containing actomyosin bundles [28]. Intriguingly, the canonical UCS domain is necessary for assembling NM–II–containing contractile rings during cytokinesis [7]. Moreover, the UCS domain which is responsible for the chaperone activity of UNC-45A, binds to and activates the myosin motors [7,29,30]. Therefore, UNC-45A also functions as both a myosin-specific molecular chaperone and an Hsp90 co-chaperone for myosin [7,31]. However, the function of the central domain of UNC-45A is unknown. Two LXXLL motifs have been found to be present in the central domain [25,26]. Hence, there are four putative LXXLL motifs in UNC-45A, with the other two located in the UCS domain [25,26]. The LXXLL motifs, where L is leucine and X is any amino acid, are referred to as nuclear receptor (NR) boxes in transcriptional co-regulators [32]. The four NR boxes, which are responsible for binding to NRs, suggest that UNC-45A may be a transcriptional co-regulator of NRs (Fig. 2) [25,26,33].

3. Expression of UNC-45A in malignant tumors

Although human UNC-45A is ubiquitously expressed in somatic cells [25], it is differentially expressed in malignant tumors compared to normal cells. Moreover, the upregulation of UNC-45A at both the protein and RNA levels correlates with disease severity [18].

For example, serous ovarian cancer expressed aberrantly elevated levels of UNC-45A compared to normal ovarian surface epithelium and benign cystadenomas [34]. Moreover, the high stage exhibited greater UNC-45A expression than the low stage of serous cancer [34]. Furthermore, Habicht et al. reported that UNC-45A was highly expressed in paclitaxel-resistant ovarian cancer cells [18]. In human breast cancers and cell lines derived from breast cancer metastases, the mRNA and protein expression levels of UNC-45A were also elevated [29]. Moreover, the elevation correlated with tumor grade and metastatic properties of the cell lines [29].

4. Subcellular localizations of UNC-45A in malignant tumors

Previous studies have suggested that UNC-45A is predominantly localized in the cytoplasm of both tumorigenic and non-tumorigenic cells [17,18,26,28,34–37]. While some studies have claimed that UNC-45A displays diffuse cytoplasmic localization in tumor cells [26,34,36], others have reported that UNC-45A co-localizes with specific organelles. For instance, Bazzaro's group reported that although UNC-45A was diffuse within the cytoplasm of interphase SKOV-3 ovarian cancer cells, UNC-45A accumulated with NM-II at the cleavage furrow during cytokinesis. It was consistent with the indispensable role of UNC-45A in assembling NM–II–containing contractile rings during cytokinesis [34]. Coincidentally, Lehtimäki's group reported that UNC-45A displayed dynamic localization to contractile NM–II–containing actomyosin bundles in human osteosarcoma U2OS cells, in order to promote the generation of contractile actomyosin bundles through synchronized NM-II folding and filament-assembly activities [28]. Besides, UNC-45A has been proven to be a mitotic spindle-associated protein. In clinical ovarian cancer specimens, UNC-45A was present in the mitotic spindle of metaphase ovarian cancer cells [18]. In COV-362 human ovarian cancer cells and HeLa human cervical cancer cells, UNC-45A co-localized with microtubules during both mitosis and interphase [17,18]. The co-localization might be the basis for UNC-45A to act as a regulator of mitotic progression via destabilizing microtubules [17]. UNC-45A is also referred to as a novel centrosomal protein [35]. UNC-45A, which was essential for checkpoint kinase 1 (ChK1) phosphorylation and centrosomal localization, co-localized with γ-tubulin and ChK1 to the centrosome in HeLa and U2OS cell lines [35].

In addition to aggregating in the cytoplasm, UNC-45A was also present in the nuclei of breast tumor tissues and cellular models [16]. The nuclear localization of UNC-45A is consistent with its transcriptional activation of glucocorticoid receptor (GR) [16].

Altogether, it's speculated that the dynamic subcellular localization of UNC-45A is closely associated with its particular roles in the progression of specific malignant tumors [38].

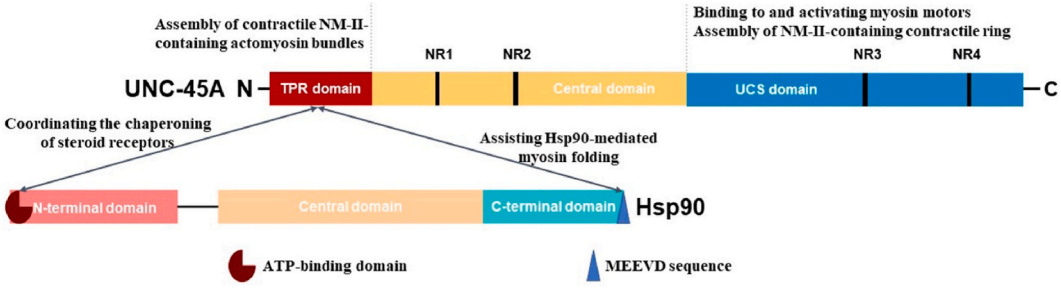

Fig. 2. Domains and functions of UNC-45A.The TPR, central and UCS domains of UNC-45A are colored in red, orange, and blue, respectively, whereas domains of Hsp90 are in pink (the N-terminal domain), light yellow (the central domain) or light blue (the C-terminal domain). NR, nuclear receptor; MEEVD, the C-terminal pentapeptide. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

5. The role of UNC-45A in tumor progression

5.1. Promotion of tumor cell proliferation

Studies have shown that UNC-45A is closely associated with tumor cell proliferation. In other words, elevated UNC-45A levels enhance proliferation rates, whereas UNC-45A knockdown suppresses proliferation [16,29,34,35]. Some researchers have claimed that UNC-45A is essential for tumor cell proliferation both *in vitro* and *in vivo* [16,35]. Nevertheless, the reported mechanisms by which UNC-45A promotes tumor cell proliferation vary (Table 1).

5.1.1. UNC-45A promotes tumor cell proliferation by regulating NM-II

NM-II is the primary protein involved in generating contractile forces that drive cell division [39,40]. The correct regulation of NM-II activity and its positioning preserves genome integrity, whereas altered activity and localization of NM-II can induce genetic abnormalities that are linked to tumors [40]. UNC-45A is a chaperone necessary for NM-II activity and its incorporation into the contractile ring during cytokinesis [7,34]. UNC-45A depletion resulted in slightly delayed cytokinesis and multinucleated cells because of the decreased NM-IIA filament stack lengths and amount of NM-II at the division plane in UNC-45A knockout human osteosarcoma U2OS cells [28].

However, a different mechanism has been reported in ovarian and breast cancer cells, where the knockdown of endogenously overexpressed UNC-45A slowed the proliferation rates of cancer cells. UNC-45A was concentrated with NM-II in the cleavage furrow during cytokinesis in ovarian cancer cells [34]. Moreover, studies have observed that there was no significant change in the expression of NM-II in UNC-45A-depleted cells [29,34,35]. As cytokinesis is powered by the interaction between NM-II and actin in the contractile ring, it has been proposed that the interaction between NM-II and actin filaments is reduced in UNC-45A-knockdown cells [29,41].

5.1.2. UNC-45A promotes tumor cell proliferation by regulating the transcriptional activity of NRs

NRs are a superfamily of transcription factors that orchestrate complex regulatory networks in many biological processes, including cell proliferation, metabolism, immunity, development, reproduction, ageing, and tumor progression [42,43]. Each NR exerts its transcriptional effects in concert with a number of co-regulators, including co-activators and co-repressors [43]. Interactions with co-activators promote the recruitment of transcriptional machinery and chromatin remodelling [42]. UNC-45A has been reported as a transcriptional co-regulator of NRs in several studies. Currently, the known NRs co-regulated by UNC-45A include the GR, retinoic acid receptor (RAR), progesterone receptor (PR) and peroxisome proliferator-activated receptor (PPAR) [16,25,26].

Eisa et al. reported that nucleus-located UNC-45A upregulated the transcriptional activity of GR, thereby promoting the expression of the mitotic kinase NIMA-related kinase 7 (NEK7), which was required for cell cycle progression because of its ability to regulate mitotic spindle formation and cytokinesis [16].

In contrast, Epping's group reported that UNC-45A negatively regulated retinoic acid (RA), PR, and PPAR signalling pathways *in vitro* by inhibiting the ligand-dependent transcriptional activities of RAR, PR, and PPAR respectively [25]. This study highlighted the role of UNC-45A in RA signalling. RA plays a fundamental role in regulating the balance between the proliferation and differentiation of multiple neuronal cells. It has been known to inhibit proliferation and promote cell death in multiple neuroblastoma cell lines [44]. UNC-45A was then proven to act as an inhibitor of RA-induced proliferation arrest and differentiation of human neuroblastoma cells [25]. Further analysis revealed that UNC-45A significantly attenuated the mRNA expression levels of the RA target genes (RARβ and CRABP2), which were associated with cell cycle arrest, as well as the mRNA levels of the critical neural differentiation markers (TRKB and RET) involved in RA-induced differentiation in neuroblastoma cells [25]. However, no direct physical interaction between RAR and UNC-45A was observed, and none of the NR boxes in UNC-45A was required for the observed interference with RA signalling [25].

Although Chadli et al. claimed that UNC-45A blocked PR signalling in simplified cell-free systems, a different mechanism was reported [26]. UNC-45A inhibited the hormone-binding activity of PR via the Hsp90 chaperone pathway [26]. Interestingly, UNC-45A was verified as a positive co-regulator of the cellular transcriptional activity of PR in further experiments using HeLa cells [26]. In this respect, Chadli et al. interpreted that UNC-45A entered the PR chaperone by Hsp90 at an intermediate stage, where its inhibitory action served a purpose; however, this inhibition was relieved by subsequent events that were missing from the *in vitro* system [26]. Furthermore, this was consistent with Eisa et al.'s study, which showed that UNC-45A could bind directly to PR [26]. Moreover, the LXXLL sequences of UNC-45A are not essential for the binding of UNC-45A to PR, either [26].

Table 1
Mechanisms of UNC-45A in promoting tumor cell proliferation.

Mechanism	Tumors	Refs.
Activating NM-II and incorporating it into the contractile ring during cytokinesis	Osteosarcoma	[28]
Regulating the interaction of NM-II with actin filaments	Ovarian and breast cancer	[29,34]
Up-regulating the transcriptional activity of GR, thereby controling the transcription of NEK7	Cervical and breast cancer	[16]
Inhibiting the transcriptional activity of RAR, PR and PPAR	Neuroblastoma	[25]
Inhibiting the hormone-binding activity of PR via the Hsp90 chaperoning pathway	Cervical cancer	[26]
Activating ChK1 by inducing its phosphorylation at S345, thereby regulating its tethering to the centrosomes	Cervical cancer	[35]

5.1.3. UNC-45A promotes tumor cell proliferation by regulating ChK1 phosphorylation at S345

Jilani et al. reported the essential role of UNC-45A in tumor cell proliferation *in vitro* and tumor growth *in vivo* [35]. Instead of interacting with NM-II or NRs, UNC-45A affected tumor cell proliferation by regulating ChK1 phosphorylation at S345 in an Hsp90-independent manner [35]. The inhibition of UNC-45A expression reduced ChK1 activation and its tethering to the centrosome, causing premature centrosome separation and the accumulation of multinucleated cells [35]. Ultimately, apoptosis was triggered [35].

Collectively, UNC-45A promotes the cell proliferation of different types of malignant tumors via various molecular mechanisms. Even different mechanisms in identical tumor cell lines have been reported. As mentioned, UNC-45A may function as a chaperone for myosin, a co-chaperone for Hsp90, and a transcriptional co-regulator of NRs as well. Besides, UNC-45A resides not only in the cytoplasm but also in the nuclei of tumor cells. As we know, protein subcellular localization is an essential and highly regulated determinant of protein function [45]. Accordingly, we speculate that the different mechanisms of UNC-45A in promoting tumor cell proliferation may correlate with its subcellular localization. UNC-45A in the cytoplasm might induce tumor cell proliferation either by regulating NM-II as a myosin chaperone or via the hsp90 chaperoning pathway as a co-chaperone, while UNC-45A in the nuclei through the transcriptional regulation of NRs. What' more, intra- and intertumor heterogeneity might also contribute to the various mechanisms underlying the pro-proliferative function of UNC-45A in tumors.

5.2. Promotion of tumor metastasis and invasion

UNC-45A has been confirmed to play important roles in metastasis and invasion of several malignant tumors, such as ovarian cancer, breast cancer, osteosarcoma, etc. UNC-45A knockdown was found to reduce the spreading ability of ES-2 ovarian and MDA-MB-231 breast cancer cells [29,34]. Additionally, U2OS osteosarcoma cells with UNC-45A knockout displayed a drastic migratory phenotype defined by deficient tail retraction and multiple lamellipodial protrusions extending in different directions [28]. The aberrant UNC-45A knockout migratory phenotype might eventually lead to a drastically reduced cell migration speed [28,46,47]. Conversely, ectopic overexpression of UNC-45A in SKOV-3 ovarian cancer cells significantly enhanced the rate of spreading [34].

Except for cell cycle regulation, NM-II plays a key role in tumor metastasis and invasion, whether during amoeboid cell migration, mesenchymal cell migration, collective cell migration, or reversible mesenchymal-amoeboid and individual-collective transitions [40,48,49]. In addition, Peng et al. reported the different roles of NM-II isoforms in the migration of MDA-MB-231 breast cancer cells. The non-muscle myosin IIA (NM-IIA) isoform located at the leading edge of cells binds to actin filaments to form actomyosin bundles, which participate in focal adhesion maturation, lamellipodia formation and cytoskeletal dynamics, while the non-muscle myosin IIB (NM-IIB) isoform distributed in the perinuclear region of cells contributes to traction force generation and polarized distribution [50].

UNC-45A and NM-II were found to partially co-localize at the leading edges of migrating ovarian carcinoma and osteosarcoma cells [28,34]. Furthermore, UNC-45A knockout cells manifested faster random migration velocity, similar to the reported effects of NM-IIA depletion on cell migration [28]. Finally, it was uncovered that UNC-45A promoted the assembly of contractile NM–II–containing actomyosin bundles, which were crucial for migration [28]. However, the isoform-specific regulation of NM-II by UNC-45A remains to be studied.

5.3. Drug resistance to chemotherapy

Epping's and Mooneyham's groups independently reported that overexpression of UNC-45A confers resistance to histone deacetylase inhibitors in human osteosarcoma U2OS cells and paclitaxel in ovarian cancer [17,25]. Epping et al. reported that UNC-45A mediated resistance to histone deacetylase inhibitors via the RA signalling pathway, whereas Mooneyham et al. reported another mechanism [17,25].

It is well known that paclitaxel exerts its antitumor effect through stabilising microtubule polymerisation, thereby blocking the microtubule breakdown during cell division and causing chromosome mis-segregation and aneuploidy [51,52]. Mooneyham et al. found that UNC-45A was overexpressed in human clinical specimens from paclitaxel-resistant ovarian cancer and that UNC-45A overexpressing cells resisted chromosome mis-segregation and aneuploidy when treated with clinically relevant concentrations of paclitaxel [17]. UNC-45A was then demonstrated to bind directly to the paclitaxel-stabilised microtubule lattice and act as an ATP-independent microtubule destabiliser to resist paclitaxel [17]. Moreover, UNC-45A depletion exacerbated the paclitaxel-mediated stabilisation of mitotic spindles and restored sensitivity to paclitaxel [17].

Collectively, UNC-45A may serve as a marker of chemoresistance or a molecular target for the treatment of chemoresistant human tumors.

6. Therapeutic strategies targeting UNC-45A

6.1. Small molecules or peptides targeting protein-protein interactions

In malignant tumors, protein-protein interactions form signalling nodes and hubs that transmit pathophysiological cues along molecular networks to achieve an integrated biological output, thereby promoting tumorigenesis, tumor progression, invasion, and/or metastasis [53]. Recent studies indicate that targeting protein-protein interactions has become an increasingly popular strategy for the treatment of malignant tumors. As stated earlier, UNC-45A promotes tumor progression by binding to and activating NM-II or by interacting with the general chaperone Hsp90. Therefore, modulators interfering with the binding of the UNC-45A to NM-II or selectively disrupting the interaction between the UNC-45A and Hsp90 can be screened. Up to date, there are three types of

modulators, including small molecules, antibodies and peptides [54]. However, the application of antibodies is limited to the extracellular targets. Accordingly, small molecules or peptides can be assessed.

6.2. RNA-based therapies

RNA-based therapy is a promising strategy for cancer treatment by introducing exogenous nucleic acids, such as messenger RNA (mRNA), small interfering RNA (siRNA), microRNA (miRNA) and antisense oligonucleotides (ASO), to modulate gene expression in specific cells [55,56]. Pre-clinical studies in different tumor models, using UNC-45A knockdown or knockout as a therapeutic strategy, have not only confirmed the effect of UNC-45A on tumor progression, but also shown encouraging results that RNA-based therapies might be a potential treatment for malignancies.

6.3. Microtubule destabilizing agents

Microtubules are dynamic filamentous cytoskeleton proteins composed of tubulin and are important targets for the treatment of malignancies [57]. UNC-45A has been demonstrated to be a microtubule-associated protein that binds to the microtubule lattice leading to microtubule bending, breakage and depolymerization [17–19]. Besides, UNC-45A destabilizes microtubules independent of its effects on NM-II activity [19]. This discovery provides evidence for the application of microtubule destabilizing agents in specific human tumors. Nevertheless, the characterization of human malignancies suitable for microtubule destabilizing agents is also mandatory.

6.4. Strategies based on the ubiquitin-proteasome system

Guo et al. have verified that the primary mechanism of UNC-45A protein degradation is through the ubiquitin-proteasome system [29]. Hence, strategies based on the ubiquitin-proteasome system, such as proteolysis-targeting chimera (PROTAC) or molecular glues, can be applied to induce the ubiquitination and proteasomal degradation of UNC-45A.

Heterogeneous bifunctional PROTACs contain a ligand for recruiting E3 ligase, a linker, and another ligand to bind to the target protein for degradation [58]. The induced proximity of the target protein of interest and the E3 ligase fostered by PROTACs triggers the ubiquitination and subsequent degradation of the target protein by the 26S proteasome [59]. Additionally, the first oral PROTACs, ARV-110 and ARV-471, have respectively shown encouraging results in clinical trials for the treatment of prostate cancer and breast cancer [60].

Unlike PROTACs, molecular glues induce or stabilize protein-protein interaction between the target protein and E3 ligase, resulting in protein ubiquitination and subsequent proteasomal degradation [61]. For instance, the molecular glue CC-90009 coopts the CRBN E3 ubiquitin ligase to selectively target GSPT1 for ubiquitination and proteasomal degradation [62]. What's more, a phase I/Ib study of CC-90009 is currently being conducted in patients with acute myeloid leukemia (NCT02848001, NCT04336982).

7. Conclusion

UNC-45A plays a significant role in the proliferation, metastasis, invasion, and drug resistance of malignant tumors. Moreover, UNC-45A is dispensable for normal cell survival [16]. Consequently, UNC-45A is a promising new therapeutic target for tumor therapy [16–18]. Nevertheless, the multiplicity and heterogeneity of the molecular mechanisms underlying the involvement of UNC-45A in tumor progression highlight the desirability to get a comprehensive understanding of the tumor-specific roles of UNC-45A. Thus, based on better comprehension of the underlying molecular mechanisms, the therapeutic strategies targeting UNC-45A for malignant tumors could be more precise.

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Ethics approval

Ethics approval was not applicable in this review.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Hong Wang: Writing – original draft, Funding acquisition, Conceptualization. **Fude Sun:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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