Review

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Prognostic Value and Biological Functions of Neuropilin-1 in Gynecological Cancers: A Narrative Review

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Gynecological cancers (GCs), which primarily encompass cervical cancer (CESC), ovarian cancer (OC), and endometrial cancer (EC), represent a group of malignancies that pose a severe threat to women's health. The advancement of precision medicine holds profound significance for enhancing the diagnosis and treatment of gynecological cancers. The application of molecular-targeted drugs, coupled with progress in surgical concepts and techniques, has substantially improved the survival outcomes of patients with ovarian cancer. Neuropilin-1 (NRP1) was initially identified as a neuronal guidance protein. Recent studies have revealed multifaceted roles of NRP1 in cancers, including its regulatory effects on tumor cell proliferation, growth, metastasis, and angiogenesis. NRP1 functions as a potent modulator of immune cells in the tumor microenvironment. Suppressing NRP1 results in antitumor immune responses and affects the efficacy of cancer immunotherapy. Alterations in NRP1 expression are associated with poor prognosis across a spectrum of malignancies, indicating its potential as a biomarker for evaluating the prognosis of cancer patients. In the present review, we first aim to summarize the expression characteristics and clinical associations of NRP1 in gynecological cancers; second, we elaborate on the role and molecular mechanisms of NRP1 in the progression of these cancers. Therapeutic strategies targeting NRP1 to prevent the development of gynecological cancers will also be discussed. In conclusion, this review highlights the pivotal role of NRP1 in the progression of gynecological cancers and the development of targeted therapeutic strategies, suggesting that NRP1 is a key target for personalized treatment.

Keywords: neuropilin-1; ovarian cancer; cervical cancer; endometrial cancer; gynecological cancer; tumor immunity; targeted therapy

Introduction

According to statistics on newly diagnosed female cancer cases worldwide in 2022, gynecological malignancies account for 14.6% of the total number of female cancer cases, with associated deaths accounting for 15.2% [1]. Cervical cancer (CESC), ovarian cancer (OC), and endometrial cancer (EC) are the three most prevalent types of gynecological malignancies [2]. Overall, the incidence rates of these three cancers all exhibited an increasing trend, among which the increase in CESC incidence was the most prominent, followed by that of EC. Among gynecological malignancies, OC ranks first in terms of mortality, primarily because of its low early diagnosis rate and the high proportion of patients diagnosed at an advanced stage [3,4]. Additionally, the disease burden of CESC has decreased across all age groups of women, whereas that of OC has shifted toward younger women. In contrast, EC has a characteristic pattern of increasing incidence but decreasing mortality across all female age groups [5]. Consequently, early detection and standardized treatment represent pivotal strategies for improving survival outcomes. Current therapeutic modalities include surgery, chemotherapy, radiotherapy, and chemoradiotherapy, among others [6]. Gynecological malignancies encompass a wide spectrum of pathological subtypes, each with distinct clinical manifestations and significant variations in therapeutic sensitivity. With advancements in molecular biology research, targeted therapies involving PARP inhibitors have substantially improved the prognosis of a subset of OC patients [7]. Additionally, immunotherapy (e.g., pembrolizumab) has been approved by the FDA for the treatment of cervical cancer, providing a novel therapeutic option for this disease [8]. Moreover, targeted therapies have yielded breakthroughs in gynecological cancer treatment by intervening in core tumor-associated signaling pathways. A multitude of drugs that target mechanisms such as angiogenesis, DNA repair, and immune checkpoints have been approved for clinical application. More in-depth investigations are now focused on enhancing therapeutic efficacy, overcoming drug resistance, and advancing treatment toward comprehensive precision [9].

Neuropilin-1 (NRP1), a nontyrosine kinase receptor subtype belonging to the NRP protein family, is a type I transmembrane protein. Its structure comprises an N-terminal signal peptide, two CUB domains (a1/a2), two coagulation factor V/VIII-like domains (b1/b2), one MAM domain (c), a transmembrane helix, and a short cytoplasmic domain [10,11]. These specific domains function as coreceptors by binding to ligands such as vascular endothelial growth factor (VEGF) and semaphorin proteins, thereby participating in the regulation of diverse signaling pathways (Fig. 1). Thus, NRP1 plays multiple crucial roles in cell survival, migration, invasion, angiogenesis, and axon guidance [12,13]. Studies have demonstrated that NRP1 serves as a key driver of malignant tumor progression. It facilitates tumor progression and metastasis by promoting cancer cell migration and invasion, inducing tumor angiogenesis, and enhancing cancer cell survival and proliferation [14]. NRP1 can act as a coreceptor for a variety of receptor tyrosine kinases (RTKs), including VEGF receptor (VEGFR), hepatocyte growth factor receptor (c-MET), platelet-derived growth factor receptor (PDGFR), and transforming growth factor-β receptor (TGF-βR). By participating in the regulation of tumor growth and tumor immune microenvironment (TIME) remodeling, NRP1 has garnered extensive attention in recent years [15]. NRP1 plays a role in the recruitment of regulatory T cells (Tregs) and in $CD8^+$ T-cell responses [16,17]. NRP1 impairs antitumor immune memory by suppressing the c-Jun/AP-1 signaling pathway, which in turn induces T-cell exhaustion and abrogates the formation of memory T cells [18]. NRP1 blockade not only enhances T-cell-mediated tumor killing but also exerts a synergistic effect with anti-PD-1 therapy to improve antitumor efficacy, thereby providing a novel strategy for combination immunotherapy [17].

In breast cancer (BC), increased NRP1 expression is significantly associated with an unfavorable clinical prognosis [19]. Among patients with metastatic BC receiving bevacizumab combined with taxane-based therapy, those with lower plasma NRP1 levels exhibit significantly longer overall survival (OS) [20]. Soluble NRP1 (sNRP1) has been identified as an independent biomarker for poor prognosis in early-stage BC [21]. In triple-negative BC (TNBC) xenograft models, knockout of the NRP1 gene markedly retards tumor growth and inhibits the formation of lung metastases [22]. These studies suggest that NRP1 shows significant alterations in gynecological cancers and that it can influence tumor progression by regulating a variety of biological functions. The multifaceted roles of NRP1 render it an attractive target for therapeutic intervention in gynecological cancers. The further development of NRP1-targeted strategies will contribute to advancing the treatment of gynecological cancers.

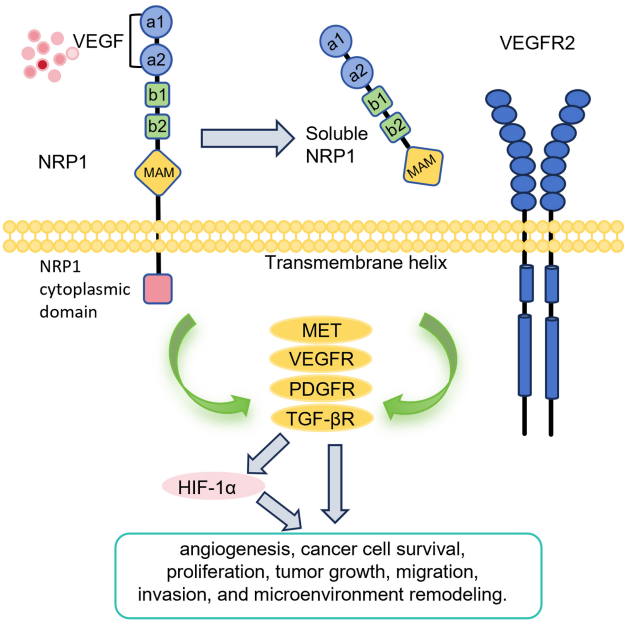

Fig. 1. Structure of NRP1 and its coreceptors. This figure summarizes the structure of NRP1 and its core receptor functions. NRP1 binds to ligands such as VEGF or SEMA3 through its specific extracellular domains and acts synergistically with a variety of signaling receptors (e.g., HIF-1α, MET, VEGFR, PDGFR, and TGF-βR). Therefore, it plays a core regulatory role in multiple physiological and pathological processes, including angiogenesis, axon guidance, and tumor progression. NRP1, neuropilin-1; VEGF and VEGFR, vascular endothelial growth factor and its receptors; SEMA3, Class 3 Semaphorinclass 3 semaphorin; MET, hepatocyte growth factor receptor; PDGFR, platelet-derived growth factor receptor; TGF-βR, transforming growth factor-beta receptor. Fig. 1 is created by authors using Microsoft PowerPoint (Redmond, Washington, USA).

Expression Characteristics of NRP1 in Gynecological Cancers

The expression of NRP1 is significantly altered in gynecological malignancies, including CESC, EC, and OC. Moreover, the expression changes of NRP1 have close associations with the clinical parameters of those cancers (Table 1 (Ref. [23–32]), Fig. 2).

Cervical Cancer (CESC)

Two studies determined the protein expression of NRP1 in CESC, CIN (cervical intraepithelial neoplasia), and normal tissues. The results of IHC suggested that NRP1 is significantly upregulated in CESC and CIN tissues (compared with normal tissues), and CESC tissues had higher NRP1 expression than that in CIN tissues. sNRP1, which was detected by ELISA, showed similar changes (Table 1) [23,24]. It is primarily distributed in the cytoplasm of dysplastic tumor cells, vascular endothelial cells, and immune

Table 1. Expression of NRP1 in gynecological tumors and its clinical significance.

Tumor Type	Study Group (n)	Control Group (n)	Detection methods	Expression	Prognosis	Ref.
CESC	CSCC (135), CIN (58)	normal cervical tissues (36)	RT–PCR, IHC	Upregulated	poor	[23]
	CESC (306)	normal tissues (13)	RNA-Seq	Downregulated	poor	[25]
	CIN (14), CESC (40)	normal cervix (20)	IHC	Upregulated	N.A.	[24]
EC	EC tissues (45)	hyperplastic endometrial tissues (15)	IHC	Upregulated	N.A.	[26]
	EC (174)	normal tissues (91)	RNA-Seq	Downregulated	N.A.	[25]
	Serum from EC patients (93)	Serum from patients with noncancerous endometrial lesions (66)	ELISA	Upregulated	N.A.	[32]
OC	benign ovarian tissues (n = 7) and in OC tissues (63)	normal tissues (7)	IHC	Upregulated	N.A.	[28]
	OC tissues (125)	normal tissues (15)	RT–PCR	Upregulated	poor	[27]
	Tumor (426)	normal tissues (88)	RNA-Seq	Downregulated	N.A.	[25]
	OC tissues (28)	normal tissues (12)	RT–PCR	Downregulated	N.A.	[29]
	OC patients (88)	healthy controls (30)	ELISA	not significant	poor	[30]
	borderline tumors (18), OC tissues (64)	benign cystadenomas (23)	IHC	Upregulated	not significant	[31]

Note: CESC, cervical cancer; CIN, cervical intraepithelial neoplasia; CSCC, cervical squamous cell carcinoma; OC, ovarian cancer; EC, endometrial cancer; NRP1, neuropilin-1; N.A., not available; IHC, immunohistochemistry; RNA-Seq, RNA sequencing; RT–PCR, reverse transcription–polymerase chain reaction; ELISA, enzyme–linked immunosorbent assay.

cells within the tumor microenvironment, with partial expression also localized on the cell membrane. NRP1 protein expression in poorly differentiated tumor cells was lower than that in moderately differentiated and well-differentiated tumors. This phenomenon suggests a complex relationship between NRP1 expression and the differentiation status of tumor cells [24]. RNA-seq analysis revealed that the NRP1 mRNA level was lower in CESCs than in normal tissues [25]. However, higher *NRP1* mRNA (detected by RT–PCR) expression was detected in CESCs than in normal cervical tissues and CIN tissues. The NRP1 level was further increased in the tumor tissues of CESC patients at higher FIGO stages and patients with positive lymph node metastasis [23]. Higher NRP1 protein and mRNA levels are significantly associated with poorer prognosis [23,25]. Additionally, the level of circulating sNRP1 showed good ability in distinguishing normal tissues from cervical cancer (area under curve (AUC) = 0.7955, p = 0.0002187) and CIN (AUC = 0.7865, p = 0.002916) [24]. Those studies indicate the potential roles of NRP1 as a diagnostic biomarker in CESC both at early and late stages. However, considering the clinical heterogeneity among patients with CESCs as well as different detection methods, the expression changes of NRP1 in CESC are difficult to conclude based on those three studies. More studies, especially those with large clinical samples, are needed to verify the mRNA and protein expression features of NRP1 in CESC.

Endometrial Cancer (EC)

NRP1 is specifically expressed in the cytoplasm of EC cells but is barely detectable in normal endometrial tissues [26]. Based on IHC analysis, NRP1 expression showed negative expressions in normal tissues, but was found to be significantly upregulated in EC tissues, and its expression intensity is closely associated with the degree of tumor malignancy. Specifically, the NRP1 level in moderately differentiated (G2) and poorly differentiated (G3) tumors was significantly augmented than that in well-differentiated (G1) tumors—reaching 1.9-fold greater than that in the G1 group—and increased progressively with increasing pathological grade (from G1 to G3) [26].

In a transgenic MISIIR-TAg mouse OC model, Neural precursor cell expressed, developmentally downregulated 9 (Nedd9) deficiency restrained tumor growth, dissemination, and oncogenic signaling [33]. In endometrioid adenocarcinoma (EA), NEDD9 was found significantly enhanced than that in the normal proliferative endometria with benign uterine fibroids. Elevated NEDD9 was markedly correlated with the clinical stage, lymph node, histological grade, and metastasis of EA [34]. Those two studies suggest that NEDD9 functions as an oncogenic and prometastatic factor in OC or EC. Interestingly, NRP1 expression is significantly correlated with the expression of NEDD9, suggesting that NRP1 might mediate the metastatic potential of EC [35]. However, the mRNA level of NRP1, which was determined by RNA-seq, showed a significant decline in EC tissues compared to that in normal tissues [25]. These results suggest that NRP1 shows altered expression in patients with EC, and its level might be associated with their prognosis. However, further investigations are needed to verify that.

Ovarian Cancer (OC)

Several preclinical studies have revealed that the NRP1 mRNA and protein levels are elevated in OC tissues and are positively correlated with advanced International Federation of Gynecology and Obstetric (FIGO) stage and lymph node metastasis [27,28,32]. For example, Jiang *et al.* [27] evaluated alterations in NRP1 in epithelial ovarian cancer (EOC, n = 125) (the most common pathological type of OC) and normal ovarian epithelium (n = 15). They reported a greater NRP1 mRNA level in EOC than in normal ovarian epithelium. Elevated NRP1 mRNA levels were significantly correlated with advanced FIGO stage (p = 0.025), poorly differentiated histological grade (p = 0.049), lymphatic metastasis (p = 0.006), and distant metastasis (p = 0.024). NRP1 levels are not significantly altered in OC patients of different ages, tumor sizes, or histological types [27]. Adham *et al.* [28] reported that the NRP1 protein (determined by IHC) is markedly increased in EOC compared with normal and benign cases. Among the three subtypes of EOC, serous cystadenocarcinoma, endometrioid adenocarcinoma, and mucinous cystadenocarcinoma, the NRP1 protein level is not significantly altered [28]. Baba *et al.* [36] also reported that NRP1 detected by IHC has a positive expression rate of 95.7% in EOC, whereas it is not expressed in all normal ovarian surface epithelium cells or benign ovarian tumor cells. Bednarek *et al.* [37] evaluated NRP1 expression in 53 EOC tissue samples via immunohistochemistry (IHC). The data revealed that 41.5% of EOC cases had negative NRP1 staining, whereas 24.5% had weak (+) staining or strong (++) staining. Moreover, NRP1 expression was not significantly altered in EOCs with different menopausal statuses or histological types [37].

Additionally, enhanced NRP1 protein level is associated with shortened OS in patients, suggesting that NRP1 is an independent prognostic factor for poor outcomes in patients with OC [27]. At the circulatory level, Klotz *et al.* [30] determined sNRP1 via ELISA. Although no significant difference in sNRP1 levels was found between healthy controls (n = 30) and OC patients (n = 88), higher sNRP1 levels were correlated with reduced progression-free survival (PFS) (p = 0.037) and OS (p = 0.032) in OC patients [30].

The downregulated expression of NRP1 in OC has been reported in several studies. RNA-seq analysis revealed that the NRP1 mRNA level was lower in OC tissues than in normal tissues [25]. Vescarelli *et al.* [29] performed RT–PCR to examine NRP1 mRNA levels in OC (n = 28, in-

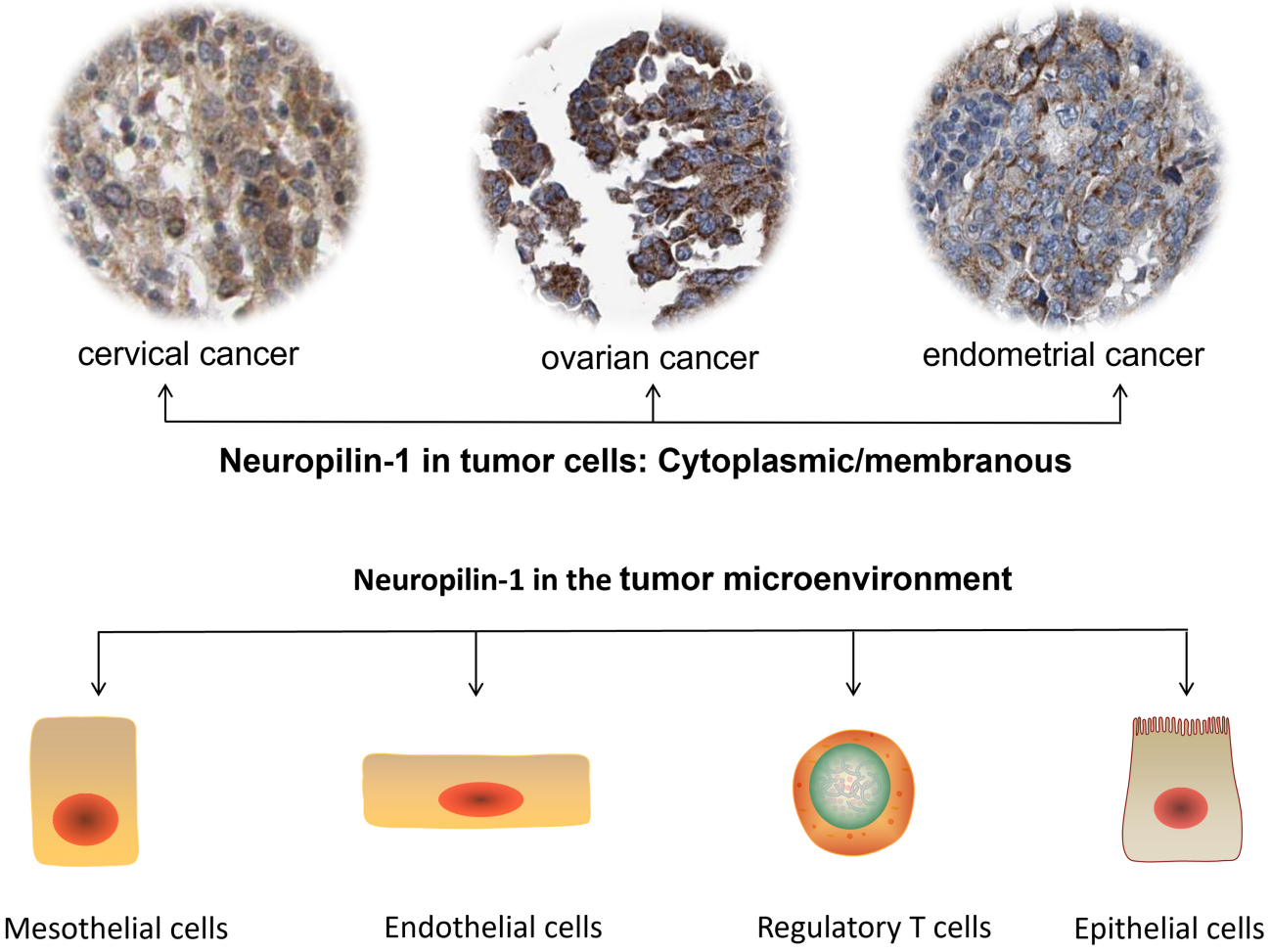

Fig. 2. Cellular expression and localization of NRP1 in gynecological cancers. This schematic diagram summarizes the typical distribution pattern of NRP1 in major gynecological cancers. Generally, NRP1 is mainly expressed in cytoplasm and cell membrane of tumor cells from these cancers. In cervical cancer, NRP1 is widely distributed in the tumor cells, vascular endothelial cells, and immune cells (Tregs, dendritic cells). In endometrial cancer, NRP1 is mostly expressed in cancer cells, without disruption on other cellular components. The expression of NRP1 in three gynecological cancers was analyzed via the Human Protein Atlas (https://www.proteinatlas.org/). Fig. 2 is created by authors using Microsoft PowerPoint (Redmond, Washington, USA).

cluding 26 patients with serous carcinomas and 2 with mucinous carcinomas) and normal ovarian tissues. They reported reduced NRP1 levels in OC tissues (0.6-fold change compared with normal ovarian samples). In addition, the mRNA and protein levels of NRP1 were lower in UWB and UWB-BRCA cells (two serous OC cell lines) than in SKOV3 cells (an ovarian adenocarcinoma cell line) [29]. From the perspective of cellular localization, NRP1 is localized primarily in the nucleus and cytoplasm of normal ovarian epithelial cells. A stronger fluorescence intensity of NRP1 was found in EOC samples [27,28]. Within the tumor microenvironment of OC, NRP1 is highly expressed in mesothelial cells and exists in either a membrane-bound form on the cell surface or a soluble form in ascites [38].

On the basis of current studies, NRP1 expression has distinct characteristics in terms of OC histological subtypes and clinicopathological stages. The expression pattern of NRP1 may be influenced by tumor heterogeneity and histological subtype. In addition, different detection methods, including RNA-seq, RT–PCR, ELISA, Western blotting, and IHC, which can measure NRP1 expression at different levels, might also affect the results. For example, NRP1 mRNA was reduced in CESC, EC and OC tissues (compared with normal tissues) according to RNA-seq data [25]. However, two studies in which RT–PCR was used to detect NRP1 mRNA revealed opposite results [23,27]. At the protein level, most studies have suggested that NRP1 is upregulated in these three tumor tissues. These inconsistent results indicate that the expression pattern of NRP1 is likely regulated by multiple factors. Future investigations, especially a comprehensive analysis of NRP1 expression in a large number of samples, are necessary to confirm the diagnostic role of NRP1 in OC.

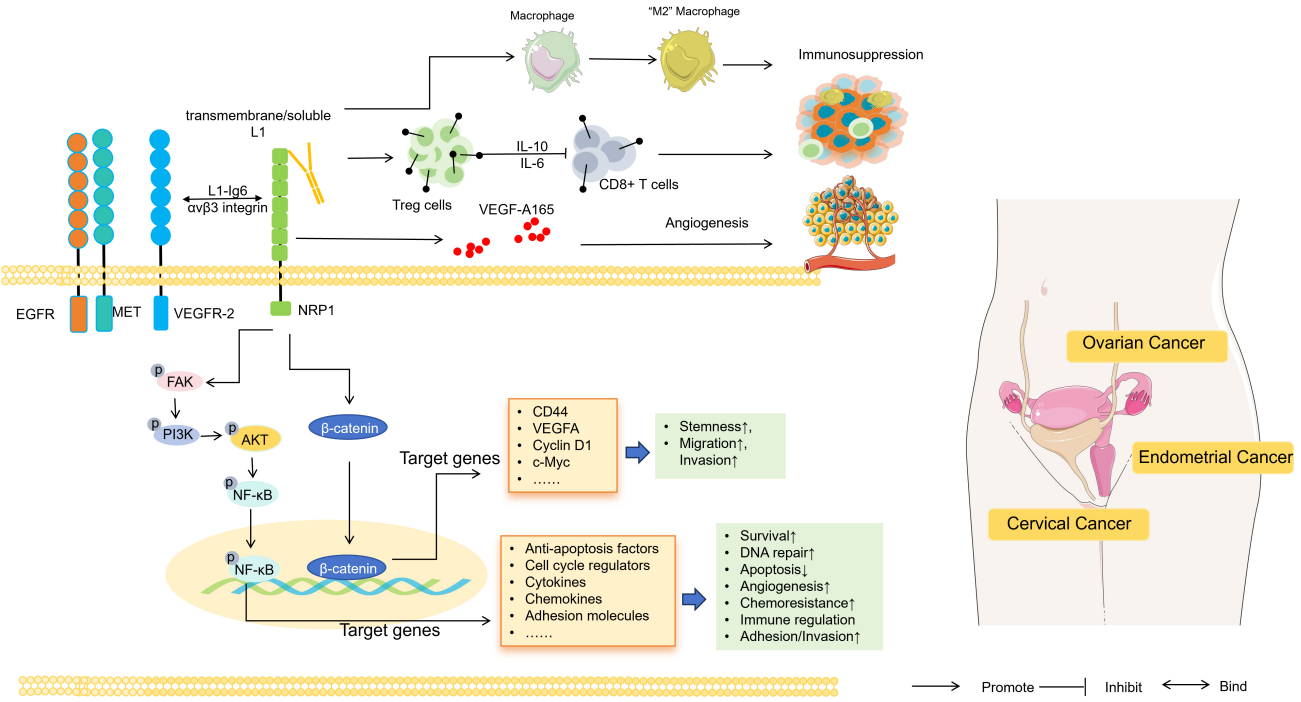

Fig. 3. Biological functions and molecular mechanisms of NRP1 in gynecological cancers. NRP1 plays a role in mediating multiple biological processes, including angiogenesis, survival, apoptosis, growth, migration, invasion, metastasis, stemness, and chemoresistance, and affects the tumor immune microenvironment. NRP1 drives the malignant progression of tumors through multiple pathways. NRP1 binds its coreceptors, including MET, EGFR, or VEGFR-2. PI3K/AKT/NF-κB signaling and Wnt-β-catenin signaling are subsequently activated. Multiple genes are regulated by those signaling pathways, which play essential roles in cell migration, invasion, angiogenesis, stemness, survival, DNA repair, and anti-apoptosis. In the tumor microenvironment, NRP1 enriches Treg cells, inhibits the function of $CD8^+$ T cells, and induces the polarization of macrophages toward the M2 phenotype, thereby reshaping the immunosuppressive state. Fig. 3 is created by authors using Microsoft PowerPoint (Redmond, Washington, USA).

Functions of NRP1 in Gynecological Cancers

As a multifunctional coreceptor, NRP1 plays a pivotal role in the initiation, progression, and metastasis of gynecological cancers. Moreover, NRP1 is also able to mediate tumor angiogenesis, antitumor immunity, and antitumor resistance (Fig. 3).

Tumor Angiogenesis

Considering the great importance of antiangiogenic therapy in gynecological cancers, a better understanding of the mechanisms involved in angiogenesis is urgently needed. Studies have shown that in CESC, tumor neovascularization is associated with an aggressive disease trajectory, with vascular markers visualized via colposcopy, elevated microvessel density, and CD31 positivity all serving as predictors of poor prognosis [39]. In EC, high expression of factors such as VEGF-C is significantly correlated with aggressive characteristics, including clinical stage, lymph node metastasis, and depth of myometrial invasion [40]. In OC, upregulation of the VEGF/VEGFR signaling pathway underpins the formation of ascites and metastatic dissemination [41,42]. NRP1 acts as a key regulatory factor in angiogenesis. As a coreceptor for VEGF-A, NRP1 forms a complex with VEGFR2, thereby mediating optimal VEGF signaling and cell migration to facilitate angiogenesis [43]. Collectively, these findings underscore the critical role of NRP1 in the pathogenesis of gynecological cancers by virtue of its ability to promote angiogenesis.

Tumor Growth, Invasion, and Metastasis

In CESCs, NRP1 is involved in regulating the endothelial–mesenchymal transition (EndMT) process. Studies have shown that the expression level of NRP1 is positively correlated with the protein expression of multiple EndMT markers and can promote EndMT in CESC cells, thereby enhancing the malignant phenotype of these cells. The results of functional experiments demonstrated that downregulation of NRP1 significantly inhibited the proliferation, migration, and invasion abilities of CESCs. In xenograft mouse models, CESCs with low NRP1 expression exhibited a significantly reduced ability to grow [23].

In EC, NRP1 significantly enhances the migration and invasion abilities of EC cells by mediating tamoxifen-induced epithelial–mesenchymal transition (EMT). Silencing NRP1 can effectively suppress the aforementioned ma-

lignant behaviors, suggesting that targeting NRP1 holds promise as a novel therapeutic strategy for preventing tamoxifen-associated EC metastasis [44]. NRP1 acts as a key oncogenic mediator in the initiation and progression of OC by mediating cell proliferation, invasion, and evasion of contact inhibition [36].

Mediating the Antitumor TIME

NRP1 plays a pivotal role in maintaining the function, stability, and survival of Tregs within the TME [45]. NRP1 significantly suppresses long-term antitumor immune reactions. In CESCs, the upregulation of NRP1 contributes to the formation of an immunosuppressive TME [46]. Studies have further revealed that neoadjuvant chemoradiotherapy can specifically deplete the $NRP1^+$ Treg subset in tumor-draining lymph nodes (TDLNs) while simultaneously promoting the recruitment and expansion of effector T cells and natural killer (NK) cells, ultimately leading to the shrinkage of primary tumors. Additionally, a reduction in $NRP1^+$ Tregs within TDLNs is directly positively correlated with favorable therapeutic responses in patients [47].

Chemoresistance

NRP1 plays a crucial role in olaparib resistance in OC, as its expression level is closely associated with drug sensitivity. NRP1 is highly expressed in the drug-resistant SKOV3 cell line; following long-term olaparib treatment, its expression is also upregulated in some sensitive cell lines (e.g., UWB-BRCA), and this upregulation correlates with poor drug response. These results demonstrated that selective inhibition of NRP1 can effectively reverse olaparib resistance in SKOV3 cells. Silencing NRP1 restored the sensitivity of drug-resistant OC cells to olaparib, suggesting that blocking NRP1 expression may serve as a potential strategy to increase the response of resistant cells to PARP inhibitors. Specifically, after olaparib treatment, downregulation of NRP1 in drug-resistant SKOV3 cells significantly inhibited cell viability, reduced colony-forming capacity, and induced apoptosis. These findings further confirmed that depletion of NRP1 can restore cell sensitivity to PARP inhibitors. In summary, targeting NRP1 can significantly increase the antitumor efficacy of olaparib in drug-resistant OC cells, providing a novel potential therapeutic strategy for reversing PARP inhibitor resistance in clinical practice [29]. Chen *et al.* conducted a bioinformatics analysis and revealed that NRP1, which is targeted by miR-130a and miR-130b, is a hub gene involved in multidrug resistance in EOC [84].

Molecular Mechanisms of NRP1 in Malignant Gynecological Cancers

VEGF Signaling Pathway and Tumor Angiogenesis

NRP1 promotes tumor angiogenesis in OC through multiple mechanisms. NRP1 is coexpressed with VEGFR-2 on endothelial cells and functions as a coreceptor to enhance the biological response to VEGF165, thereby amplifying VEGF-mediated angiogenic signal transduction [49]. Additionally, NRP1 can directly bind to VEGF-A165, a critical regulator of pathological angiogenesis, further driving the angiogenic process [50,51]. In addition to the VEGF pathway, NRP1 also participates in the proangiogenic pathway mediated by the L1 molecule. Studies have demonstrated that transmembrane L1 expressed by OC cells can bind to NRP1 on the surface of mesothelial cells. Soluble L1 derived from patients' ascites is also capable of interacting with NRP1 [38]. In glucose-starved EOC cells, VEGF transcription and secretion are increased. The protein levels of VEGFR2 and NRP1 were reduced. In contrast, the mRNA level of NRP1 was elevated, suggesting a mechanism of feedback upon protein reduction. This study revealed that VEGF/VEGFR2 expression was modulated by glucose and further indicated that the metabolic status of OC patients may affect the effectiveness of antiangiogenic therapies [50]. Wang *et al.* [52] determined the correlation between VEGFR-1, VEGFR-2, NRP1, NRP2, VEGF (121), and VEGF-A165 levels and cell invasion in EOC cell lines. They reported that VEGF and VEGFR-2 levels are increased in EOC cell lines with increased invasiveness. In addition, VEGFR-2 expression in OC tissues is correlated with tumor grade [52].

Invasion and Metastasis Regulation

NRP1 regulates the invasion and metastasis of tumor cells by mediating EMT. Studies in breast cancer have confirmed that NRP1 can induce key phenotypic changes in EMT by activating the NF-κB and β-catenin pathways, leading to the downregulation of E-cadherin and Occludin and the upregulation of Snail and N-cadherin [51]. EMT is a critical step in the metastasis and invasion of OC [53], CESC [54], and EC [55]. Considering that the NF-κB and β-catenin pathways have been verified to be involved in regulating EMT [56,57], NRP1 is highly likely to drive the invasive phenotype of cells through similar molecular mechanisms in malignant gynecological tumors.

Regulation of the TIME

NRP1 serves as a critical marker for identifying Treg subsets with potent suppressive functions [58]. Its high expression is positively correlated with the immunosuppressive TME. Knocking out NRP1 enhances the fragility of Tregs and facilitates the clearance of tumor cells by inducing antitumor immunity [45]. Clinical evidence shows that $NRP1^+$ Tregs are significantly enriched in the TDLNs of CESC patients, particularly in TDLNs with tumor metastasis [47]; moreover, the proportion of $NRP1^+$ Tregs in the peripheral blood of OC patients is also significantly greater than that in patients with benign lesions [59]. These findings suggest that the $NRP1^+$ Treg subset plays an important role in establishing the immunosuppressive TME of

gynecological cancers. Moreover, tumor cells can produce VEGF, which acts as a natural ligand of NRP1. Within the TME, immunosuppressive cells are recruited to and maintained in tumors through the VEGF-NRP1 signaling pathway [60]. NRP1 expression is significantly positively correlated with PD-L1 expression in CESCs, further indicating that NRP1 is involved in regulating tumor immune evasion [61]. In myeloid immune cells, NRP1 also plays a pivotal role in immunoregulation. Studies have demonstrated that within the context of CESCs, the hypoxic TME can upregulate NRP1 expression in cancer cells, which in turn induces the polarization of macrophages toward the M2 phenotype. This cascade of events directly facilitates the progression of the disease according to the FIGO staging system, as well as the occurrence of lymph node metastasis and other malignant clinical behaviors [62].

At the effector T-cell level, NRP1 signaling directly impairs the antitumor immunity of $CD8^+$ T cells. Mechanistic studies have shown that specific NRP1 ablation in $CD8^+$ T cells does not affect primary tumor control but rather endows the host with a stronger ability to resist tumor rechallenge and significantly enhances the response to anti-PD-1 therapy [17]. These findings indicate that NRP1 intrinsically weakens the long-term immune memory function of T cells and drives them toward exhaustion [18]. Thus, targeting NRP1 is expected to fundamentally prevent T-cell exhaustion, promote long-term memory formation, and thereby offer new hope for improving immunotherapy efficacy.

Multiple Pathways Inducing Therapeutic Resistance

The PI3K/AKT signaling pathway is critical for regulating cell survival, growth and apoptosis [63]. In OC, sustained activation of NRP1 can directly counteract the apoptosis induced by PARP inhibitors (e.g., olaparib) [29]. Cancer stem cells (CSCs) often cause chemotherapy failure due to their high degree of resistance [64]. Studies have shown that NRP1 plays a key role in the formation and maintenance of CSC properties in various malignancies, such as medulloblastoma, glioblastoma, triple-negative breast cancer, and squamous cell carcinoma [65–68]. In OC, NRP1 is highly expressed and thus serves as a key receptor for targeted drug delivery. Through ligand–receptor binding mediated by specific ligands (e.g., the iRGD peptide), active targeting and efficient delivery of therapeutic drugs to CSCs can be achieved, helping drugs cross biological barriers and enter cells to exert therapeutic effects [69].

Targeted Therapeutic Strategies

Genetic Intervention

Studies have revealed the therapeutic potential of targeting NRP1 in cancers. For example, knocking down NRP1 expression via small interfering RNA (siRNA) transfection potently inhibited endothelial tube formation in both *in vitro* and *in vivo* models, accompanied by downregulated expression of vascular cell adhesion molecule (VCAM) [70]. *In vivo* experiments further demonstrated that tumors treated with NRP1-targeting siRNA presented a significant reduction in microvessel density and apoptosis. These findings underscore the robust antiangiogenic effects of NRP1 inhibition [70]. In the context of adenomyosis, short hairpin RNA (shRNA)-mediated NRP1 knockdown effectively suppressed estrogen (E2)-induced EMT [71]. ShRNA- or siRNA-mediated NRP1 inhibition has been found to repress OC progression both *in vitro* and *in vivo* [29,36]. Concurrently, NWs functionalized with the PL2 peptide (a NRP1-targeting moiety) have exhibited efficient tumor-targeting and penetration capabilities, laying a critical foundation for the development of peptide-based targeted anticancer therapies [72].

The anti-NRP1 monoclonal antibody MNRP1685A specifically binds to the VEGF-binding domain of NRP1, thereby blocking the VEGF signaling pathway. This inhibition subsequently impairs pericyte coverage of blood vessels and disrupts the normal maturation of the tumor vasculature [73]. When it is combined with iRGD, a cyclic peptide that activates NRP1, the tumor delivery efficiency of cell-penetrating peptides (CPPs/PTDs) is significantly diminished. This observation indicates that NRP1 activation is a key factor influencing drug extravasation across blood vessels and targeted delivery efficiency, suggesting that coordinated regulation of the NRP1 pathway may be promising for enhancing the targeted delivery of antitumor agents [74].

MiRNA-Mediated Posttranscriptional Regulation

MicroRNAs (miRNAs) are a class of endogenous noncoding single-stranded RNAs approximately 21–24 nucleotides in length, and they mediate the degradation or translational repression of target gene mRNAs by binding to their 3′-untranslated regions (3′-UTRs), thereby exerting pivotal posttranscriptional regulation of gene expression [75,76]. Aberrantly expressed tumor-suppressive or oncogenic miRNAs are implicated in tumor progression, metastasis, and therapeutic resistance [77,78]. Notably, the expression of NRP1 is subject to precise negative regulation by multiple specific miRNAs. Studies have demonstrated that miR-148 and miR-124 can directly target NRP1, acting as upstream suppressors of its signal transduction [79,80]. In adenomyosis, miR-124-3p inhibits the migration of endometrial stromal cells and the EMT process through direct targeting and suppression of NRP1 [81], and this regulatory relationship has significant pathological relevance across various cancers. In gastric cancer, miR-590 directly targets and inhibits NRP1 expression, blocking the VEGF signaling pathway and thereby significantly suppressing tumor angiogenesis, as well as cancer cell migration, invasion, and metastasis [82]. In pancreatic cancer, miR-141 has also been confirmed to negatively regulate NRP1, sug-

gesting that the miR-141/NRP1 axis represents a potential therapeutic target for this disease [83]. In EOC, miR-130a/b modulates NRP1 expression via direct targeting, which is associated with the development of multidrug resistance [84]. Additionally, re-expressing miR-200c can effectively reverse the resistance of OC cells to olaparib by downregulating NRP1 [29]. Collectively, these studies underscore broad prospects for improving cancer treatment by targeting the miRNA-NRP1 axis.

Antitumor Agents Targeting NRP1

The development of drugs targeting NRP1 has emerged as a novel strategy for antitumor therapy, with relevant candidate agents exhibiting diverse mechanisms of action. In preclinical models expressing NRP1, the novel monoclonal antibody A6-11-26 has been demonstrated to effectively inhibit tumor growth by targeting the b1b2 domain of NRP1 [48]. By potently inhibiting the binding of VEGF-A to NRP1, the small-molecule antagonist EG01377 combines antiangiogenic activity, the ability to suppress tumor cell migration and invasion, and immunomodulatory functions. EG01377 not only directly reduces VEGF-driven angiogenesis but also inhibits the activity of Tregs by attenuating TGF-β production, thereby demonstrating comprehensive antitumor potential [85]. Recently, pitavastatin was identified as a potent NRP1 inhibitor via virtual screening. Pitavastatin can bind to NRP1 in a direct manner and induce zinc finger X-chromosomal protein (ZFX) degradation, thus disrupting the NRP1-ZFX axis and overcoming multidrug resistance in HCT116 colorectal cancer cells and A549 lung cancer cells [86]. Interestingly, previous studies have verified the potent antitumor effects of pitavastatin in CESCs [87] and OCs [88,89] through the enhancement of apoptosis, oxidative stress, and DNA damage. These studies indicate that targeting NRP1 is an effective antitumor strategy.

NRP1 acts as a coreceptor of multiple receptors, such as EGFR, Met, and VEGFR2, and then activates multiple downstream signaling pathways. Therefore, NRP1 plays a role in adaptive resistance to targeted agents (e.g., lenvatinib), and targeted inhibition of NRP1 has shown potential in reversing chemical resistance [90]. Similarly, in melanoma and breast cancer, targeted therapies (e.g., BRAF or HER2 inhibitors) can upregulate NRP1 expression via the c-Jun N-terminal kinase (JNK) signaling pathway, thereby increasing EGFR/IGF1R signaling and triggering therapeutic resistance, whereas interference with NRP1 can improve drug efficacy [91]. These findings suggest that NRP1 may serve as a cross-cancer hub molecule that mediates therapeutic resistance. A previous study revealed that increased NRP1 expression is a key factor contributing to resistance to the PARP inhibitor olaparib in OC [29]. The roles of NRP1 in mediating therapeutic resistance, including resistance to conventional chemotherapy and radiotherapy, need to be investigated.

Current research on the development of NRP1-targeted nanomaterials has focused primarily on other cancer types, such as hepatocellular carcinoma and prostate cancer. Previous studies have demonstrated that NRP1-targeted nanotherapeutic strategies exhibit significant efficacy in multiple tumor models. For example, the intratumoral delivery of NRP1-targeted nanobodies can significantly inhibit tumor growth by blocking the NRP1/Sema3A axis and remodeling the TIME (e.g., increasing the ratio of proinflammatory macrophages and antigen-specific $CD8^+$ T cells) [92]. Additionally, Fmoc-Gffy-AP-CK2, a self-assembling nanopeptide, can specifically target NRP1. It exerts potent antitumor potential by inducing GSDME-mediated pyroptosis and synergistically enhancing the efficacy of PD-1 blockade [93]. Another study constructed gold nanoparticles functionalized with an NRP1-targeting peptide, which enables efficient delivery of platinum drugs to prostate cancer cells. Its cellular uptake and therapeutic efficacy are strictly dependent on the NRP1 receptor, demonstrating its potential for precise targeted therapy [94]. These successful cases from different cancer types provide solid proof-of-principle and promising research directions for extending NRP1-targeted nanotherapeutic strategies to the field of gynecological cancers.

In addition, the development of small-molecule inhibitors with high selectivity and favorable bioavailability represents another critical direction for intervention in the NRP1 signaling pathway. Currently, this strategy has demonstrated promising therapeutic potential in several cancers. For example, EG01377, the small-molecule inhibitor mentioned earlier, exerts both antiangiogenic and immunomodulatory effects by blocking the binding of VEGF-A to NRP1 [85]. In renal cancer models, the small-molecule inhibitor EG00229 blocks the VEGF-NRP1 axis, leading to the inhibition of tumor angiogenesis and the intrinsic growth of tumor cells [95]. Despite these studies providing robust proof-of-concept for NRP1 targeting, exploration of such small-molecule inhibitors in gynecological cancers remains extremely limited. Given the pivotal role of NRP1 in angiogenesis, metastasis, and the formation of an immunosuppressive TIME in malignant tumors, future research urgently needs to validate the efficacy of these small-molecule inhibitors in gynecological cancer models.

Recent studies have preliminarily revealed the pleiotropic roles of NRP1 in tumor progression. However, its intricate upstream and downstream molecular regulatory networks in gynecological cancers remain to be systematically elucidated. Research has demonstrated that SEMA3A can activate NRP1 signaling, thus enhancing the migratory capacity and anoikis resistance of tumor cells and contributing to the immunosuppressive TIME. These coordinated actions synergistically promote metastasis and immune evasion in pancreatic cancer [96]. Previous studies have shown that VEGF-VEGFR2-neuropilin-1 signaling regulates cancer stem-like cell viability and

tumor growth [68,97,98]. NRP1 has been identified as a coreceptor of VEGFR2. The PI3K/AKT pathway, which plays a potent role in maintaining the stemness of cancer cells [99], is considered a vital modulator of downstream VEGF-VEGFR2 signaling [100]. Other coreceptors of NRP1, such as EGFR [101,102] and MET [103], have been confirmed to mediate cancer stemness by activating the PI3K/AKT pathway. These findings provide crucial clues and directions for in-depth exploration of NRP1 regulatory mechanisms in gynecological cancers. Systematic delineation of the upstream and downstream molecular networks of NRP1 in gynecological cancers not only holds significant theoretical value but also offers novel molecular targets and a theoretical basis for the development of precise combination-targeting strategies.

Limitations

The present study presents a narrative review of the expression, functions, and regulatory mechanisms of NRP1 in three main gynecological cancers. Some limitations need to be described to improve future investigations in this field. First, the evaluation of the expression characteristics of NRP1 was based mainly on conclusions from researchers in separate studies. The detection techniques, tumor heterogeneity, and histological subtypes were not comprehensively analyzed via quantitative methods. These factors pose critical limitations when conclusions are drawn. Second, we searched the literature via PubMed, and most of the included literature was in English. Some literature published in other databases or languages might have been missed. Therefore, literature selection bias cannot be completely avoided. Third, therapeutic strategies targeting NRP1 are summarized on the basis of currently published articles. More sources, such as gray literature and clinical trials, should be included for analysis. Fourth, current studies have investigated the roles of targeting NRP1 in mediating therapeutic resistance in OCs; however, we have gained less knowledge about the effects of NRP1 regulation on therapeutic resistance in CESCs and ECs due to limited literature.

Conclusions

Current studies suggest that NRP1 expression is increased (especially the protein levels of NRP1 in tumors and sNRP1 in the serum) in CESCs, ECs, and OCs. A high NRP1 level was associated with advanced clinical stage and poor outcomes in patients with gynecological cancers. The functions of NRP1 in these cancers differ. In EC, NRP1 mainly promotes tumor migration, invasion, and EMT. In CESCs, NRP1 contributes to the induction of an immunosuppressive TME. In OC, NRP1 modulates tumor cell growth and chemoresistance and has potential roles in angiogenesis and the immunosuppressive TME. Multiple strategies, such as genetic interventions, miRNA-mediated posttranscriptional regulation, and specific targeted drugs, have been developed to treat CESCs, ECs, and OCs.

Availability of Data and Materials

Not applicable.

Author Contributions

HJ collected and analyzed the literature data and wrote the main manuscript text. MC conceived the idea and wrote and edited the manuscript. Both authors contributed to the critical revision of the manuscript and read and approved the final version. Both authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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