

REVIEW

The role of glial cell line-derived neurotrophic factor family member artemin in neurological disorders and cancers

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Abstract

Artemin (ARTN) is a member of the glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs), which encompasses family members, GDNF, neurturin (NRTN) and persephin (PSPN). ARTN is also referred to as Enovin or Neublastin, and bears structural characteristics of the TGF- β superfamily. ARTN contains a dibasic cleavage site (RXXR) that is predicted to be cleaved by furin to yield a carboxy-terminal 113 amino acid mature form. ARTN binds preferentially to receptor GFR α 3, coupled to a receptor tyrosine kinase RET, forming a signalling complex for the regulation of intracellular pathways that affect diverse outcomes of nervous system development and homeostasis. Standard signalling cascades activated by GFLs via RET include the phosphorylation of mitogen-activated protein kinase or MAPK (p-ERK, p-p38 and p-JNK), PI3K-AKT and Src. Neural cell adhesion molecule (NCAM) is an alternative signalling receptor for ARTN in the presence of GFR α 1, leading to activation of Fyn and FAK. Further, ARTN also interacts with heparan sulphate proteoglycan syndecan-3 and mediates non-RET signalling via activation of Src kinases. This review discusses the role of ARTN in spinal cord injury, neuropathic pain and other neurological disorders. Additionally, ARTN plays a role in non-neuron tissues, such as the formation of Peyer's patch-like structures in the lymphoid tissue of the gut. The emerging role of ARTN in cancers and therapeutic resistance to cancers is also explored. Further research is necessary to determine the function of ARTN in a tissue-specific manner, including its signalling mechanisms, in order to improve the therapeutic potential of ARTN in human diseases.

1 | INTRODUCTION

Glial cell line-derived neurotrophic factor (GDNF) was identified by its ability to support the survival of midbrain dopaminergic neurons, and as a distant relative of the transforming growth factor-beta

(TGF- β) superfamily.¹ The GDNF family ligands (GFLs), including GDNF, neurturin (NRTN), artemin (ARTN) and persephin (PSPN), are vital for the development and maintenance of homeostasis of the central and peripheral neurons of the mammalian nervous system.^{2,3} ARTN is also known as Enovin⁴ or Neublastin,⁵ and exhibits structural

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which undergoes further protein cleavage at the dibasic motif (RXXR) predicted to be cleaved by furin to yield a carboxy-terminal 113 amino acid mature form of functional ARTN with a disulphide-linked homodimer of 28 kDa protein (Figure 2A).^{4,5,9} ARTN bears sequence similarity with GDNF, NRTN and PSPN which also contain putative furin cleavage site of RXXR at amino acid residues 77, 95 and 60, respectively (Figure 2A).⁹ Recombinant ARTN proteins were expressed and purified from bacterial hosts, and exhibited biological activity associated with disulphide structural folding.^{13,14} Three dimensional structure of ARTN is known, and it resembles that of GDNF and NRTN, and has some homology with TGF-beta family members (Figure 2B).¹⁵

At the transcriptional level, ARTN mRNAs were reported to be expressed in developing nerve roots,⁹ Schwann cells⁶ and embryonic vascular smooth muscle cells.¹¹ The expression of ARTN was regulated by the master activator protein 1 (AP-1) transcription factor, c-Jun, in Schwann cells.¹⁶ Upregulation of ARTN was also identified in mesenchymal stem cells (MSCs) transplanted onto the cortex of brain injured rats, indicating a potential role of ARTN in central neural tissue regeneration.¹⁷

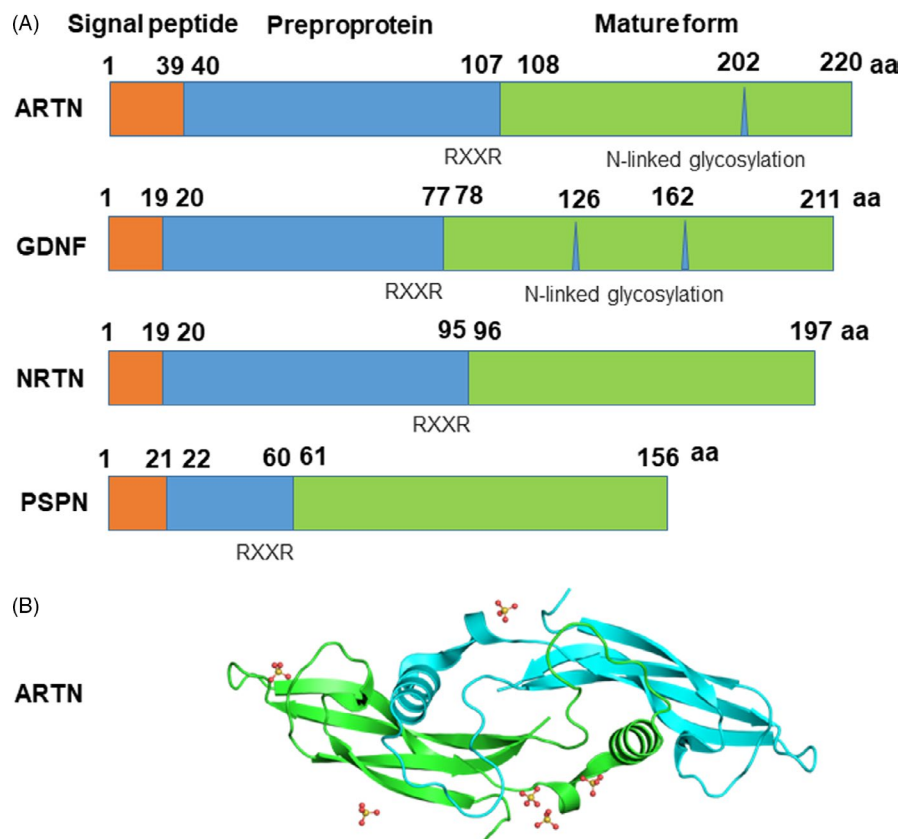
3 | ARTN RECEPTOR AND SIGNALLING PATHWAYS

GFLs, including ARTN, signal by the formation of a complex receptor system consisting of a ligand-specific non-signalling receptor subunit GFR α , coupled to a receptor tyrosine kinase, RET (Figure 3).¹⁸⁻²⁰

Four GFR α receptors have been identified (GFR α 1-4), and ARTN first binds to GFR α 3 which is attached to the membrane via glycosylphosphatidylinositol (GPI) anchor.^{9,21} And then the ARTN-GFR α 3 complex binds to and activates receptor tyrosine kinase RET by triggering phosphorylation of RET intracellular tyrosine residues,^{21,22} and this pathway is essential for migration, axonal growth and axon guidance of developing sympathetic neurons.²³ GFR α 3 was found to be strongly expressed in dorsal root ganglia cells and Schwann cells,²⁴ and in the developing brain, as well as in developing and adult peripheral nerves.²⁵ Consistently, RET mRNA was strongly expressed in motor neurons and dorsal root ganglion neurons.²⁴

Several cascades activated by GFLs via RET include the phosphorylation of MAPK (p-ERK, p-p38 and p-JNK), PI3-AKT and Src (Figure 3).²⁶⁻²⁹ GFL signalling is diverse, and ARTN could also signal independently of RET in combination with other receptors.^{2,7,9,30} The GFR α 1 has been suggested to be a receptor for ARTN,^{9,31} but displays much weaker binding to ARTN than GDNF³² and lack of functional role in ARTN-mediated cell activity.^{30,33,34} In addition, GDNF signalling was identified via the neural cell adhesion molecule (NCAM), which is distinct from RET signalling receptor for GDNF family ligands. Interaction of NCAM with GFR α 1 facilitates high-affinity binding of ARTN to NCAM, leading to activation of non-receptor tyrosine-protein kinase Fyn and focal adhesion kinase (FAK) in cells lacking RET (Figure 3).^{32,35} ARTN also binds to the heparin sulphate side chains of syndecan-3 and activates Src pathways, and this signalling does not require the presence of GFR α receptors (Figure 3).^{7,36}

FIGURE 2 Molecular structure of ARTN. A, Human homolog of ARTN contains an N terminal signal sequence and is expressed as a preproprotein, which contains a putative furin cleavage site of RXXR at amino acid residue 107, and is further processed as a mature form of a 113 amino acid functional ARTN with a putative glycosylation site, and disulphide-linked homodimer of 28 kDa peptide. ARTN shares a similar structure with GDNF, NRTN and PSPN which also contain putative furin cleavage site of RXXR at amino acid residues 77, 95 and 60, respectively. B, Tertiary structure analysis showing that ARTN shares typical features of TGF- β superfamily as predicted by EBI-based bioinformatics (<https://www.ebi.ac.uk/pdbe/entry/pdb/2ASK>)



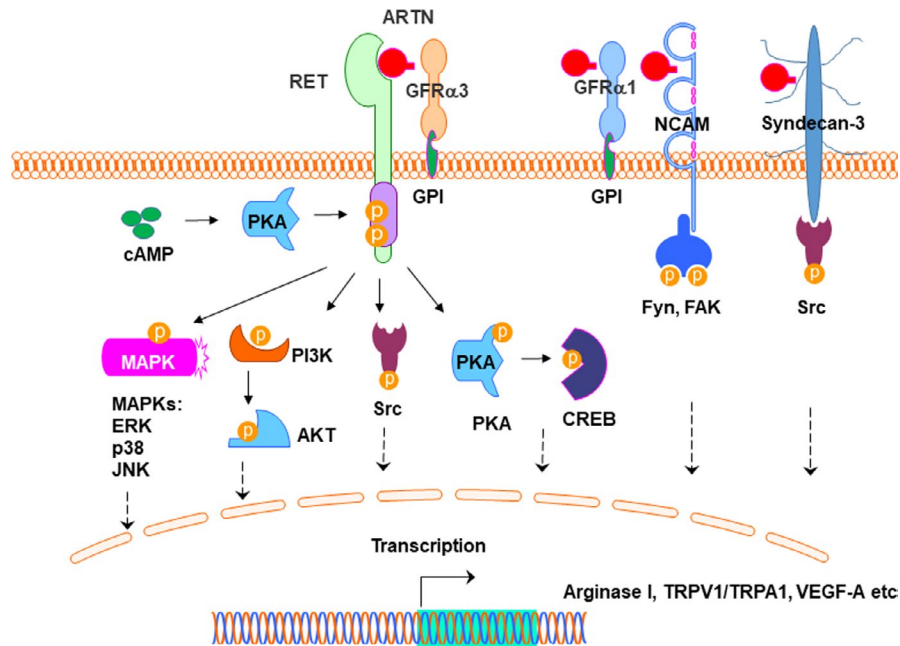


FIGURE 3 ARTN signalling. ARTN mediates the activation of the GFR α 3/RET receptor complex. ARTN binds to GFR α 3 which is attached to the membrane via GPI anchor. The GFR α 1/RET complex has also been suggested to be a putative receptor for ARTN. Several cascades activated by GFLs via RET include the phosphorylation of MAPK (p-ERK, p-p38 and p-JNK), PI3K-AKT and Src. In addition, NCAM is an alternative signalling receptor for ARTN only in the presence of GFR α 1, leading to activation of Fyn and FAK. Further, ARTN also interacts with heparan sulphate proteoglycan syndecan-3 and mediates non-RET signalling via activation of Src-type kinases. Interestingly, PKA might act as regulator of upstream of RET via cAMP, or as a downstream regulator of RET

It was observed that intracellular cyclic adenosine monophosphate (cAMP) elevation leads to the activation of protein kinase A (PKA) in neuronal cells.³⁷ Serine 696 in RET was identified as a putative phosphorylation site by upstream PKA, whereas phosphorylation of tyrosine 1062 in RET is crucial for the downstream activation of phosphatidylinositol 3-kinase (PI3K).³⁷ Consistently, using Ret-null Wolffian ducts in a budding experiment, it was shown that PKA is involved in GDNF-dependent effect.³⁸ (Figure 3). On the other hand, PKA might also act as a downstream regulator of RET. Using primary dorsal root ganglion neurons in culture, ARTN was found to support the extension of neurites through activation of PKA to phosphorylate cAMP-response element binding protein (CREB) (Figure 3).³⁹

The utility of ARTN signalling is exemplified by regulating the expression of genes involved in various biological processes, including arginase I in spinal cord neurons,³⁹ TRPV1 in cutaneous sensory neurons,⁴⁰ TRPA1 in trigeminal afferents,⁴¹ VEGF-A in human microvascular endothelial cells,⁴² and TRIO and F-actin binding protein (TRIOBP) and integrin, beta 5 (ITG β 5) in SMMC-7721 cells.⁴³ However, the transcription regulations by ARTN-mediated signalling are incompletely defined and require further investigation.

4 | THE ROLE OF ARTN IN SPINAL CORD INJURY REPAIR

Spinal cord injury (SCI) is debilitating and often has a poor prognosis, significantly due to our lack of understanding of its complex

pathogenesis. Functional recovery following SCI requires axon regrowth into the site of injury with synaptic connectivity to target tissues.⁴⁴ Increasing evidence shows that ARTN plays an important role in the functional recovery after spinal cord injury.^{39,45-47} Further, ARTN was found to enhance neurite extension in vitro by overcoming myelin inhibition and may have the potential to improve motor recovery following SCI in a rodent model.³⁹ Consistently, ARTN has been shown to preserve small types of nerve fibres, and type C fibre conduction velocity in the dorsal horn after SCI in a rodent model,³⁰ and administration of ARTN led to the formation of sensory fibres reaching to the site of injury, and facilitated the restoration of sensory function following SCI.⁴⁸ ARTN also modulates neurite initiation and neurite elongation, and the branching of unmyelinated sensory neurons in the spinal cord dorsal root ganglion (DRG) of mature rats,^{29,49} as well as the regeneration of myelinated axons.⁵⁰ Further, in DRG injury rats, the expressions of GFR α 1 and GFR α 3 were increased whereas the expression of GFR α 2 was unchanged.⁵¹ ARTN was found to promote neurite outgrowth and actin polymerization in mature DRG by affecting the transcription of many target genes⁴⁹ and stimulate the topographically correct regeneration of DRG axons in rodent dorsal root crush models.⁵² ARTN also induced and the regeneration of large, myelinated sensory afferents,⁴⁶ and the peripheral nerve regeneration, and functional restoration of nerve fibres in partial lesions distal to DRG,⁵³ which may be partially attributed to decreased caspase 3 and activating transcription factor 3 (ATF3) gene expression.⁵³

5 | THE ROLE OF ARTN IN NEUROPATHIC PAIN

ARTN and fellow GDNF family members also regulate the sensitivity of thermal nociceptors and hyperalgesia induced by inflammation,⁵⁴ which appears to be mediated by ARTN-GFR α 3 interactions.⁵⁵ Systemically administered ARTN was able to restore nociceptive and sensorimotor functions following injury.⁴⁸ Further, peripherally derived ARTN appeared to play an important role in inflammatory and neuropathic pain through the regulation of TRPV1/A1 (members of the TRP family of cation channels, that are activated by noxious thermal and chemical stimuli) expression in primary afferent neurons in DRG.⁵⁶ ARTN also modulates heat hyperalgesia and cold responses via TRPM8-associated signalling in mice,⁵⁷ which might involve the regulation of nicotinic acetylcholine receptor (nAChR) gene expression in thermal hypersensitivity.⁵⁸ In the light of the important role of ARTN in neuropathic pain, ARTN might serve as a potential target for pain therapeutics.⁵⁹ For example, small molecule BT13 that mimics the effect of ARTN has been shown to selectively activate RET signalling and to support neurite growth in a similar way to ARTN, providing additional indication of the potential of ARTN for developing medications to treat neuropathic pain.⁶⁰ In particular, ARTN could be delivered selectively to neurons that are responsible for cold pain,⁶¹ potentially through modulation of the expression of TRPV1 (a polymodal calcium-permeable cation channel activated by heat and inflammatory stimuli) and TRPA1 (an ionotropic channel responsive to cold and chemical stimuli) in cutaneous sensory neurons.⁴⁰ Recently, ARTN (BG00010) was trialled clinically for pain relief of unilateral sciatica.^{62,63} Results of the trial supported the further development of ARTN (BG00010) for the treatment of neuropathic pain.⁶² Further, randomized, double-blinded, placebo-controlled phase 2 trial showed evidence of pain relief ARTN (BG00010) with adverse event of headache, feeling hot and pruritus.⁶⁴ Consistently, ARTN appears to mediate hypersensitivity and itch to warmth, leading to abnormal peripheral innervation, thermal hyperalgesia and provoked itch sensation in pruritic skin disorders, such as atopic dermatitis (AD).⁶⁵ More recently, ARTN is involved in bone pain behaviour in a model of inflammatory bone via the activation and sensitization of bone afferent neurons.⁶⁶

6 | THE ROLE OF ARTN IN OTHER NEUROLOGICAL DISORDERS

In addition to SCI, increasingly data have implicated a role of ARTN in other neurological disorders. For instance, ARTN was found to induce neurite outgrowth from sympathetic neurons in the early stages of embryos⁶⁷ and exert distinct effects on the generation, survival and growth of sympathetic neurones in vivo.⁶⁸ ARTN could also enhance the regeneration of sensory axons in the brainstem.⁴⁶ ARTN was detected expressed in blood vessels during periods of early sympathetic differentiation, where it is considered to be a guidance factor, possibly by chemoattractive activity, for the growth of sympathetic fibres.¹¹ Using in vitro isolated mouse embryonic motor

neurons, ARTN was shown to act as a survival factor for parasympathetic preganglionic motor neurons through GFR α 3/Syndecan-3 activation.^{69,70} Further, ARTN was found to improve functional outcome after sciatic nerve injuries in rats.⁷⁰ In that study, the sciatic nerve was transected and treated with a fibrin sealant containing ARTN, and the results revealed that ARTN increased the number of regenerating motor neurons.⁷⁰ Interestingly, ARTN receptor GFR α 3 was found expressed in Schwann cells and not in motor neurons, suggesting that the effect on motor neuron axon regeneration was due to a paracrine effect through Schwann cells in the injured nerve.⁷⁰ Lentivirus-based transfer of the ARTN gene demonstrated a neuroprotective effect on the nigral dopamine neurons in vivo, comparable to GDNF.⁵ It is generally accepted that dopamine neurons do not express GFR α 3, and in the absence of GFR α 3 from dopamine neurons, ARTN (in high concentration) is likely to act via GFR α 1. Further, a GFR α 3 knockout mice study revealed that GFR α 3 signalling was required for the rostral migration of the superior cervical ganglion (SCG) precursors and for the survival of mature SCG neurons.⁷¹ GFLs, including ARTN, may provide a neuroprotective effect against excitotoxicity induced by compounds, such as *N*-methyl-D-aspartate (NMDA), as determined in a culture model of hippocampal brain slices.⁷²

In addition, gene polymorphisms or mutations of ARTN appear to be associated with Hirschsprung disease, a developmental disorder in the enteric nervous system.^{73,74} ARTN is also implicated in the antidepressant activity of acetyl-L-carnitine (ALCAR),⁷⁵ in dural afferent activity and migraine pain through modulation of primary afferent and sympathetic systems.⁷⁶ Further, the expression of ARTN is reported to be associated with other neurological disorders, including generalized anxiety disorder (GAD),⁷⁷ the pathogenesis of migraine,⁷⁸ the iNOS-mediated trigeminal pain pathway,⁷⁹ a hereditary form of ptosis⁸⁰ and autonomic neural dysplasia.⁸¹ Upregulation of ARTN mRNA was detected in the auditory nerve in association with deafness, indicating a possible role in the regulation of the auditory nerve system.⁸² Transgenic overexpression of ARTN in the tongue increases the expression of TRPV1 and TRPA1 in trigeminal afferents with altered oral sensation.⁴¹ ARTN also augments survival and axon regeneration in axotomized retinal ganglion cells in the optic nerve system.⁸³

7 | THE ROLE OF ARTN IN NON-NEUROLOGICAL DISORDERS

In addition to neural tissues, ARTN might affect non-neural organs. For instance, ARTN is a strong attractant of gut haematopoietic cells, inducing the formation of ectopic Peyer's patch-like structures, which is suggestive of a role in intestine organogenesis.⁸⁴ It was revealed that haematopoietic cells in the gut exhibit a random pattern of motility before forming the unique primordia structure of Peyer's patches via RET signalling. Knockout mice study showed that GFR α 3 deficiency exhibited impaired Peyer's patch development, suggesting that ARTN/ GFR α 3/RET mediates this process.⁸⁴

Overexpression of ARTN in chronic pancreatitis disturbs tissue homeostasis, leading to pancreatic fibrosis.⁸⁵ Using quantitative PCR (polymerase chain reaction) and Western blot analyses, it was found that ARTN and GFR α 3 were significantly overexpressed in chronic pancreatitis, and positively correlated with the severity of fibrosis. Further, transforming growth factor beta1 (TGF- β 1) upregulated the expression of ARTN in human pancreatic stellate cells (hPSCs) which might contribute to this pathogenesis.⁸⁵

8 | THE EMERGING ROLE OF ARTN IN CANCERS

Recently, a role of ARTN in tumorigenesis, tumour metastasis and drug resistance is emerging.⁸⁶ ARTN was found to promote metastasis and poor survival outcome in patients with estrogen receptor (ER) negative mammary carcinoma (ER-MC) via its cooperation with twist family BHLH transcription factor 1 (TWIST1). In this study, using a cohort of patients with ER-MC and ER-MC cell lines, it was revealed that overexpression of both ARTN and TWIST1 was associated with a poor survival outcome, whereas underexpression of both ARTN and TWIST1 predicted complete relapse free and overall survival in patients with ER-MC. Further, *in vitro* assays showed that ARTN promoted an increase in TWIST1 expression via the activation of AKT/PKB (protein kinase B) pathway, and knockdown of TWIST1 expression by siRNA abolished ARTN-mediated cellular metastasis behaviour.⁸⁷ ARTN also plays a role in mammary carcinoma progression and metastasis via enhancing endothelial cell proliferation, migration, invasion and Matrigel tube formation. Using xenograft experiments, mammary carcinoma cells overexpressing ARTN were found to induce tumour formation with increased microvessel density, accompanied by increased VEGF-A expression.⁸⁸ ARTN expression induced by oestrogen in mammary carcinoma is involved in resistance to tamoxifen therapy, whereas antagonism of ARTN appears to enhance the efficacy of anti-oestrogens and may represent an adjunctive therapeutic approach.⁸⁹ Genetic manipulation studies indicate that upregulation of ARTN increases the resistance of mammary carcinoma cells to trastuzumab; silencing of ARTN enhanced the efficacy of trastuzumab.⁹⁰ ARTN was found to enhance the population of CSCs and increase the resistance of CSCs to trastuzumab via upregulation of BCL-2 *in vitro*.⁹⁰ The expression of ARTN and receptor subunits may predict the progression and outcome of mammary carcinoma subtypes.⁹¹

In non-small-cell lung carcinoma (NSCLC), ARTN was identified to arbitrate the progression of human NSCLC, as determined by clinical and laboratory findings.⁹² NSCLC tissues showed increased expression of ARTN and advanced lymph node metastasis, which was accompanied by increased migration and invasion of NSCLC cells via upregulation of BCL2 transcription.⁹² Overexpression of ARTN was also found to promote the proliferation and invasiveness of lung cancer cells *in vitro*.⁹³ Similarly, the prognostic significance of ARTN expression in laryngeal squamous cell carcinoma (LSCC) may serve as predictors of LSCC progression and outcome in patients with LSCC.⁹⁴

In pancreatic adenocarcinoma (Pca), ARTN appears to participate in the generation of pancreatic neuropathy⁹⁵ and to stimulate the invasion and neurotrophic function of Pca *in vivo* and *in vitro*.⁹⁶ Consistently, ARTN and CXC chemokine receptor 4 (CXCR4) were found to be overexpressed in pancreatic cancer tissues, and the migration and invasion of pancreatic cancer cells appears to be promoted by Akt and ERK 1/2/NF- κ B signalling and the stromal cell-derived factor 1 α (SDF-1 α)/CXCR4 axis.⁹⁷

In hepatocellular carcinoma (HCC), ARTN was found to promote the growth and progression of HCC based on increased clinical tissue expression, increased tumour size, increased relapse and shorter survival time.⁹⁸ Further laboratory investigation found that HCC cells overexpressing ARTN demonstrated reduced apoptosis, increased proliferation and EMT, and increased motility via hypoxia-induced factor 1- α (HIF-1 α) regulated AKT signalling, indicating that ARTN may function in a hypoxic environment and promote HCC.⁹⁸

In endometrial carcinoma (EC), the expression levels of ARTN proteins were found to be positively correlated with the stage of EC and lymphatic metastasis.⁹⁹ Additionally, ARTN is implicated as a pathogenic factor for certain acute myeloid leukaemia (AML) patients, which warrants further investigation.¹⁰⁰ Activation of ARTN/GFR α 3-mediated RET signalling in AML cells requires further clinical investigation.¹⁰⁰ Further, downstream RET-mTORC1 signalling is found to promote AML cell growth through the suppression of autophagy and stabilization of leukaemia-genic drivers, indicating the potential of RET as a therapeutic target in subgroups of AML patients.¹⁰⁰

More recently, it was found that in the enlarged spleen of hosts bearing advanced tumours, erythroblast-like cells are enriched and boost tumour progression via producing ARTN into the blood.⁴³ Using hepatocellular carcinoma (HCC) tissues from HCC patients, the protein levels of GFR α 3 and phosphorylated RET were examined by immunohistochemistry (IHC) with automated cell acquisition. It was revealed that higher GFR α 3 mRNA expression and RET phosphorylation in HCC tissues were correlated with the reduced disease-free survival of HCC patients. Further, the higher levels of serum ARTN were correlated with the higher levels of GFR α 3 expression or higher RET phosphorylation in HCC tissues in patients with shorter disease-free survival.⁴³ Consistently, *in vivo* depletion or deficiency of ARTN inhibits the growth of HCC and abolishes tumour-promoting ability of erythroblast-like cells.⁴³

Bioinformatics gene analyses indicate that the ARTN transcripts are expressed in human and mouse cancers, most abundantly in Ewing's sarcoma in human and in melanoma in mouse (Figure 4).¹⁰¹ However, the mechanism by which ARTN is differentially expressed and involved in various types of cancers warrants further investigation.

9 | CONCLUSIONS

ARTN, a member of GDNF family ligands, plays a fundamental role in the development and homeostasis of the nervous system. ARTN is conserved among mammalian species and bears characteristics of

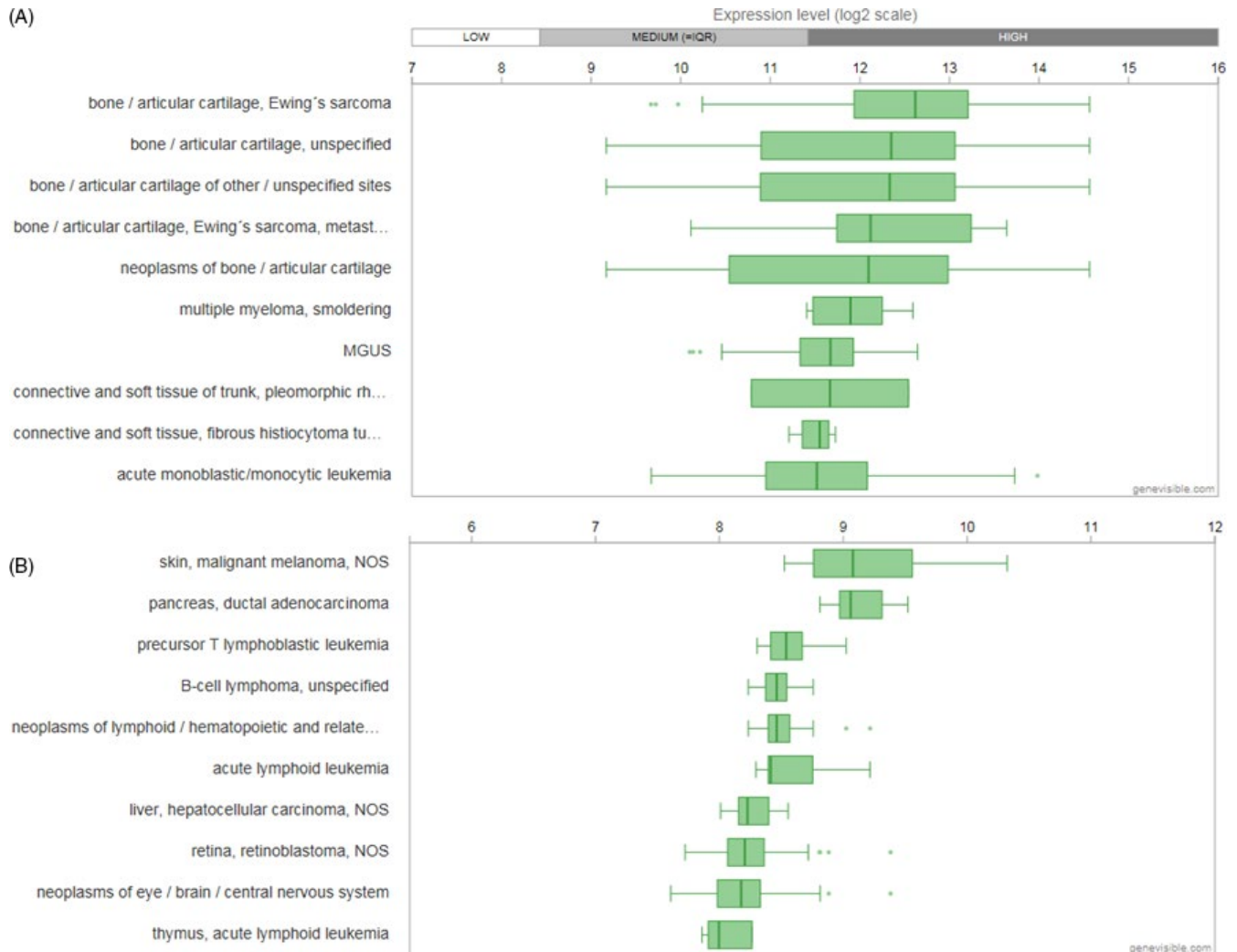


FIGURE 4 Bioinformatics analyses of ARTN gene expression in cancers. A, 10 human cancer types containing highest ARTN expression levels. B, 10 mouse cancer types containing highest ARTN expression levels. Analyses were performed by Genevisible[®] bioinformatics based on data from Affymetrix human genome U133 plus 2.0 array, and Affymetrix mouse genome 430 2.0 array, respectively (<http://genevisible.com>)

the TGF- β superfamily. Mechanistically, ARTN interacts preferentially with receptor GFR α 3, forming a signalling complex with RET which induces intracellular pathways and the transcriptional activity of target genes. Evidence suggests that ARTN plays an important role in functional recovery and neural regeneration following SCI and peripheral nerve injury. ARTN appears to be involved in other neurological disorders, such as Hirschsprung and motor neuron disease. ARTN also attracts hematopoietic cells to participate in the formation of Peyer's patch-like lymphoid tissue in the gut. Emerging evidence indicates that ARTN is involved in the tumorigenesis, tumour metastasis and therapeutic resistance to cancers, such as mammary carcinoma, pancreatic adenocarcinoma and acute myeloid leukaemia. ARTN, therefore, emerges as a potential therapeutic target for regenerative medical applications in the treatment of spinal cord injury, neuropathic pain and cancers. Further research is needed to develop the therapeutic potential of ARTN and GFL members, including GDNF.

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CONFLICT OF INTEREST

No conflict of interest.

AUTHOR CONTRIBUTION

Sipin Zhu and Yihe Li conducted research and drafted the manuscript. Samuel Bennett, Junhao Chen, Isabel Ziwei Weng and Lin Huang performed the protein structural analysis and provided evaluation and assistance in the process of drafting and revision of the manuscript. Huazi Xu and Jiake Xu supervised the study and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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