Role of angiomotin family members in human diseases (Review)

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Abstract. Angiomotin (Amot) family members, including Amot, Amot-like protein 1 (Amotl1) and Amot-like protein 2 (Amotl2), have been found to interact with angiostatins. In addition, Amot family members are involved in various physiological and pathological functions such as embryonic development, angiogenesis and tumorigenesis. Some studies have also demonstrated its regulation in signaling pathways such as the Hippo signaling pathway, AMPK signaling pathway and mTOR signaling pathways. Amot family members play an important role in neural stem cell differentiation, dendritic formation and synaptic maturation. In addition, an increasing number of studies have focused on their function in promoting and/or suppressing cancer, but the underlying mechanisms remain to be elucidated. The present review integrated relevant studies on upstream regulation and downstream signals of Amot family members, as well as the latest progress in physiological and pathological functions and clinical applications, hoping to offer important ideas for further research.

Contents

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1. Introduction

Studies have shown that angiogenesis and the formation of new blood vessels are closely related to the growth of malignant tumors (1,2). Angiostatin was one of the first angiogenesis inhibitors to inhibit endothelial cell migration (3). It inhibits tumor growth by inducing apoptosis *in vitro* and interfering with angiogenesis *in vivo* (4).

Amot was identified by its ability to bind to angiostatin in a yeast two-hybrid screening (5). Subsequently, Amotl1 and Amotl2, which share significant sequence homology with Amot, have been identified as family proteins (5). Amot is expressed in two different isoforms: Amot-p80 and Amot-p130 (6). During embryonic development, Amot family proteins regulate cell polarity, migration and proliferation through different signaling pathways (7). In zebrafish, *Amot* knockdown inhibits vascular migration (8). Knockdown of *Amotl2* inhibits cell proliferation and migration in cultured human umbilical vein endothelial cells and inhibits blood vessel formation (9). Amot family proteins have subsequently been found to play roles in the control of cell motility and assembly of endothelial cell-cell connections (6). An increasing number of studies have investigated the role of Amot-p130 in neuronal development in the central nervous system (10-12). Yes-associated protein (YAP)/Tafazzin (TAZ), a transcriptional regulator, is the major determinant of the sustained proliferation of neural stem cells (NSC) (11). During this process, Amot-p130 is strongly associated with YAP and triggers its degradation through a proteasome-mediated pathway (12).

The role of the Amot family members in cancer remains controversial (13). This protein may mediate the inhibitory effect of angiostatin on the migration of endothelial cells to growth factors during the formation of new blood vessels thereby inhibiting the proliferation of cancer cells (5). However, emerging studies have shown that *Amot* is an oncogene (1,14-20). In breast carcinoma (BRCA), osteosarcoma, colon adenocarcinoma (COAD), prostate adenocarcinoma

(PRAD), head and neck squamous cell carcinoma (HNSCC), cervical cancer (CCA), liver hepatocellular carcinoma (LIHC) and renal carcinoma (RCA), Amot family members all promote cancer cell proliferation and invasion (1,14-20). Conversely, Amot family members serve tumor suppressor roles in glioblastoma multiforme (GBM), diffuse large B-cell lymphoma (DLBCL), gastric cancer (GC), small cell lung cancer (SCLC), ovarian serous cystadenocarcinoma (OV) and lung squamous cell carcinoma (LSCC) (21-25). The present review summarized the structure, physiological function, upstream and downstream signal transduction pathways of each Amot family member, its function in tumors and other diseases and clinical targeted therapy.

2. The structure of Amot family

Amot-p130 is composed of 1084 amino acids and has an estimated molecular weight of 130 kDa (26) (Fig. 1A). Under alternative splicing between exons 2 and 3, the N-terminus of Amot-p130 is 409 amino acids longer than that of Amot-p80 (27). Amotl1 and Amotl2 are composed of 956 and 779 amino acids, respectively (27). All four classes of proteins contain conserved coiled-coil domains and a C-terminal PDZ motif (5). In addition to Amot-p80, the other three Amot family proteins contain the LPTY and PPXY motifs (28). All three L/P-PXY motifs of Amot-p130 can bind to the WW domain of Nedd4, leading to poly-ubiquitylated proteasomal degradation of Amot-p130 (28). The PPXY motif specifically interacts with YAP1/TAZ through its WW domain of YAP1/TAZ, thereby linking the Amot family proteins with the Hippo signaling pathway (29). In addition, LPTY is essential for the YAP1 interaction and its deletion leads to the failure of Amot family proteins to bind to YAP1 (28). Notably, the binding of different Amot family proteins to YAP1 serves opposite roles. In LIHC, Amot promotes the nuclear import and transcriptional activity of YAP1 to play a carcinogenic role (19). However, in GBM, Amotl2 acts as a tumor suppressor by binding to YAP1 and inhibiting its nuclear translocation (22). Through the PDZ motif, Amot family proteins were found to be associated with protein associated with Lin seven (PALS-1), PALS-1-associated tight junction protein (Patj, partition defective 3 (PAR3), the Rho GTPase-activating protein (GAP) and ARHGAP17 (RICH1/NADRIN) binding, thereby mapping how Amot family proteins are recruited to tight junctions (30). At present, the function of the coiled-coil domain has been less studied (31). One finding was that Amot family proteins interact with themselves through this domain, such as Amotl1, which binds to Amot-p80 through its coiled-coil domain (31).

3. Upstream and downstream regulation of the Amot family proteins

Translational modifications of the Amot family proteins. The expression of the Amot family proteins has been reported to be positively or negatively regulated by multiple factors (Table I). Studies have found that microRNA (miR)-205 and small interfering (si)RNA significantly reduces the invasiveness of BRCA by knockdown of Amot (32,33). In addition, miR-205 can downregulate the level of Amot in human umbilical vein endothelial cells, thus becoming a new molecular target for the development of anti-vascular drugs for tongue squamous cell carcinoma (33). Moreover, miR-497 acts as a suppressor of Amot gene expression, thereby inhibiting the proliferation and invasion of osteosarcoma cells (34). Another study showed that lncRNA small nucleolar RNA host gene 12 (SNHG12) promoted cell proliferation and migration by upregulating the Amot gene expression in osteosarcoma cells (15). Linc01555 was found to competitively bind to miR-122-5p and target CLIC1 (CLIC1 mediated miR-122-5p) to influence the occurrence and development of SCLC (24). Inhibition of linc01555 can upregulate Amot-p130 through the miR-122-5p/CLIC1 axis, thereby inhibiting SCLC growth *in vivo* (24). In CCA, miR-124 inhibits vasculogenic mimicry and cell motility by targeting the 3' untranslated region (3' UTR) of Amotl1 (35).

Post-translational modifications of the Amot family proteins. Experiments demonstrated that Amot-p130 (Ser^{175}) is phosphorylated as a direct substrate of LATS1/2, disrupting the interaction between Amot-p130 and F-actin, reducing F-actin stress fibers and local adhesions and mediating the function of the Hippo signaling pathway in endothelial cell migration and angiogenesis (36). Alternatively, Amotl1 (Ser^{262}) and Amotl2 (Ser^{159}) can also be phosphorylated by LATS1/2, thereby triggering the release of the Amot family proteins from cortical F-actin into the cytoplasm (37). Amotl1 (Ser^{793}) can be phosphorylated by AMPK, thereby increasing Amotl1 stability to inhibit YAP signaling (38).

Three members of neuronal precursor cell-expressed developmentally downregulated 4 (NEDD4)-like ubiquitin E3 ligases, NEDD4-1, NEDD4-2 and Itch/AIP4, mediate the polyubiquitination of Amot-p130, leading to Amot-p130 proteasomal degradation (28). However, Itch/AIP4-mediated non-degradative ubiquitination of Amot-p130 can enhance its stability (28,39). Amot has an unusually high affinity for NEDD4-1/NEDD4-2 and its binding is essential for stimulating HIV-1 viral envelopment and promoting infectivity (40). HECW2, a novel endothelial cell (EC) ubiquitin E3 ligase, plays a key role in stabilizing endothelial intercellular junctions by regulating the stability of Amotl1 (41). The Amotl2 protein is ADP-ribosylated by Poly ADP-ribose polymerase tankyrase-2 (TNKS2) and subsequently ubiquitinated and degraded by RNF146, an E3 ubiquitin ligase that recognizes ADP-ribosylated substrates (42). The ubiquitin-degradation is mediated by DNA damage-inducible 1 homolog 2 (43). In addition, USP9X functions as a deubiquitinating enzyme for Amot-p130 and Amotl2, which positively regulate the Hippo signaling pathway and enhance LATS kinase to inhibit tumor growth (44). A recent study has found that WWC proteins recruit USP9X stabilization Amot family proteins to regulate spinal cord genesis and cognition (45).

Downstream regulation of the Amot family proteins. YAP and Amotl1 are bound together in the nucleus (46). It has previously been found that Fat4 can sequestrate Amotl1 from the nucleus, which drives the nuclear translocation of YAP to promote the proliferation of cardiomyocytes (46). It has also been found that the phosphorylation state of Amot can be downregulated by flow shear stress via p38-Amot-YAP signaling, which promotes the translocation of Amot into the nucleus for the proliferation of periodontal ligament cells (47).

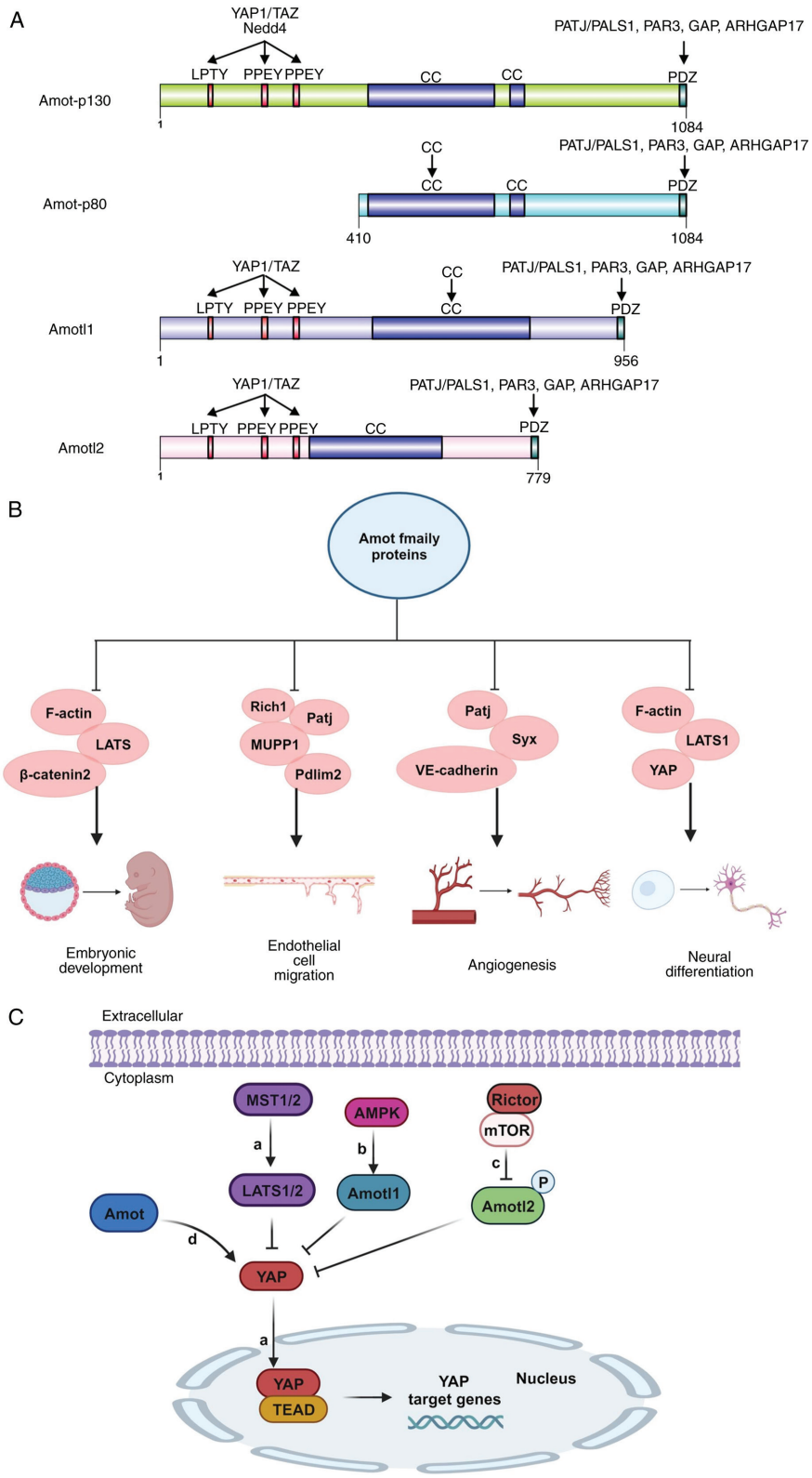

Figure 1. Biological functions of Amot family proteins and associated signal transduction pathways. (A) The structure of Amot family. (B) Role of the Amot family proteins in physiological regulation. (C) Signal transduction pathways involved in Amot family proteins. (a) In the Hippo signaling pathway, YAP enters the nucleus and forms a transcriptionally active complex with TEAD and other transcription factors to drive the expression of pro-proliferative or anti-apoptotic genes. (b) AMPK phosphorylates Amotl1, thereby inducing YAP retention in the cytoplasm to suppress tumorigenesis. (c) In glioblastoma multiforme, mTOR interacts with Rictor and phosphorylates Amotl2, making it unable to bind YAP and increasing YAP nuclear entry and transcriptional activity. (d) In liver hepatocellular carcinoma, Amot promotes the nuclear entry and transcriptional activity of YAP. Amot, angiomotin; Amotl1, Amot-like protein 1; Amotl2, Amot-like protein 2; LPTY, LPTY motif; PPEY, PPEY motif; Nedd, neuronal precursor cell-expressed developmentally downregulated; YAP, Yes-associated protein; TAZ, Tafazzin; PALS1, protein associated with Lin seven; Patj, PALS-1-associated tight junction protein; PAR3, partition defective 3; GAP, GTPase-activating protein; ARHGAP17/Rich1, Rho GTPase activating protein 17; MUPP1, multiple PDZ domain protein; Pdlim2, PDZ and LIM domain 2; Syx, Syntaxin; VE-cadherin, vascular endothelial cadherin; TEAD, transcriptional enhanced associate domains; MST1/2, mammalian STE20-like protein kinase 1/2; LATS1/2, large tumor suppressor homolog 1/2; AMP, adenosine 5'-monophosphate; AMPK, AMP-activated protein kinase; Rictor, recombinant protein.

Table I. Regulations of Amot family.

Regulation	Regulator	Promotes/inhibits Amot family	Function
Translational regulation	miR-205	Inhibits Amot	Reduces the invasiveness of BRCA
	miR-497	Inhibits Amot	Inhibits the proliferation and invasion of tumor cells
	lncRNA SNHG12	Promotes Amot	Promotes the proliferation and migration of osteosarcoma cells
	linc01555	Promotes Amot-p130	Inhibition of linc01555 can upregulate Amot-p130 through miR-122-5p/CLIC1 axis, thereby inhibiting SCLC growth *in vivo*
	miR-124	Inhibits Amotl1	Inhibits vasculogenic mimicry and cell motility
Post-translational modification	LATS1/2	Inhibits Amot	Mediates the function of the Hippo pathway in endothelial cell migration and angiogenesis
	LATS1/2	Inhibits Amotl1 and Amotl2	Triggers the release of the Amot family from cortical F-actin into the cytoplasm
	AMPK	Promotes Amotl1	Increases Amotl1 stability and promote YAP inhibition
	Nedd4-1, Nedd4-2,	Inhibits Amot-p130	Mediates the polyubiquitination of Amot-p130, leading to Amot-p130 proteasomal degradation
	Itch/AIP4,		
	Itch/AIP4	Promotes Amot	Enhances their stability
	Nedd4-1, Nedd4-2,	Inhibits Amot	Stimulates HIV-1 release and infection
	HECW2	Promotes Amotl1	Stabilizes endothelial intercellular junctions
	TNKS2	Inhibits Amotl2	ADP-ribosylates the Amotl2 protein, which is ubiquitinated and degraded by RNF146
	USP9X	Promotes Amot-p130 and Amotl2	Positively regulates the Hippo signaling pathway and enhances LATS kinase to inhibit tumor growth
Downstream regulation	Fat4	Promotes Amotl1	Sequestration of Amotl1 from the nucleus drives YAP nuclear translocation, thereby promoting cardiomyocyte proliferation
	Rich1	Inhibits Amot-p80	Competes with Merlin for binding to Amot-p80
	FSS	Promotes Amot	Promotes the localization of Amot in the nucleus for the proliferation of periodontal ligament cells
	TAp73	Promotes Amot	A direct transcriptional target of Amot and controls endothelial junction dynamics through the regulation of angiomotin
	WWOX	Inhibits Amot-p130	Negatively affects the export of filovirus VP40 virus-like particles
	KIKAT/LINC01061	Promotes Amot	Mediates the rearrangement of KDM4A from the Amot promoter region TSS and the transactivation of Amot.
	eIF4A	Promotes Amot	Their interaction is related to the protein synthesis ability of trophoblast cells

Amot, angiomotin; miR, microRNA; BRCA, breast carcinoma; lncRNA, long noncoding RNA; linc, long intergenic non-protein coding; CLIC1, chloride intracellular channel 1; SCLC, small cell lung cancer; LATS1/2, large tumor suppressor homolog 1/2; AMP, adenosine 5'-monophosphate; AMPK, AMP-activated protein kinase; Nedd4-1, neuronal precursor cell-expressed developmentally downregulated 4-1; Nedd4-2, neuronal precursor cell-expressed developmentally downregulated 4-2; Itch/AIP4, atrophin 1 interacting protein 4; HIV-1, human immunodeficiency virus-1; HECW2, C2 and WW domain-containing protein 2; TNKS2, tankyrase-2; ADP, adenosine diphosphate; RNF146, ring finger protein 146; USP9X, ubiquitin-specific protease 9X; Amotl1, Amot-like protein 1; YAP, Yes-associated protein; ARHGAP17/Rich1, Rho GTPase activating protein 17;; FSS, flow shear stress; TAp73, TP73 generates transactivating forms; WWOX, WW domain-containing oxidoreductase; VP40, virion protein 40; KIKAT, KSHV-induced KDM4A-associated transcript; KDM4A, recombinant lysine specific demethylase 4A; TSS, transcription start site; eIF4A, Eukaryotic translation initiation factor 4A.

TAp73 is a direct transcriptional target of *Amot* and controls endothelial junction dynamics by regulating angiomotin (48). RICH1 can compete with Merlin for binding to Amot-p80, which activates the kinase cascade of the Hippo signaling pathway and inhibits the stemness of BRCA cells (49). WWOX interacts with Amot-p130 and promotes its degradation and the decreased expression of Amot-p130 negatively affects the export of filovirus VP40 virus-like particles (50-52). In addition, the KSHV-induced KDM4A-associated transcript (KIKAT)/LINC01061 interaction mediates the rearrangement of KDM4A from the *Amot* promoter region transcription start site and the transactivation of Amot (53). Eukaryotic translation initiation factor 4A (eIF4A) is an interactor of Amot and its interaction is related to the protein synthesis ability of trophoblast cells (54).

4. The role of Amot family proteins in physiological regulation

Amot family proteins are involved in many physiological processes, including embryonic development, cell migration, angiogenesis and neural cell differentiation (Fig. 1B).

Regulating embryonic development. In the pre-gastrula stage of mouse embryo, the visceral endoderm (VE) migrates from the distal to the anterior position to serve as an antecedent identity for ectoderm development (55). The anterior visceral endoderm (AVE) then combines with the embryonic ectoderm and subsequently forms the yolk sac (56). Amot expression was detected in both AVE and VE (56). Moreover, most Amot-mutated mice die soon after gastrulation (56). This illustrates that Amot regulates the morphology required for embryo survival (56). In zebrafish chimeric embryos, *Amotl2*-deficient cells failed to migrate normally, suggesting that Amotl2 is essential for cell motility in vertebrate embryos (57). In wild-type zebrafish embryos, knockdown of *Amotl2* results in embryonic dorsalization, which can be antagonized by co-knockdown of β-catenin2 (7). In addition, Amot as a substrate can be phosphorylated by LATS1/2, thereby inhibiting endothelial cell migration *in vitro* and angiogenesis in zebrafish embryos (58).

Enhanced Amot expression in rat and human placentas is associated with intrauterine growth restriction (54). The formation of trophectoderm and inner cell mass depends on the differential activity of the Hippo signaling pathway between the outer and inner cell populations (59). Amot activates the Hippo signaling pathway by recruiting and activating LATS at the inner cell adhesion junctions (AJs) and inhibits the Hippo signaling pathway by interacting with F-actin at the apical membrane of outer cells (59). In preimplantation embryos, it was found by mapping the polar-dependent distribution of angiotensin; in nonpolar inner cells, Amot localizes to AJs and the Hippo signaling pathway is activated through intercellular adhesion (37). In outer cells, Amot is sequestered from the basolateral AJs to the apical domain and the Hippo signaling pathway is suppressed by cell polarity (37). In addition, proper activity of the Hippo signaling pathway is regulated by Rho-associated kinase (ROCK) by ensuring the correct subcellular localization of Amot proteins in outer cells (60).

Amot, Amotl1 and Amotl2 are differentially expressed in peri-implantation uterine cells and are regulated by progesterone and estrogen (61). Amot and Amotl1 are expressed in stromal cells on the 3rd and 4th day of embryo implantation (61). However, the expression of Amotl2 is lower. As the embryo develops, Amot and Amotl1 are expressed in secondary decidual cells, whereas Amotl2 expression decreases to undetectable levels (61).

Regulating cell migration. *In vitro*, angiostatin acts as a circulating angiogenesis inhibitor, suppressing endothelial cell migration, proliferation and tube formation and inducing apoptosis (3). Amot mediates the inhibitory effects of angiostatin on endothelial cell migration and tube formation, thereby stimulating cell motility and increasing cell migration (3). When the PDZ-binding motif of Amot is absent, endothelial cells lose their responsiveness to chemokines (62).

Amot can induce the association of YAP with Zonula occludens-1 (ZO-1) and its downregulation dissociates YAP from ZO-1, reducing cell migration (63). Using yeast two-hybrid screening, multiple PDZ domain protein (MUPP1) was found to interact with Amot, Amotl1 and Amotl2 (64). In addition, Amot family proteins interact with Paactin, a close relative of MUPP1, to regulate the formation of tight junctions (TJs) and epithelial polarity and their binding is dependent on the C-terminal PDZ-binding motifs of the Amot family (64). PDZ and LIM domain 2 (PDLIM2), a member of the actin-associated LIM protein subfamily of cytosolic proteins, interacts with two actin-associated podocyte proteins (α-actin-4 and Amotl1) to play a role in the pathogenesis of glomerular diseases (65).

In Madin-Darby canine kidney (MDCK) epithelial cells, RICH1 and Amot maintain TJ integrity through coordinated regulation of Cdc42 (66). In zebrafish, knockdown of *Amot* impairs intersegmental vascular migration by reducing the number of filopodia in endothelial tip cells (67). In mouse muscle cells, *tissue factor pathway inhibitor-1* (*TFPI-1*) deficiency may accelerate the development of atherosclerosis by promoting the proliferation and migration of vascular smooth muscle cells (68).

Regulating angiogenesis. Studies have shown that Amot, Amotl1 and Amotl2 exert similar effects on endothelial cell migration and TJ formation *in vitro* (9,64,66). In a mouse endothelium-specific genetic model, knockout of *Amot* inhibited the migration and expansion of physiological and pathological vascular networks (69). Amot is involved in angiogenesis and vasodilation in psoriasis (2). Loss of function studies in zebrafish and mice suggest that synectin-binding guanine exchange factor (Syx) and Amot have specific roles in angiogenesis in the vascular bed, which may be related to vascular sprouting (70). Alternatively, Amot forms a ternary complex with Patj (or its homolog MUPP1) and Syx to control directional capillary migration in the embryo (30). Syx is cross-linked to Amot via the Crumbs polarity protein Patj (71). The two isoforms of Amot, Amot-p80 and Amot-p130, are abundantly expressed during retinal angiogenesis *in vivo* (8). Among these, Amot-p80 is expressed in the migratory stage, whereas Amot-p130 is expressed in the vascular stabilization and maturation stages (8). Amotl1 is

involved in actin-cytoskeleton-based processes and is important for angiogenesis (31). In addition, Amotl1 is essential for the establishment of a normal vascular network as a novel chaperone of the N-cadherin complex in the postnatal mouse retina and transgenic breast cancer models (72). HECW2, an E3 ligase, stabilizes endothelial intercellular junctions and promotes angiogenesis by regulating the stability of Amotl1 (41). Inactivation of Amotl2 dissociates VE-cadherin from the cytoskeleton in zebrafish, mice and endothelial cell culture systems (73). Amotl2 is required for aortic lumen dilation and transmits mechanical forces between the endothelial cells by binding to VE-cadherin (73). In addition, TAp73 affects Amot/YAP signaling by integrating the transcriptional program to maintain junction dynamics and integrity and balance endothelial cell rearrangements in angiogenic vessels (48).

Amot is expressed in both capillaries and muscle fibers (74). Exercise training was induced in obese and non-obese rats by modulating angiotensin levels and the results showed that plantar angiogenesis capacity was related to the RhoA-ROCK signaling pathway (74). In addition, the angiogenic capacity of skeletal muscle increases with increasing p80/p130 ratios (74). In mice, 75% of *Amot* knockout mice exhibit severe vascular insufficiency in the interstitial region, as well as vasodilation in the brain (67). In endothelial cells differentiated from embryonic stem cells, the response of Amot deficient cells to VEGF was suppressed in terms of differentiation and proliferation, suggesting a key role of Amot in angiogenesis (67).

Amot-p130 in the nervous system. As the core of nervous system development, neural stem cells (NSCs) have unlimited potential for self-renewal and multi-directional differentiation (75). They are widely found in the ventricular-subventricular zone (V-SVZ) of the lateral ventricular wall (76). All cells of the nervous system are derived from proliferation and differentiation and neural progenitor cells (NPCs) are no exception (75,77). NPCs eventually differentiate into neurons and glial cells (77). Neurogenesis is closely related to Parkinson's disease, Huntington's disease and Alzheimer's disease (78). Therefore, stem cells have great potential as a treatment for these brain diseases (78).

The proliferation and differentiation of NSCs are closely related to the Hippo signaling pathway (10,79). In addition, the Hippo signaling pathway plays a key role in regulating the number of neural progenitor cells (80). The Hippo signaling pathway is closely related to the proliferation and differentiation of neural stem cells and the expression of YAP plays a decisive role in the continuous proliferation of NSC (11). Amot-p130 expression is increased during neural differentiation, leading to YAP nuclear exclusion, which affects the fate of human pluripotent stem cells (12). Alternatively, Amot-p130 acts as an intermediate signal transducer that allows neural stem cells to sense and respond to extracellular stiffness signals (81). Amot-p130 can bind F-actin and the neural inhibitory transcriptional co-activator YAP to affect signaling transduction in neural stem cells (81). Among them, *SORBS3* deletion increase F-actin binding to Amot, which has been implicated in autophagy in normal brain aging (82). On soft substrates, Amot-p130 deletion greatly reduced neurogenesis, whereas on hard substrates, Amot-p130 deletion negated the rescue of neurogenesis normally induced by the pharmacological inhibition of myosin activity (81). During the growth of NSCs on soft substrates, Amot-p130 is dissociated from the actin skeleton by phosphorylation, enhancing its binding to YAP, thereby stimulating β-catenin activity leading to NSC differentiation (83). In addition, both YAP and Amot-p130 levels are regulated by the proteasome and the ubiquitin proteasome system is essential for the timely removal of self-renewing NSCs (84).

Amot-p130 is important for dendritic circuits developments and synapse formation (10). Amot-p130 is particularly critical for dendritic morphogenesis in hippocampal cells and brain Purkinje cells and its loss results in reduced complexity of Purkinje cell dendritic trees, abnormal cerebellar morphology and impaired motor coordination (10). Amot-p130 interacts with YAP to control dendrite growth and branch formation in developing neurons (85). In addition, Amot-p130 and YAP regulate dendritic development by affecting the phosphorylation of S6 kinase and its target ribosomal protein S6 (rpS6) (85). As a marker of neuronal activity, rpS6 phosphorylation is closely related to the activation of (mTOR1 signaling activation (86,87). Its biological role in neurons remains to be elucidated (86).

The stability of dendritic spines and rods is essential for proper functioning of the adult brain and the loss of stability may lead to psychiatric and neurodegenerative diseases (88). The exploratory movement of dendritic filopodia is closely related to synaptogenesis and is a very important dynamic subcellular structure during neurogenesis (89). Additionally, the actin cytoskeleton is an important component of structural changes in dendritic spines that form new synapses (90). To stabilize the actin cytoskeleton, Amot-p130 is enriched in mature dendritic spines and couples with F-actin to the postsynaptic protein scaffold (90). Amot-p130 is closely related to normal spinal morphogenesis and its loss may lead to spinal defects and neurological diseases (90).

5. Role of Amot family proteins in cancer and other disease

In recent years, research on Amot family proteins in cancer and other diseases has become increasingly popular, but there are many controversies (Table II). They can inhibit cell proliferation and promote tumor growth. The role of Amot family members in the Hippo-YAP signaling pathway has not been clearly demonstrated. For example, Amot family proteins were found to have dual effects on YAP. In LIHC cells, Amot-p130 promoted YAP nuclear entry and transcriptional activity, whereas in U87 cells, a primary glioblastoma cell line, Amotl2 bound to YAP, inhibiting nuclear translocation and subsequent YAP target gene activation and inhibiting cell proliferation (19,22). In addition, the involvement of Amot family members in tumor regulation is also involved in signal pathways such as the Hippo signaling pathway, AMPK signaling pathway and mTOR signaling pathways (22,38) (Fig. 1C).

Amot. Overexpression of *Amot* promotes the growth and metastatic potential of COAD cells mainly by activating the YAP-ERK/AKT signaling pathway (91). Experimental data demonstrate that Amot is not only a very useful prognostic indicator for BRCA but also functions as a potentially effective therapeutic target (14). In addition, Amot expression enhances

Table II. Role of Amot family proteins in cancer and other diseases.

Amot family	Type of cancer	Function	Mechanism
Amot	Unknown	Oncogene	Bind to YAP, preventing YAP phosphorylation and enhancing its activity against a specific set of genes that promote tumorigenesis.
	COAD	Oncogene	Activate the YAP-ERK/AKT signaling pathway
	BRCA	Oncogene	Enhance ERK1/2-dependent MCF-7 cell proliferation
	CCA	Oncogene	Promotes the upregulation of YAP through the circRNA_000585 /miR-615-5p/Amot/YAPpathway, thereby promoting tumor proliferation, angiogenesis and chemotherapy resistance
	RCA	Oncogene	Promotes the nuclear aggregation and activity of YAP
	LSCC	Tumor suppressor	Knockdown of *Amot* initiated cancer cellproliferation, migration, invasion and epithelial-mesenchymal transition
	OV	Tumor suppressor	Phosphorylated by PKCι at a unique site of Amot, Thr750, Phosphorylation of this site inhibits YAP1 binding and thus YAP1 enters the nucleus and causes carcinogenesis
	DLBCL	Tumor suppressor	Inhibits DDR
	Psoriatic		Angiogenesis and vasodilation
Amot-p80	PRAD	Oncogene	Cadherin11-mediated migration
	HNSCC	Oncogene	Increased cell proliferation and migration
Amot-p130	LIHC	Oncogene	Promotes YAP nuclear translocation by inhibiting the interaction between YAP and LATS1/2
	GC	Tumor suppressor	Inhibits epithelial-mesenchymal transition of GC cells
	SCLC	Tumor suppressor	Unknown
Amotl1	BRCA	Oncogene	Triggers tumor cell migration and proliferation by activating c-Src
	CCA	Oncogene	Inhibits vasculogenic mimicry, migration and invasion of CCA cells, thereby promoting CCA metastasis
	Splenic marginal zone lymphoma	Oncogene	Unknown
Amotl2	BRCA	Oncogene	Unknown
	COAD	Oncogene	Unknown
	GBM	Tumor suppressor	Binds to YAP and prevent its nuclear translocation and subsequent activation of target genes, thereby inhibiting GBM invasion and metastasis

Amot, angiomotin; COAD, colon adenocarcinoma; BRCA, breast carcinoma; CCA, cervical cancer; RCA, renal carcinoma; LSCC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; DLBCL, diffuse large B-cell lymphoma; PRAD, prostate adenocarcinoma; HNSCC, head and neck squamous cell carcinoma; LIHC, liver hepatocellular carcinoma; GC, gastric cancer; SCLC, small cell lung cancer; GBM, glioblastoma multiforme; YAP, Yes-associated protein; ERK, extracellular regulated protein kinases; AKT/PKB, protein kinase B; MCF-7, Michigan Cancer Foundation-7; circRNA, circular RNA; miR, microRNA; PKCι, protein kinase Cι; DDR, DNA damage response; LATS1/2, large tumor suppressor homolog 1/2; c-Src, C-terminal Src.

ERK1/2-dependent MCF-7 cell proliferation, thereby inducing tumor growth in breast cells (92). Amot downregulation results in a significant decrease in cell proliferation and invasiveness (93). In CCA, the expression of circRNA_000585 is upregulated, which promotes the upregulation of Amot and YAP through the circRNA_000585 /miR-615-5p/Amot/YAP pathway, thereby promoting tumor proliferation, angiogenesis and chemotherapy resistance (1).

Table III. Clinic application through targeting Amot family.

First author, year	Targeted therapeutic agents	Regulatory mechanism	(Refs.)
Holmgren *et al*, 2006	Amot DNA vaccines	Impaired tumor vascularization	(102)
Barutello *et al*, 2015	Neu vaccine	Maternal immunity	(23)
DeRan *et al*, 2014	Metformin (Glucophage) and phenformin	Increasing the AMP proportion and activating AMPK to phosphorylate Amotl1 led to an increase in its stability	(38)
DeRan *et al*, 2014	AICAR	A direct activator of AMPK, phosphorylation ofAmotl1 increases its stability	(38)
Levchenko *et al*, 2008	B06	Inhibition of endothelial cell migration by resistance to Amot	(103)

Amot, angiomotin; AICAR, 5-aminoimidazole-4-carboxamide-β-ribofuranoside; AMPK, AMP-activated protein kinase.

Amot-p80 promotes Cadherin11-mediated migration of PRAD cells (17). In LIHC, Amot-p130 promotes YAP nuclear translocation by inhibiting the interaction between YAP and LATS1/2 (19). In addition, Amot-p130 can inhibit the epithelial-mesenchymal transition of GC cells and play a tumor suppressor role (94). Amot is also essential for nuclear aggregation and activity of YAP in RCA cells (20). Transient transfection of Amot-p80 into HNSCC cells results in increased cell proliferation and migration (18). In LSCC, *Amot* knockdown initiates cancer cell proliferation, migration, invasion and epithelial-mesenchymal transition (21,95). *PRKCI* copy number gain drives growth and tumorigenicity by activating atypical protein kinase Cι (PKCι)-dependent cell-autonomous Hedgehog (Hh) signaling in LSCC (96). Amot (Thr750) can be phosphorylated to inhibit YAP1 binding, allowing YAP1 to enter the nucleus and cause OV (96). A recent study has shown that Amot-p130 inhibits the growth of SCLC cells and cisplatin resistance (24). In addition, Amot plays a tumor suppressive role by inhibiting the DNA damage response, thereby reducing the viability of DLBCL cells while increasing the sensitivity of DLBCL cells to doxorubicin (25). Amot expression is upregulated in psoriatic dermal mesenchymal stem cells and closely related to angiogenesis and vasodilation (2).

Amotl1 and Amotl2. Amotl1 binds the WW domain of YAP via its PPXY motif and inhibits the nuclear translocation and pro-apoptotic function of YAP (97). Amotl1 expression can trigger tumor cell migration and proliferation by activating c-Src (98). In BRCA, both canonical and non-canonical Hippo signaling pathways regulate Amotl1 levels (98). As an oncogene in CCA, Amotl1 can inhibit vasculogenic mimicry, migration and invasion of CCA cells, thereby promoting CCA metastasis (35). In addition, Amotl1 is a frequently mutated gene in splenic marginal zone lymphoma and its mechanism of action has not been found in humans (99).

In polarized MDCK cells, knockdown of *Amotl2* leads to YAP activation, promotion of proliferation and inhibition of apoptosis (100). In the cytoplasm of H441 human lung cells, the WW domain of TAZ and the PPXY motif at the N-terminus of Amotl2 interact to regulate the cytoplasmic to nuclear translocation of TAZ (101). In paraffin-embedded BRCA and COAD tissues, the expression of Amotl2 protein was significantly increased according to immunohistochemical staining (16). In GBM, Amotl2 can bind to YAP and the prevent its nuclear translocation and subsequent activation of target genes, thereby inhibiting GBM invasion and metastasis (22).

6. Clinic application through targeting Amot family proteins

With the in-depth study of Amot family proteins over the years, new clinical applications have also begun to be developed (Table III).

For instance, the combination of DNA vaccines encoding Amot and the extracellular and transmembrane domains of the human EGF receptor 2 (Her-2)/neu oncogene impairs tumor vascularization, thereby inhibiting BRCR progression (102). On this basis, maternal immunity could also provide anti-tumor protection to BALB-neuT offspring (23). When a mother was vaccinated with neu, the tumor-free survival of BALB-neuT offspring born and fed by her was significantly prolonged (23).

The Amot family proteins are involved in the Hippo signaling pathway, a key pathway in tumorigenesis (46). AMPK can phosphorylate Amotl1 at Ser^{793} to enhance its stability of Amotl1, thus inducing the retention of YAP in the cytosol to suppress tumorigenesis (38). Metformin (glucophage) and phenformin, as indirect activators of AMPK, activate AMPK by reducing ATP, thereby exerting anti-tumor effects (38). As a direct activator of AMPK, 5-aminoimida-zole-4-carboxamide-1-b-riboside serves a tumor suppressor role by phosphorylating Amotl1 (38). Moreover, B06 Amot antibody can inhibit tumor vessels and choroidal neovascularization by inhibiting the migration of tumor vascular endothelial cells, which has broad applicability in the treatment of angiogenesis-dependent diseases (103).

7. Conclusion and future directions

In summary, Amot plays important roles in embryonic development, cell migration and angiogenesis (7-9). Among them, Amot-p130, a member of the Amot family of proteins, has been increasingly studied in the nervous system (10). Amot acts as an intermediate signal transducer that enables NSC to sense and respond to extracellular stiffness signals (81).

In addition, increased expression of SORBS3 can inhibit autophagy during normal brain aging in species (82). However, the functional role of the Amot family proteins in different cancer types is controversial. They play a cancer-promoting role in most tumors such as BRCA, osteosarcoma, COAD, PRAD, HNSCC, CCA, LIHC and RCA (1,14-20). However, the anti-tumor effect of Amot has also been explored in GBM, DLBCL, GC, SCLC, OV and LSCC (21-25). This is partly because the function of Amot family proteins in the Hippo signaling pathway is dependent on cancer context (19,22). For example, Amot not only promotes YAP localization in the nucleus but also retains YAP in the cytoplasm of different tumor types (19,22). In addition, with an in-depth study of the Amot family proteins, some Amot vaccines and antibodies have been developed (23,102). Some drugs such as metformin have also been found to regulate the stability of Amot family proteins through energy stress (38).

With the development of circulating DNA, serum metabolic fingerprints and chromogenic detection for biomolecular analysis, cancer can be detected earlier and Amot family proteins also have extraordinary significance for the understanding of cancer (104-106). Several questions remain to be addressed in future studies. First, what is the specific function of each member of the Amot family proteins? Second, what is the underlying mechanism of the specific expression model of the three Amot family members, as well as the unique post-translational modification that determines the oncogenic or tumor suppressor roles of Amots? Third, even though the Amot family members are associated with the Hippo signaling pathway, they are also involved in other signals. Transcriptomic analysis of conditional knockout mice associated with Amot family members may help address these issues. Future studies on these issues may be of great significance in promoting knowledge of Amot family members.

Furthermore, many experiments have shown that Amot-p130 plays an important role in the nervous system, such as stem cell differentiation and neuron maturation (81). There are many future directions to investigate. Does Amot-p130 have other roles in the mature nervous system? What are the functions of Amotl1 and Amotl2 in the CNS? The study of immature and mature nerve cells may help to expand understanding of the Amot family members in the nervous system, which is very important for our future prevention and guidance for reversing neurological diseases, such as autism.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

XJ and MY conceived the study. HW and JX drafted the manuscript. HW and MY analyzed and interpreted the data. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Use of artificial intelligence tools

The Paperpal Preflight (https://paperpal.com/preflight) was used to ensure the accuracy and correctness of the review text. However, AI tools were not used in generating scientific content and drawing scientific conclusions or analyzing scientific data. In addition, the authors carefully checked and edited the text generated by the Paperpal Preflight to ensure its accuracy.

Competing interests

The authors declare that they have no competing interests.

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