DOI 10.1007/s11055-019-00890-1
Neuroscience and Behavioral Physiology, Vol. 50, No. 2, February, 2020

Mechanisms of Regulation of the Targeted Grown of Nerves and Vessels by Components of the Fibrinolytic System and GPI-Anchored Navigation Receptors

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Translated from Rossiiskii Fiziologicheskii Zhurnal imeni I. M. Sechenova, Vol. 104, No. 9, pp. 1001–1026, September, 2018. Original article submitted June 26, 2018.

The targeted growth of nerves and vessels is controlled by navigation receptors, some of which are proteins with glycosylphosphatidylinositide "anchors." Using T-cadherin and the urokinase receptor as examples, this review addresses the main molecular mechanisms of this process. T-cadherin functions as a navigation molecule negatively regulating the growth of axons and blood vessels. This substance is involved in regulating physiological and tumor neoangiogenesis. These effects are based on homophilic interactions between T-cadherin molecules and contacting cells. T-cadherin is also a receptor for low-density lipoproteins and adiponectin. The competition between these ligands seen in our studies at the level of T-cadherin-dependent intracellular signaling may constitute a new regulatory mechanism. Apart from the already known ability of the urokinase system (urokinase and its receptor and inhibitors) to stimulate cell migration, to carry out limited proteolysis of the extracellular matrix, and drive vessel growth and remodeling processes, this review presents data on its role in axon growth and branching and the recovery of nerves after damage. Data in recent years have provided evidence of the ability of the urokinase receptor to interact with other ligands. This interaction has great physiological significance for the formation and functioning of nervous system structures in health and pathology.

Keywords: GPI-anchored receptors, T-cadherin, urokinase receptor, urokinase, low density lipoproteins, adiponectin, vessel and nerve growth.

The ability of cells to enter the activated state, form processes, or undergo targeted migration in response to the appropriate stimuli (growth factors, cytokines, chemokines, and navigation receptors and their ligands) plays an important role in organ- and tissue-forming processes in embryogenesis and their functioning in the adult body [135, 139]. The literature contains data on the involvement of the fibrinolytic system and navigation receptors in stem cell differentiation processes, maintenance of the viability of neural, glial, and endothelial precursor cells, the directed growth of forming vessels and axons, the arteriovenous differentiation of the primary capillary network, and the formation of boundaries between brain tissues (for more detail see reviews [9, 95, 135, 139]).

Data have been reported on the mutual regulation of nerve and vessel growth [41, 82]. For example, during the formation of the sympathetic nervous system during embryogenesis, smooth muscle cells, working in parallel with growing vessels, produce the neurotrophic factor artemin, the gradient of which regulates the growth of nerve fibers to their peripheral targets. In turn, Schwann cells secrete vascular endothelial growth factor (VEGF), the main growth factor for vessels, which supports the parallel growth and branching of small arteries along forming nerve fibers [41, 42, 82]. Overall, the coordinated growth of vessels and nerves occurs as a result of mutual regulation and "crosstalk" involving signals produced by one tissue and directed

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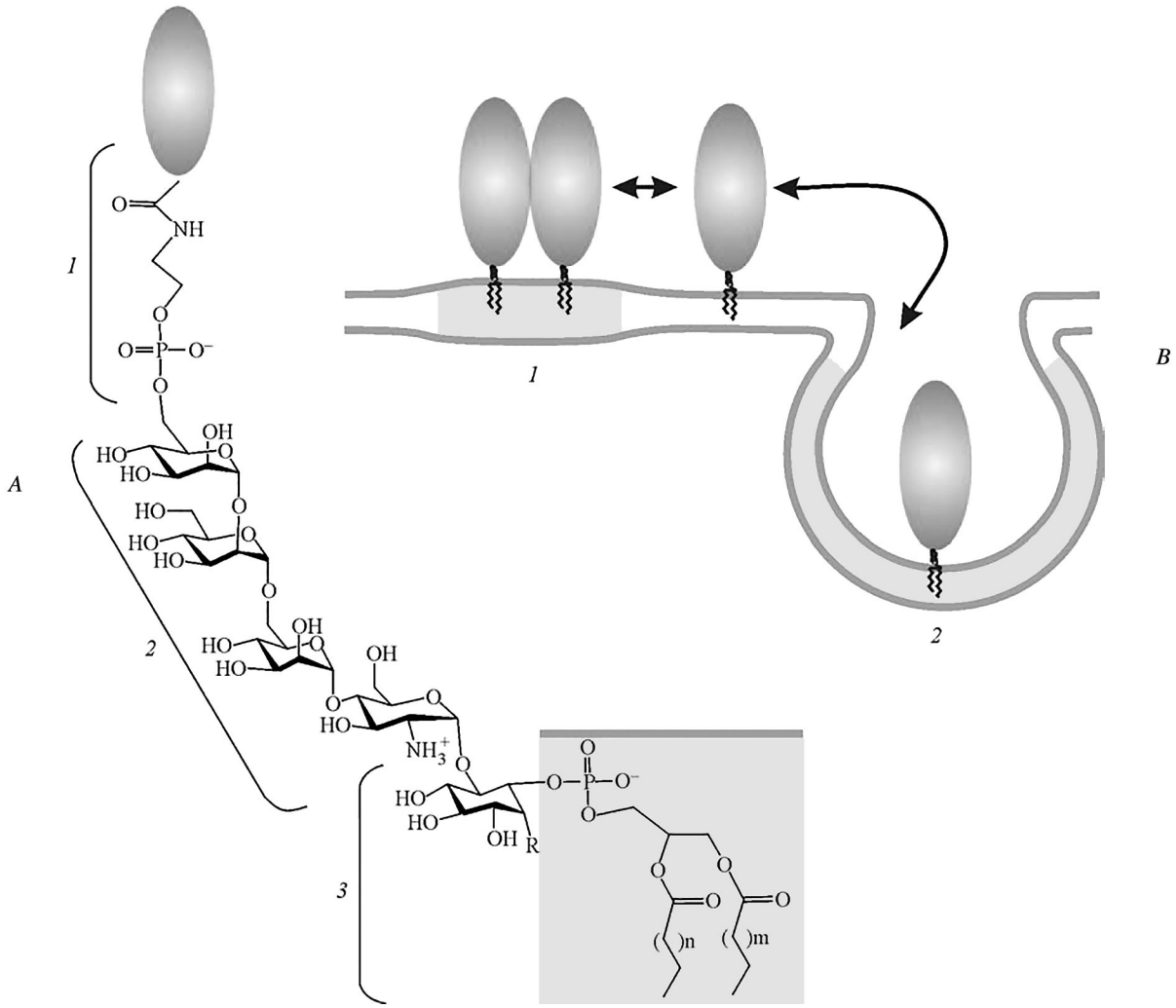

Fig. 1. Diagram showing GPI anchoring of proteins (green ovals) tot plasma membrane (orange lines). *A*) The GPI anchor consists of a phosphoethanolamine linker (*1*), a variable glycan region which can be modified by sugars and/or phosphoethanolamines (*2*), and a phosphoinositol part (*3*), to which two fatty acid residues of different lengths and saturatedness and sometimes also a palmitic acid residue (R) are attached; *B*) GPI-anchored molecules are generally seen in specific membrane domains enriched with cholesterol and sphingomyelin. Two types of rafts are identified: planar rafts (*1*), about 1 nm thicker than the rest of the membrane, and caveolae (from the Latin caveola, a small cave) (*2*), which are invaginations of the membrane containing caveolin protein.

at stimulating the growth of the components of the other tissue [55], which is important for constructing the architecture of both the nervous and vascular systems [17, 82].

Vessel and nerve growth do not occur randomly, but along a specific trajectory: growing to their targets, axons and vessels adhere to and form intercellular contacts with cells of some tissues and avoid those of others, which is apparent as "repulsion." At least four main families of molecules with navigation functions and mediating "repulsion" or cell adhesion processes are known: 1) netrins and their DCC (Deleted in Colorectal Cancer) receptors/neogenins and Unc5 (Uncoordinated-5); 2) slit ligands and their Robo receptors; 3) semaphorins and their receptors, i.e., plexins and neuropilins; 4) ephrins and their receptors [55, 172]. Interactions of ligands with their receptors in cells expressing both ligands and receptors activate intracellular signaling. This results in rearrangement of the cytoskeleton, elongation of the growing vessel/axon or its retraction [95].

GPI receptors as navigation molecules. Navigation receptors and their ligands may not only be soluble and transmembrane, but can be anchored to membranes via glycosylphosphatidylinositide (GPI) "anchors." GPI anchors consist of a phosphatidylethanolamine linker, a glycan central part, and a phospholipid tail (Fig. 1, *A*). This posttranslational modification, which provides affinity for particular membrane domains, i.e., lipid rafts, is applied to many eukaryotic proteins (Fig. 1, *B*). Furthermore, dimers/oligomers of GPI-anchored proteins are believed to promote the formation of lipid rafts (Fig. 1, *B*, *1*) [157]. Rafts in turn can aid the compartmentalization of proteins on the membrane

in polarized cells (including neurons and endothelial cells) and their concentration for activation of intracellular signaling. In the nervous and vascular systems, GPI-anchored navigation molecules include: class G netrins, semaphorin 7A, class A ephrins, and T-cadherin and the urokinase receptor (uPAR) [9, 135, 139]. The role of navigation receptors in determining vessel and nerve growth trajectories has been studied in some detail during embryogenesis and in models of tumor growth, though there has been insufficient study of analogous processes in the adult body on recovery of tissues after damage [139].

T-cadherins in embryogenesis and physiological angiogenesis. The navigational properties of T-cadherin as a cellular adhesion molecule in the embryonic nervous system regulating axon growth were first described in 1991 [122]. Using in situ hybridization methods, immunofluorescent staining of mouse embryos, and confocal microscopy, we observed that expression of the *CDH13* T-cadherin gene occurs from stage E8.75 in the developing brain in and from stage E11.5 in the heart [136]. Expression of T-cadherin at the protein level in the brain is detected from stage E9.5. Stained areas correspond morphologically to the zones of formation of vascular plexuses in the developing brain in the walls of the ventricular system in mice. The time at which T-cadherin is expressed coincides with activation of the processes of vessel formation and growth in these tissues, which suggests a role for T-cadherin in the processes of directed growth of not only axons, but also vessels [7, 136]. Analysis of T-cadherin expression at later stages (E16) confirmed that T-cadherin is expressed in vessels in the developing brain, which is evidenced by colocalization of the specific endothelium marker VE-cadherin and T-cadherin.

T-cadherin in the forming nervous system is regarded as a negative regulatory molecule which, operating by the mechanism of homophilic recognition and "repulsion," provides targeted axon growth [60, 61, 122]. We suggested that a similar mechanism may also occur in the regulation of blood vessel growth. A model based on subcutaneous implantation of Matrigel in nude mice yielded results showing suppression of vessel growth in Matrigel involving T-cadherin and a homophilic mechanism of interaction between T-cadherin molecules on vessel cells and stromal cells [131]. These results were confirmed in in vitro experiments with immobilized N-terminal EC1 T-cadherin domains, these being responsible for homophilic interactions between T-cadherin on contacting cells [131]. Thus, T-cadherin may be a potential target for the development of antitumor and antiangiogenic therapy of various oncological diseases [132].

T-cadherin and tumor growth. The literature contains contradictory data on the role of T-cadherin in tumor growth [20, 132, 140]. In cancer of the ovary and endometrium [154] and osteosarcoma [176], decreases in T-cadherin expression correlate with favorable prognoses for patients. Increases in T-cadherin expression are typical of invasive hepatocellular carcinomas [126] and astrocytomas, which have a high degree of malignancy. Some authors have suggested a possible role for T-cadherin as a tumor suppression factor. There is a relationship between loss of the chromosomal locus 16q24, which contains *CDH13*, or methylation of the *CDH13* promoter and the genesis of malignant neoplasms [20, 164]. Decreases in its expression due to allele loss or hypermethylation of the gene promoter correlate with the growth and metastasis of several types of tumor [20, 159]. Thus, suppression of *CDH13* expression correlates with the malignancy of the phenotype and the oncogenicity of breast [125], lung [142], and gallbladder [91] tumors.

We carried out a comparative analysis of T-cadherin expression in samples of normal skin, those with precancerous states, and those with different types of skin cancer and melanoma. In normal skin, T-cadherin was expressed in basal keratinocytes, stromal cells, and blood vessels in the dermis. Decreases in T-cadherin expression in keratinocytes and vascular cells in precancerous states in humans (keratoxanthoma in the stabilization stage, psoriasis, actinic keratoses, and basal cell carcinoma) were accompanied by decreases or complete loss of expression of T-cadherin on becoming malignant (metastatic cancer, squamous cell cancer, and basal cell carcinoma) [132]. We proposed the hypothesis that in precancerous states, T-cadherin functions as a tumor suppressor, which limits the proliferation and regulates the migration and interaction of keratinocytes with vascular and stromal cells in different layers. Development of malignancy is linked with loss of T-cadherin expression [132].

The results of our studies on T-cadherin expression in samples of primary human melanoma and metastasizing melanoma showed that while T-cadherin is expressed in normal skin melanocytes, its expression shows a mosaic pattern in primary human melanomas, while metastases display essentially complete loss of T-cadherin expression [140]. These data are consistent with results reported by other authors [36, 80]. These data provide evidence that development of malignancy involves loss of T-cadherin expression in tumor cells and the surrounding stroma, with impairments to its expression in the cells of vessels growing into tumors.

Studies in our laboratory seeking to clarify the possible role of T-cadherin in melanoma tumor progression used a well described experimental model based on the growth of the aggressive melanoma B16F10, metastasizing to the lungs in BDF1 mice [174]. As in a model of tumor neoangiogenesis, T-cadherin was found to suppress the ingrowth of vessels into the primary tumor. However, expression of T-cadherin in melanoma cells led to activation of compensatory mechanisms which, despite the suppression of neoangiogenesis in the primary tumor, supported increases in its growth due to recruitment of stromal cells and increases in metastatic potential [137]. Thus, T-cadherin cannot be regarded as a tumor suppressor, as expression of T-cadherin in melanoma cells was linked with onset of the expression of

genes promoting survival, migration, invasion, and metastasis [140].

T-cadherin as a receptor for low density lipoproteins and the high molecular weight forms of adiponectin. Understanding the role of T-cadherin in the processes regulating angiogenesis is made more difficult by the fact that apart from homophilic interactions on contacting vessel and nerve cells, T-cadherin also takes part in ligand-type interactions with low density lipoproteins (LDL) and high molecular weight adiponectin complexes [74, 133, 134, 161].

High blood LDL concentrations are a risk factor for the development of cardiovascular diseases. The effects of LDL in vascular cells result from accumulation of LDL within cells due to endocytosis [64] and activation of intracellular signaling occurring as a result of the binding of LDL with membrane surfaces [39]. At the beginning of the 1990s, our studies using cultured vascular smooth muscle cells (SMC) revealed atypical LDL binding sites [162]. Using membranes from SMC from the human aortic media, work in our laboratory isolated and characterized protein p105/p130, which was shown by mass spectrometry and sequencing to correspond to the T-cadherin sequence [150, 161]. Analysis of the specific binding of labeled [^{125}I]LDL with cultured cell membranes showed that LDL is a specific ligand for T-cadherin and that overexpression of T-cadherin increases the number of low-affinity LDL binding sites on cell surfaces [133].

LDL in SMC, endothelial cells, and fibroblasts is known to trigger rapid (seconds to minutes) hormone-like signaling, which is apparent as activation of the phosphoinositol cascade, increases in the cytoplasmic calcium ion concentration $[Ca^{2+}]_{in}$, and activation of protein kinase C [14, 27, 30–32, 39, 52, 77, 109, 124, 133]. Studies in our laboratory and others have shown that the signal effects of LDL are due to binding of LDL with T-cadherin and not with the classical LDL transporter (the low density lipoprotein receptor, LDLR) [4, 77, 133, 161]. Addition of LDL to the culture medium increases intracellular $[Ca^{2+}]_{in}$, increases cell migration and proliferation of cells overexpressing T-cadherin over the levels seen in controls [77, 133].

LDL is not the only ligand for T-cadherin. High molecular weight adiponectin complexes (hexameric and high molecular weight forms) are also specific ligands for T-cadherin [74]. Adiponectin is a 30-kDa protein secreted by adipocytes which regulates lipid and glucose metabolism and can also influence angiogenesis [37, 111, 167]. Negative relationships were seen between the concentration of the high molecular weight form of adiponectin and body mass index, the diabetic phenotype, insulin sensitivity, and cardiovascular diseases linked with metabolic dysfunctions [23, 47, 48, 73, 78, 112, 115, 171]. T-cadherin is required for binding of adiponectin to cell surfaces in the organs and tissues: heart, aorta, and skeletal muscle cells in T-cadherin-knockout mice are unable to bind adiponectin, which leads to significant increases in the blood hormone concentration [49, 62, 92, 113]. Lack of the T-cadherin *CDH13* gene in knockout mice leads to the development of cardiac hypertrophy and increases in myocardial infarct zones in models of cardiovascular pathology [49]. Studies in T-cadherin-knockout mice demonstrated that T-cadherin expression is required for adiponectin-mediated revascularization of cardiac muscle after infarction [113]. Adiponectin evidently has a protective antiatherogenic action in vessel walls. Previous studies have shown that adiponectin prevents the formation of atherosclerotic lesions in mice lacking the gene for apoE protein [107] and can prevent binding of LDL to proteoglycans and LDL accumulation in the arterial wall [79]. Recent studies observed that the adiponectin-T-cadherin complex decreases neointimal cell proliferation and prevents formation of atherosclerotic plaques [62]. These data point to the need for more detailed studies of the mechanism of binding of T-cadherin with its ligands and the processes activating intracellular signaling arising as a result of ligand-receptor interactions and homophilic binding involving T-cadherin.

LDL can suppress homophilic interactions between T-cadherin molecules and prevent the adhesion of cells overexpressing T-cadherin [123], thanks to the formation of T-cadherin-LDL complexes (dissociation constant $K_{D\ dimer}$ = = 41 μM [45], $K_{D\ LDL}$ = 0.1 μM [162]). Recent data indicate that the T-cadherin-adiponectin complex has a dissociation constant of K_{dA} = 1 nM [63], i.e., is it even more stable. The blood concentrations of T-cadherin ligands are greater than their dissociation constants: for LDL from 0.6 g/liter = = 1.1 μM (in terms of protein) [67], while for the high molecular weight forms of adiponectin the value is about 4.5 mg/liter = 12.5 μM [73, 170], pointing to possible competition between the two ligands for T-cadherin binding. The first data confirming competition between LDL and the high molecular weight form of adiponectin on cells expressing T-cadherin were obtained in our laboratory (Fig. 2) [24, 25]. In vitro experiments on single HEK293 cells, controls (not expressing T-cadherin) or stably overexpressing T-cadherin, demonstrated the ability of adiponectin to suppress the effects of LDL at the signaling level, i.e., to inhibit the LDL-induced release of calcium from intracellular depots (Fig. 2).

The mechanisms of activation of intracellular signaling when ligands interact with T-cadherin lacking an intracellular domain and a transmembrane domain are not clear. It is also not understood what role is played by the GPI anchor. Both T-cadherin ligands – LDL and adiponectin – are large and complicated molecular complexes (about 25 nm). Mechanisms of signal transmission within cells due to clustering of receptor molecules on interaction with ligands have been described for other GPI anchor proteins [155, 156]. These clusters have a size of less than 200 nm, which is smaller than the resolving power of light microscopes. However, methods providing for detection of Förster resonance energy transfer (FRET) allow molecules approaching to distances of 1–10 nm to be studied. Evidence of the clustering of T-cadherin on interaction with ligands on the mem-

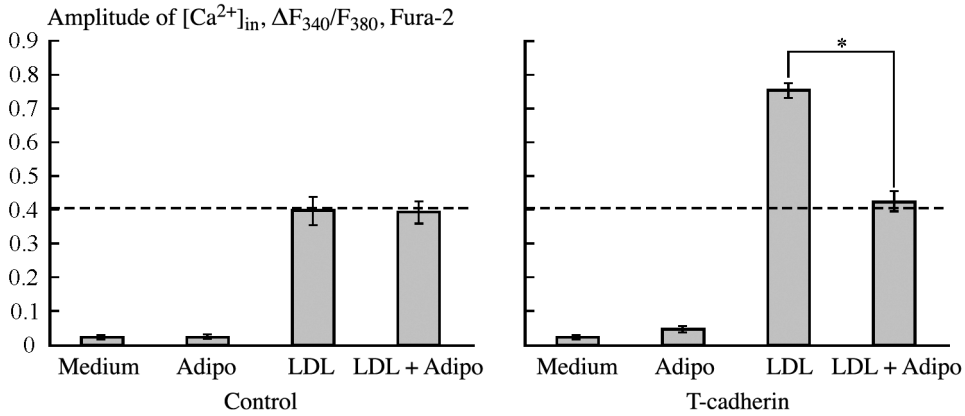

Fig. 2. Amplitude of the $[Ca^{2+}]_{in}$ response to addition of T-cadherin ligands to the incubation medium of HEK293 cells. Data were obtained using the fluorescent probe Fura-2 and a fluorescent microscope. Left (controls): amplitude of the $[Ca^{2+}]_{in}$ response in control HEK293 cells not expressing T-cadherin. Right (T-cadherin): amplitude of the $[Ca^{2+}]_{in}$ response in HEK293 cells overexpressing T-cadherin. Changes in the amplitude of the calcium response in cells were analyzed after addition of standard culture medium (Medium), adiponectin (Adipo) 10 μg/ml, LDL 25 μg/ml, or a combination of adiponectin and LDL. Data are presented as mean ± standard error and reflect the amplitude of $[Ca^{2+}]_{in}$ for more than 160 cells in three independent experiments. Groups were compared using analysis of variance with an a posteriori test, $^*p < 0.001$.

branes of living cells has been obtained using FRET with confocal microscopy and flow cytometry [2, 24]. We observed that addition of both ligands (LDL and adiponectin) stimulates dimerization of T-cadherin molecules, though the kinetics of their formation differ strongly [1]. Addition of both ligands increased FRET, though addition of LDL (25 μg/ml) stimulated rapid dimer formation, with spontaneous breakup in a short time frame (less than 12 sec), while addition of adiponectin (10 μg/ml) stimulated the slow formation of long-lived dimers with a characteristic lifetime on the membrane of about 36 sec. The FRET value on simultaneous addition of LDL and adiponectin was the same as on addition of adiponectin alone.

Formation of dimers and oligomers of GPI-anchored proteins can stimulate the formation of planar lipid rafts in the lipid bilayer and induce the binding of lipidated proteins on the inner surface of the membrane (G_{ai}, Src kinases), which leads to activation of intracellular calcium signaling [156, 157]. We suggest that the complex of LDL with T-cadherin dimer activates intracellular signaling due to stabilization of short-lived planar rafts, while the complex of adiponectin with T-cadherin dimer produces longer-lasting caveola rafts but with inhibitory signaling [1, 24] (Fig. 1, *B*). Thus, using T-cadherin as an example, we demonstrated a means of regulating intracellular signaling by GPI-anchored receptors via its interaction with two different ligands: formation of one complex leads to activation of calcium signaling, while formation of the other does not. In all probability, formation of molecular complexes on the outer side of the lipid bilayer of the plasma membrane is also important for activation of intracellular signaling and cellular responses, as for assembly of signalosomes on the inner surface. The effects of ligands interacting with GPI-anchored T-cadherin navigation receptors on the organization and rearrangement of the submembrane cytoskeleton [147] may play an important role in forming axon growth or the specialized structures leading the cell (cell "tips") at the ends of growing vessels and are of interest for further study of the mechanisms of their targeted growth.

Significant attention has been paid by researchers in recent years to studies of polymorphisms in the T-cadherin *CDH13* gene in cardiovascular and metabolic diseases [44, 57, 103, 120]. Studies in our laboratory established statistically significant correlations between the numbers of the minor alleles of the polymorphic markers rs11646213, rs4783244, and rs12444338 of the *CDH13* gene with body mass index [3]. Patients with smaller numbers of minor alleles more often have normal body weight. A cumulative influence for polymorphic markers of this gene, i.e., rs11646213, rs4783244, and rs12444338 on body mass index has also been demonstrated in patients with ischemic heart disease [3]. Another of our studies demonstrated that the G/T genotype of rs12051272 is linked with development of myocardial infarcts in patients without coronary histories [43]. Associations between polymorphisms of the T-cadherin gene with adiponectin concentrations and cardiovascular and metabolic diseases have also been demonstrated in several other studies [25].

Extensive data have been reported evidencing interactions between polymorphisms in the human *CDH13* gene and impairments to cognitive functions in diseases such as attention deficit hyperactivity disorder, alcohol and drug addiction, autism, and schizophrenia [22, 34, 66, 83, 85, 93, 105, 129, 166, 169, 175]. The effects of T-cadherin on neuron migration and axon growth in the forming brain have been convincingly demonstrated using a variety of mouse models [51, 59, 68, 128]. In addition, cocultivation of cells of epidermal origin with cells of mesodermal origin in an in vitro model of the human epiblast demonstrated that full differentiation of neural precursor cells into autonomic ner-

vous system neurons requires them to make direct contact with SMC in the blood vessels forming in parallel [15]. This contact is mediated by a homophilic interaction between T-cadherin molecules [15]. The role of the ligand-receptor interactions of T-cadherin in the nervous system remains to be clarified.

The fibrinolytic system in vessel and nerve growth processes. Urokinase (uPA), the urokinase receptor (uPAR), and urokinase inhibitors (PAI-1 and PAI-2) are components of the fibrinolytic system [28, 149]. uPA is a serine protease – a multidomain protein secreted by many cell types, including cells of the cardiovascular and nervous systems. Urokinase binds specifically to cell surfaces with their GPI-anchored uPAR receptor and cleaves precursor protein plasminogen, converting it into proteolytically active serine protease plasmin, which has a wide spectrum of action. Plasmin activates a cascade of proteolytic reactions, leading to local degradation of extracellular matrix proteins and release of growth factors deposited in the matrix, such as VEGF, hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), angiopoietin, and various others [28, 149]. Operating via controlled proteolysis, urokinase also activates a series of proangiogenic growth factors which stimulate endothelial cell migration and proliferation [19, 119]. Binding of urokinase with uPAR focuses urokinase on the leading edge of migrating cells and provides local proteolysis of the extracellular matrix in the direction of movement [29].

In addition, urokinase may take a role in regulating gene transcription. Single-chain inactive uPA (scuPA), binding the cell membrane, can be internalized from the cell surface and undergo translocation into the nucleus. Thus, induction of phenotypic modulation and conversion of fibroblasts into α-actin-expressing myofibroblasts occurs via a mechanism involving scuPA after its translocation into the nucleus, where it takes part in controlling gene transcription [152]. Mutation analysis and use of RNA interference methods have shown that transport of scuPA into the nucleus does not require expression of uPAR and LDL-like receptor (LRP), which is important for internalization of the ternary uPA/uPAR/PAI complex. However, the presence of a kringle domain in the structure of urokinase, allowing it to bind with the shuttle protein nucleolin, is a key factor for its nuclear translocation [152].

Many investigators have demonstrated that uPAR also takes part in activating intracellular signaling, which ultimately controls processes such as cell viability, proliferation, and migration, as well as invasion [46, 54, 149]. Signaling involving uPAR leads to activation of the MAPK (mitogen-activate protein kinase) signal pathway, focal adhesion kinase (FAK), Src kinase, small G proteins (Rho and rac), JAK kinase, (janus kinase), transcription factors STAT, PI3K kinase (phosphatidyl inositide 3-kinase), and the Akt signal pathway [149]. The signal effects of uPAR are mediated by its side interactions with tyrosine kinase receptors (RTKs), seven-domain transmembrane receptors (7TMRs), or G-protein-coupled receptors (GPCRs, such as FPRL1, FPRL2, FPR), the cytokine receptor gp130, integrins, LRP receptors, caveolin, and various other proteins [21]. uPAR and integrins form the main complex of the signalosome, which apart from uPAR includes α5β1 integrins and c-Src kinase, which control cell adhesion and migration. uPAR can stimulate cell proliferation via organization of a supramolecular signal complex – the proliferasome, which, apart from uPAR, can include α5β1 integrins and RTKs, for example epidermal growth factor receptor (EGFR) or platelet-derived growth factor receptor β (PDGFRB) [21, 149].

The urokinase system in angiogenesis processes. The role of urokinase and its receptors in regulating the functions of vascular cells in vascular growth and remodeling processes has been quite thoroughly characterized using both in vitro models of cell migration, proliferation, and the formation of capillary-like structures [13, 46, 65, 96, 97, 104, 117, 163] and ex vivo models of spheroids and vessel ringlet explants [11, 38, 114, 146, 165]. Experimental models of hindlimb ischemia and myocardial infarction, including those using transgenic animals with knockout of the genes of the urokinase system, have shown that introduction of a plasmid construct for expression of urokinase effectively restores blood flow. This involves a significant increase in the number of capillaries and arterioles forming, along with decreases in the sizes of infarcts and necrosis zones [71, 165].

The results of our studies using an experimental model of restenosis showed that components of the urokinase system are actively expressed by migrating and proliferating vascular cells, while exogenous application of recombinant urokinase to the walls of damaged vessels stimulates the development of the neointima and neoadventitia, along with the migration, proliferation, and phenotypic modulation of vessel cells [8].

Using ex vivo mouse aorta explant cultures, we found that urokinase is required for migration of vessel SMC and the formation/branching of capillary-like CD31-positive structures. In cultures from cells obtained from animals with knockout of the *PLAU* urokinase gene, the rate of SMC migration was significantly lower than in controls. It should be noted that in transgenic mice lacking the uPA gene (*PLAU*), the level of expression of the uPAR receptor in vessels was lower than that in controls, which was evidently reflected in a general reduction in the migratory potential of vascular cells [11, 146]. In explant cultures from *PLAU* mice, blockade of uPAR leads to changes in the phenotype of SMC such that SMC lose their fusiform shape and become flattened, losing the ability to undergo targeted migration. In addition, knockout of urokinase and blockade of uPAR produce increases in the branching of capillary-like CD31-positive structures. The number of branch points in the growing vessel reflects the number of leading ("tip") cells. Impairments to the branching process in the growing vessel can be reflected either as impairment to the specialization of endothelial cells at the top (tip cells) or stalk cells,

or failure in the endothelial cell recognition system to identify navigation signals in the microenvironment [11, 146].

We recently observed a novel mechanism for the involvement of urokinase in angiogenesis processes. In endothelial cells, scuPA is translocated into the nucleus due to binding with nucleolin and inactivates transcription factors HHEX/PRH (hematopoietically expressed homeodomain protein or proline-rich homeodomain protein). These transcription factors are known for their inhibitory actions on the promoters of the genes for proteins *VEGFR1* and *VEGFR2*. Inactivation of HHEX/PRH decreases their inhibitory influences on the promoters of these genes. Thus, urokinase has a proangiogenic effect, increasing VEGFR1 and VEGFR2 expression on the endothelium surface and their sensitivity to the actions of VEGF, stimulating migration and proliferation. These data allow urokinase to be regarded as a potential target for treatment in pathological angiogenesis [94, 151].

The urokinase system and tumor progression. The involvement of the urokinase system in the processes of tumor progression is based on three main mechanisms -stimulation of cell proliferation, potentiation of invasion/metastasization, and suppression of apoptosis [89]. Stimulation of tumor cell proliferation occurs as a result of the known ability of urokinase to activate growth factors (VEGF, EGF, FGF-2, TGF-β) by partial proteolysis. The involvement of the urokinase system in tumor cell invasion and metastasization is due to degradation of the extracellular matrix, which facilitates both the migration of tumor cells themselves, as well as the development of vessels (neoangiogenesis) into tumors. In addition, the side interactions of uPAR with integrins or growth factor receptors (e.g., EGFR) also promote tumor cell adhesion and migration and, as a result, invasion and metastasis [89]. Suppression of the expression or functional activity of urokinase or its receptor using siRNA or blocking antibodies activates caspase expression and apoptosis in cells in ovary and breast cancer [153]. Our data provide evidence that suppression of uPAR expression in Neuro 2A neuroblastoma cells using CRSPR/Cas9 genome editing technology decreased the rate of proliferation and decreased the number of Ki-67-positive cells in the cell cycle [10, 76, 141]. Cells in which uPAR expression is suppressed showed decreased phosphorylation of AKt and increased phosphorylation of p38 MAPK, reflecting reductions in the viability of Neuro 2A cells. Suppression of uPAR in these cells increases the content of activated caspase-3, which induces cleavage of PARP-1 (poly(ADP-ribose)-polymerase), a protein protecting DNA from fragmentation, which leads to apoptosis [141].

Our comparative analysis of biopsy material obtained from patients with psoriasis and basal cell carcinoma (basalioma) showed increases in the expression of uPA, uPAR, and PAI-1 in the epidermis in psoriasis and in skin cancer cells as compared with normal skin tissue samples. Elevated uPAR expression was also seen in the dermis of skin samples in psoriasis and in the stroma surrounding the tumor cells. These data provide evidence of the important role of the urokinase system in potentiating proliferation and invasion of cells of epidermal origin. Increased uPAR levels in the stroma surrounding tumor cells suggests the presence of a uPA-uPAR interaction and activation of the tumor stroma, promoting the proliferation of and invasion by tumor cells [138].

Published data provide evidence that aberrant expression of uPA or uPAR is detected in a whole series of oncological diseases. Studies more than 30 years ago showed that uPA activity is significantly elevated in samples of breast cancer as compared with controls [106]. Commercial ELISA kits were developed for diagnosis of uPA/PAI-1 expression levels, which were recommended by the American Society of Clinical Oncologists (ASCO) as the most significant prognostic markers supplementing estrogen receptors and HER2 [89]. High levels of uPA and uPAR expression are typical not only of breast cancer, but also of tumors of the prostate, uterus, ovaries, and lungs, as well as hepatocellular carcinoma, squamous cell skin cancers, gastric cancer, pancreatic adenocarcinomas, melanomas, glioblastomas, acute myeloid leukemias, etc., and correlate with increased aggressivity and metastasis [33, 35, 53, 58, 70, 81, 84, 89, 90, 100–102, 108, 121, 138, 143, 158, 160].

The soluble form of the urokinase receptor (suPAR) in tumor samples and blood, and sometimes the urine of patients with tumors of the prostate, ovaries, uterus, and large bowel, is associated with low levels of survival and poor prognoses in general terms [89]. In this regard, agents for the treatment of oncological diseases based on inhibitors of the catalytic activity of uPA, peptides or antibodies blocking uPA-uPAR interactions or uPAR-integrin interactions are under active development, as are approaches using antisense nucleotides, siRNA, ribozymes, and DNA techniques for suppressing the expression/activity of the urokinase system [89]. We have developed the novel urokinase inhibitor (5-bromo-benzisothiazol-3-yl)-guanidine, which selectively inhibits its activity; this compound is currently undergoing clinical assessment of efficacy in a variety of experimental models [26].

The urokinase system in neurogenesis processes. Components of the urokinase system are expressed not only in "tip" cells in growing vessels, but also in axon growth cones [78, 131]. uPA and uPAR are known to take part in the processes of nervous system formation in embryogenesis, including the migration of neuron precursors, the growth of axons to their targets, and synapse formation. In adults, the urokinase system plays an important role in regulating neuronal plasticity, apoptosis, and the regeneration of peripheral nerves and central nervous system (CNS) axons after damage [69, 116]. The urokinase system is believed to promote neurite growth and cell migration via local degradation of the extracellular matrix and release and activation of matrix metalloproteinases, activation of growth factors, and

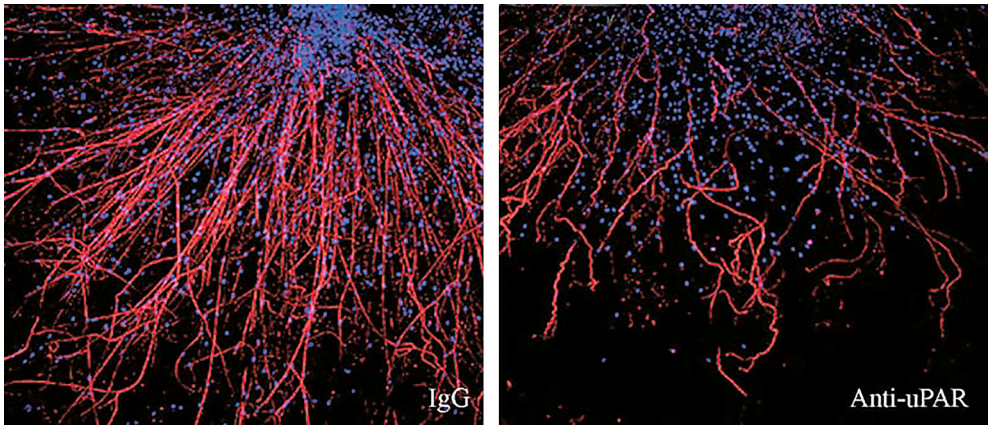

Fig. 3. Blockade of the urokinase receptor impairs the growth trajectory of axons in Matrigel. Blocking antibodies were mixed with Matrigel before cultivation of DRG in the three-dimensional matrix started. Immunofluorescent staining with antibodies to the mature axon marker NF200 (red fluorescence) after 14 days of ex vivo culture; nuclei were counterstained with DAPI (blue fluorescence). Left – IgG, control antibodies; right – anti-uPAR, i.e., uPAR-blocking antibodies.

degradation of inhibitory molecules (fibrin, F-spondin, myelin proteins) [168]. Furthermore, it has been shown that uPA can activate FAK kinase, which leads to cytoskeletal rearrangement and formation of active axon growth cones and stimulates the growth of axons to their targets [87].

The developing CNS is characterized by high levels of uPA and uPAR expression, especially in neurons, microglia, and astrocytes [98, 99]. Apart from binding urokinase and supporting proteolysis, the urokinase receptor has a number of other functions in the developing brain. Thus, uPAR has been shown to take part in neuron differentiation and migration processes. *PLAUR* mice, with knockout of the uPAR gene [50], show a decreased number of parvalbumin-expressing GABA interneurons in the cortex [86, 118]. These mice are predisposed to spontaneous epilepsy, while chemically induced epilepsy is lethal. *PLAUR* mice show increased anxiety and deviant behavior [72, 86, 118]. Lack of GABA interneurons in the cortex is believed to result in dominance of excitatory signals, which correlates with changes in uPAR and uPA expression in defined areas of the brain and is characteristic of epilepsy, schizophrenia, and autism in humans [145]. The literature contains data on the correlation between polymorphisms of the *PLAUR* gene and its ligand *SRPX2* (Sushi repeat-containing protein, X-linked 2) and a high risk of developing autism, stroke, multiple sclerosis, Alzheimer's disease, cerebral malaria, and HIV-associated leukoencephalopathy in humans [40, 87].

Studies in our laboratory yielded data on the expression of uPAR in brain structures associated with cognitive functions, i.e., the hippocampus and cortex: interneurons migrating from the ganglionic eminence (where they are generated) to the cortex (where they mature), as well as in the axons of the conducting/associative pathways of the brain [145]. In adults, uPA and uPAR expression in the CNS significantly decreases as compared with the level in the embryonic brain; however, it can again increase in response to damage, for example in stroke or other neurodegenerative diseases [98, 99].

The role of the urokinase system in the formation and regeneration of peripheral nerves is less well understood. Data from some authors indicate that sensory neurons and motoneurons in the spinal cord in embryogenesis and on regeneration express mRNA for tPA, uPA, and uPAR [16, 148], while Schwann cells express tPA mRNA [110]. The highest level of expression of mRNAs for these proteins coincides with the phase of active axon growth [16, 18, 69, 110, 148]. Data from other authors, obtained by histological analysis of samples of various neuropathies of the human peripheral system and regenerating tissue after traumatic damage to peripheral nerves in mice, provide evidence that uPAR expression is not required in embryogenesis, though loss of uPAR is critical for regeneration [127]. Our studies using models of traumatic and ischemic injury of the peroneal and sciatic nerves showed that intramuscular combined administration of plasmid constructs expressing the genes for brain-derived neurotrophic factor (BDNF) and uPA efficiently stimulated the regeneration of structures and conduction by the damaged nerves, and also promoted rapid recovery of the functions of the muscles innervated by them [5, 12, 75]. Our studies using a model based on in vivo clamping the peroneal nerve included a comparative analysis of the posttraumatic recovery of nerve structure and function in control mice and mice lacking uPA (*PLAU*) or uPAR (*PLAUR*). These studies showed that in *PLAUR* knockout mice, recovery (in terms of amplitude and latent period) was slowed as compared with control and *PLAU* mice [6].

We suggested that uPAR has a navigation function in neuritogenesis and is needed for selection of the correct axon growth trajectory. Studies using three-dimensional explant cultures of dorsal root ganglia (DRG) harvested from control and *PLAU* mice showed that the urokinase system

plays an important role in initiating axon growth, elongation, and branching [144, 145]. Thus, addition, of exogenous urokinase in Matrigel with explant cultures of DRG led to stimulation of neuritogenesis and the migration of neural cells both in DRG from control mice and those from *PLAU* mice. Blockade of uPAR using monoclonal antibodies significantly inhibited targeted axon growth, increased branching, and induced them to form aberrant twisted structures (Fig. 3). Knockout of uPAR also induced excessive axon branching and loss of their ability to recognize navigation signals in the microenvironment [144, 145].

Analysis of uPAR expression in DRG cultures from *PLAU* mice yielded unexpected results. Firstly, *PLAU* mice had increased levels of uPAR expression over those in controls; secondly, the growth rate of neurites in *PLAU* explant cultures was significantly greater than that in controls. These data suggest that urokinase in the nervous system may not be the only ligand for uPAR. As noted above, a number of effects have been described for urokinase, not directly associated with the interaction with uPAR (translocation into the nucleus and regulation of gene transcription). Furthermore, some of the physiological effects of uPAR in the absence of urokinase are known to involve interaction of uPAR with other ligands – vitronectin, Endo180, integrins, and protein SRPX2 Sushi repeat-containing protein, X-linked 2) [56, 87, 88, 130, 173]. Our own data, obtained from comparative analysis of the dynamics of recovery of peripheral nerves after traumatic damage to control, *PLAU*, and *PLAUR* mice, provide evidence that the colocalization of uPAR and α5β1 integrins on the membranes of regenerating axons increases in *PLAU* mice in the absence of urokinase, which supports recovery of their structure and function after damage [6]. The formation of uPAR-α5β1-integrins complexes on the surfaces of cells differentiating in the neural direction promotes their adhesion and neuritogenesis [6].

Conclusions. The physiological mechanisms regulating vessel and nerve growth are controlled by angiogenic and neurotrophic factors, mainly cytokines/chemokines and growth factors. These protein molecules are secreted by tissue cells in response to hypoxia, stretching, and chemical and electrical signals. Angiogenic and neurotrophic factors act on receptors, which either have their own tyrosine kinase activity or are linked with tyrosine kinases. Cytokines interact specifically with receptors, triggering intracellular signaling involving STAT proteins and leads to activation of the transcription of particular genes. Chemokines interact with G-protein-coupled seven-domain receptors, activating intracellular signaling involving adenylate cyclases, phospholipase C, and various ion channel proteins. Studies in recent years have shown that the processes of neurogenesis and angiogenesis also involve navigation receptors. Particular attention in the present review is paid to two navigation molecules – T-cadherin and the urokinase receptor.

T-cadherin and uPAR were found to have structural similarity in the form of the GPI anchor, providing for their localization in the outer part of the lipid bilayer of the plasma membrane and supporting their molecular biological, biochemical, and biophysical properties. The physiological effects of these molecules differ depending on whether they take part in homophilic recognition or are due to interactions between these receptors and their specific ligands. Thus, for example, the role of T-cadherin is in ensuring that growing axons avoid tissues whose cells express T-cadherin (homophilic recognition). We have demonstrated an analogous role for T-cadherin in the negative regulation of vessel growth both in physiological and tumor neoangiogenesis.

LDL are known to potentiate the actions of calcium-mobilizing hormones and a number of growth factors. We found that T-cadherin is a low-affinity receptor for LDL, providing activation of intracellular calcium signaling and migration of cells along the LDL gradient. Other authors have demonstrated an interaction between T-cadherin and adiponectin, giving T-cadherin a protective function in the cardiovascular system. We found a competitive interaction between LDL and adiponectin at the signaling level, on binding with T-cadherin. These data suggest that T-cadherin can function in different compartments of the plasma membrane. As T-cadherin is mainly located on the surfaces of vascular cells (endothelial cells, SMC, and pericytes) and in the heart, these competitive relationships may underlie the development of atherosclerosis and other cardiovascular pathologies.

uPAR, like T-cadherin, is located on the cones of growing axons and in "tip" cells in growing vessels. Binding of urokinase, the selective ligand for uPAR, with the receptor focuses urokinase at the leading edge of the migrating cell, where it carries out local proteolysis of the extracellular matrix. In addition, binding of urokinase with uPAR induces signaling typical of cytokines (activation of the tyrosine kinase cascade, MAPK, JAK, STAT, etc.), which stimulates not only cell migration, but also cell proliferation. Our data obtained in the last few years provide evidence that apart from these effects, uPAR regulates the targeted growth and branching of axons and vessels. Blockade of urokinase receptors with antibodies or genetic knockout leads to impairment of the processes of neuritogenesis in cell cultures and regeneration of peripheral nerves in vivo. On the basis of these data we have constructed seven genetic therapeutic substances which have undergone preclinical studies and two – Yupicor, a genetic construct for urokinase expression, and Innervin, for BDNF expression – have entered phase II clinical trials [5, 12, 75, 165].

This work was supported by a grant from the Russian Science Foundation (project No. 14-24-00086) using human biological materials collected and stored in the framework of the science program "Scientific Basis for the Creation of a National Repository Bank for Living Systems" (Russian Science Foundation agreement No. 14-50-00029) and equipment acquired under the Lomonosov Moscow State University Development Program.

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