urokinase activates the G protein-coupled chemotactic receptor FPRL1/LXA4R. Proc. Natl. Acad. Sci. USA. V. 99. P. 1359.

Rivellini C., Dina G., Porrello E., Cerri F., Scarlato M., Domi T., Ungaro D., Carro U. Del, Bolino A., Quattrini A., Comi G., Previtali S.C. 2012. Urokinase plasminogen receptor and the fibrinolytic complex play a role in nerve repair after nerve crush in mice, and in human neuropathies. PLoS One. V. 7 P. e32059.

https://doi.org/10.1371/journal.pone.0032059

- Rysenkova K.D., Semina E. V, Karagyaur M.N., Shmakova A.A., Dyikanov D.T., Vasiluev P.A., Rubtsov Y.P., Rubina K.A., Tkachuk V.A. 2018. CRISPR/Cas9 nickase mediated targeting of urokinase receptor gene inhibits neuroblastoma cell proliferation. Oncotarget. V. 9. P. 29414.
- Sahores M., Prinetti A., Chiabrando G., Blasi F., Sonnino S. 2008. uPA binding increases UPAR localization to lipid rafts and modifies the receptor microdomain composition. Biochim. Biophys. Acta - Biomembr. V. 1778. P. 250.
- Schwab W., Gavlik J.M., Beichler T., Funk R.H., Albrecht S., Magdolen V., Luther T., Kasper M., Shakibaei M. 2001. Expression of the urokinase-type plasminogen activator receptor in human articular chondrocytes: association with caveolin and beta 1-integrin. Histochem. Cell Biol. V. 115. P. 317.
- Semina E., Rubina K., Sysoeva V., Rysenkova K., Klimovich P., Plekhanova O., Tkachuk V. 2016. Urokinase and urokinase receptor participate in regulation of neuronal migration, axon growth and branching. Eur. J. Cell Biol. V. 95. P. 295.
- Semina E.V., Rubina K.A., Shmakova A.A., Rysenkova K.D., Klimovich P.S., Aleksanrushkina N.A., Sysoeva V.Y., Karagyaur M.N., Tkachuk V.A. 2020. Downregulation of uPAR promotes urokinase translocation into the nucleus and epithelial to mesenchymal transition in neuroblastoma. J. Cell. Physiol.

https://doi.org/10.1002/jcp.29555

- Siconolfi L.B., Seeds N.W. 2001. Induction of the plasminogen activator system accompanies peripheral nerve regeneration after sciatic nerve crush. J. Neurosci. V. 21. P. 4336.
- Smith H.W., Marshall C.J. 2010. Regulation of cell signalling by uPAR. Nat. Rev. Mol. Cell Biol. V. 11. P. 23.
- Stahl A., Mueller B.M. 1995. The urokinase-type plasminogen activator receptor, a GPI-linked protein, is localized in caveolae. J. Cell Biol. V. 129. P. 335.
- Stoppelli M.P., Corti A., Soffientini A., Cassani G., Blasi F., Assoian R.K. 1985. Differentiation-enhanced binding of the amino-terminal fragment of human urokinase plasmino-

gen activator to a specific receptor on U937 monocytes. Proc. Natl. Acad. Sci. USA. V. 82. P. 4939.

- Sturge J., Wienke D., East L., Jones G.E., Isacke C.M. 2003. GPI-anchored uPAR requires Endo180 for rapid directional sensing during chemotaxis. J. Cell Biol. V. 162. P. 789.
- Sun D., Bullock M.R., Altememi N., Zhou Z., Hagood S., Rolfe A., McGinn M.J., Hamm R., Colello R.J. 2010. The effect of epidermal growth factor in the injured brain after trauma in rats. J. Neurotrauma. V. 27. P. 923.
- Tarui T., Mazar A.P., Cines D.B., Takada Y. 2001. Urokinasetype plasminogen activator receptor (CD87) is a ligand for integrins and mediates cell-cell interaction. J. Biol. Chem. V. 276. P. 3983.
- Vassalli J.D., Baccino D., Belin D. 1985. A cellular binding site for the M(r) 55.000 form of the human plasminogen activator, urokinase. J. Cell Biol. V. 100. P. 86.
- Weaver A.M., Hussaini I.M., Mazar A., Henkin J., Gonias S.L. 1997. Embryonic fibroblasts that are genetically deficient in low density lipoprotein receptor-related protein demonstrate increased activity of the urokinase receptor system and accelerated migration on vitronectin. J. Biol. Chem. V. 272. P. 14372.
- *Wee P., Wang Z.* 2017. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers. V. 9. P. 52.
- Wei Y., Yang X., Liu Q., Wilkins J.A., Chapman H.A. 1999. A role for caveolin and the urokinase receptor in integrinmediated adhesion and signaling. J. Cell Biol. V. 144. P. 1285.
- Xu L., Qu X., Li H., Li C., Liu J., Zheng H., Liu Y. 2014. Src/caveolin-1-regulated EGFR activation antagonizes TRAILinduced apoptosis in gastric cancer cells. Oncol. Rep. V. 32. P. 318.
- Yang K.H., Fang H., Ye J.S., Gong J.Z., Wang J.T., Xu W.F. 2008. The main functions and structural modifications of tripeptide N-formyl-methionyl-leucyl-phenylalanine (fMLP) as a chemotactic factor. Pharmazie. V. 63. P. 779.
- Zhang G., Cai X., López-Guisa J.M., Collins S.J., Eddy A.A. 2004. Mitogenic signaling of urokinase receptor-deficient kidney fibroblasts: Actions of an alternative urokinase receptor and LDL receptor-related protein. J. Am. Soc. Nephrol. V. 15. P. 2090.
- Zhou X., Wu Q., Lu Y., Zhang X., Lv S., Shao J., Zhou Y., Chen J., Hou L., Huang C., Zhang X. 2019. Crosstalk between soluble PDGFβBB and PDGFRβ promotes astrocytic activation and synaptic recovery in the hippocampus after subarachnoid hemorrhage. FASEB J. V. 33. P. 9588.

Urokinase Receptor: from Regulation of Proteolysis to Directed Axon Growth and Nerve Regeneration. Mechanisms of Interaction with Membrane Ligands and Intracellular Signaling

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The urokinase-type plasminogen activator was first described in the mid-20th century as a serine protease that converts plasminogen into active plasmin, which leads to degradation of fibrin in vessels and remodeling of the extracel-

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lular matrix in tissues. The proteolytic cascade plays an important role in normal and pathological tissue remodeling: wound healing, trophoblast invasion, mammary gland involution, inflammation, tumor invasion and metastasis. At one time, B. Degryse justifiably called the urokinase system "one of most fascinating and challenging molecular system". In 1985, studies of plasminogen activators received a new impulse: a urokinase binding receptor was found on the cell surface, further study of which greatly contributed to our understanding of the functioning of this system. Today, the unique functions of the urokinase receptor go beyond the framework of proteolysis mediated by binding to urokinase. The review summarizes relevant literature data, as well as the results of our own research on the role of the urokinase receptor as a protein that can interact with a wide range of membrane partners and affect their function in processes that mediate directed axon growth and nerve regeneration.

Keywords: urokinase system, urokinase receptor, nerve regeneration, axon growth, integrins, chemokine receptors, growth factor receptors

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