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Vasoactive peptide urotensin II as a new chemokine exhibiting migration/adhesion mesenchymal properties during glioma development: New therapeutic target

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One of the most potent vasoactive peptides, urotensin II (UII), is involved in endothelial cell proliferation and migration, by activating a G protein-coupled receptor, the UT receptor. We showed a high expression of UII/UT in human glioblastomas (GBM), gliosarcoma and a number of carcinoma compared to oligodendrogliomas or health brain tissue. In GBM, a strong staining in vascular and peri-necrotic area and a systematic co-expression of UII/UT with SDF1α/CXCR4 were observed. In glioma and endothelial cells, gradient concentrations of UII induced chemoattracting migratory effects and tube formation. This effect was blocked by UT antagonists and mainly involved the G13/Rho/ROCK pathway while partially requiring Gi/o/PI3K components. In contrast, we observed that homogeneous concentrations of UII blocked cell motility and stimulated cell-matrix adhesions through a UT/Gi/o signaling cascade, partially involving PI3K. Finally, homogeneous concentration of UII allowed translocation of Gα13 to the UT receptor at the plasma membrane and increased actin stress fibers, lamellipodia formation and vinculin-stained focal adhesions. UII also induced relocalization of UT pre-coupled to $G_{\alpha i}$ in filipodia and initiated integrin-stained focal points.

In C57/Bl6 mice, UT agonists stimulated matrigel sponge invasion by macrophages, endothelial and smooth muscle cells, stressing the chemokine and pro-neoangiogenic properties of UII *in vivo*. In heterotopic GBM xenografted in Nude mice, intratumoral injection of UII accelerated tumor growth and necrosis, and stimulated neo-angiogenesis through metalloprotease activation. UT Antagonists/biased ligands inhibited tumor growth, neo-angiogenesis and prolonged mice survival. Micro-SPECT imaging showed increased integrin expression, correlated with large necrotic area in tumors treated with UII. Thus, UII promotes the recruitment of pro-angiogenic cells, induces cell adhesions and stimulates necrosis and neo-angiogenesis involved in glioblastoma growth. The specific blockage of UT signalings by using antagonists or biased ligands would constitute a new route for the treatment of GBM.

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Biography

Hélène Castel started to develop different variants of the electrophysiological technique at the university of Rouen in the laboratory of Dr Vaudry (U413 Inserm) and biochemical approaches to give a comprehensive view of modulation of the GABAA receptor-channel function by interacting proteins. She received her PhD in Neurosciences, Molecular and Cell Biology at the Rouen University in 2000, and then spent 2 years on a post-doctoral position in Pr Colquhoun's laboratory at University College of London, UK. There, she has developed fast-concentration-jump techniques to mimic electrical fast synaptic inputs on recombinant NMDA receptors and acquired expertise in molecular biology through mutagenesis of NMDA receptor subunits. In 2002, she obtained a permanent position as chargée de Recherche (CR) at the French National Institute of Health (Inserm) and University of Rouen. In 2010, she became group Leader "Astrocyte and Vascular Niche" and since 2015, she is co-head of the international platform "Cancer and Cognition" under the French North-West Canceropole. She develops projects based on vasoactive and chemokine G protein-coupled receptors (GPCRs) in tumor brain, brain vascular physiopathology and on cognitive dysfunctions induced by cancer and targeted therapies.

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