Involvement of the urotensin II peptide system on the smad2/3 signaling activation and fibroblastic marker expression in sub-arachnoid hemorrhage

M. Roussel[1], M. El-Amki[1], M. Dubois[1], A. Lefevre-scelles[1], A. Mutel[1], L. Desrues[1], F. Morin[1], P. Gandolfo[1], V. Compère[1,2], F. Proust[1,3] and H. Castel[1]

[1]Inserm U982, Equipe Astrocyte et Niche Vasculaire, Laboratoire de Différenciation Neuronale et Neuroendocrine, IRIB, Université de Rouen, Mont-Saint-Aignan, France, [2], Département D'Anesthésie-Réanimation, CHU de Rouen, France ; [3], Département de Neurochirurgie, CHU de Rouen, France

Sub-arachnoid hemorrhage (SAH) is often due to a ruptured aneurysm and accounts for up to 5% of all new stroke cases. Survivors of SAH commonly experience sequels that affect their day-to-day lives and which could persist years after. The cerebral arterial vasospasm (CV) is a complication of the SAH, and likely associated with neurological deficits, microthrombosis and cerebral ischemia. The CV and microthrombis may be due to vasoactive peptides which are released locally and control the blood/brain exchange. One of the most potent vasoactive peptides is urotensin II (UII) which activates a G protein coupled receptor (GPCR) named UT.

A mouse model of SAH was also developed *via* a double injection of arterial blood into the magna cisterna during two consecutive days. Occurrence of CV of the cerebral middle, basilar and anterior arteries and a number deposition of fibrin were observed from the 2^{nd} to the 14^{th} day post-SAH, as well as increase in the activity of caspase-3 in brain cortex, hippocampus, endothelium and choroid plexus. Impaired sensorimotor functions were detected from D7 to D10.

Then, we investigated the impact of the UII system in this SAH model my means of wild-type ($UT^{+/+}$) and KO-UT ($UT^{-/-}$) mice. $UT^{-/-}$ mice do not exhibit any remarkable phenotype. Interestingly, the UT biased ligand urantide, completely prevented CV, microthrombosis and consecutive neurosensitivomotor deficits in SAH mice. In endothelial cell lines we showed that UII stimulated some key markers of the fibroblastic function including activation of the Phospho-smad2/3, inhibition of VE-Cadherin expression, and increased expression of mesenchymal markers FSP1 or N cadherin. *In vivo*, increase in FSP1 and collagen 1 immunostainings in the periventricular region and the choroid plexus were detected in SAH mice.

In conclusion, during SAH, inflammatory processes, likely accompanies changes of the signaling pathways of the endothelial to mesenchymal (EndMT) transition. We also establish that the urotensinergic system is involved in the CV and cognitive deficits consecutive to SAH, and that such UII effects might be consecutive from EndMT.

Supported by University of Rouen, Rouen CHU Hospital, Inserm and Seinari.