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Press information

A major step forward in research on small cerebral blood vessel diseases.

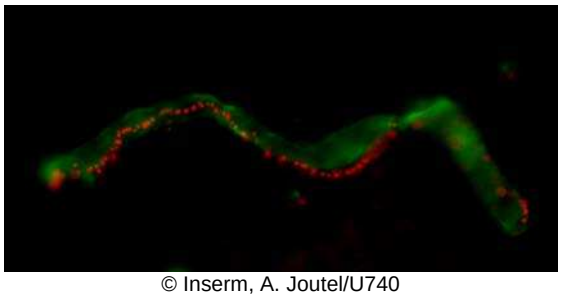
In 2010, the disorder known as CADASIL[1] syndrome is one of the most common causes of hereditary vascular dementia. However, the mechanisms involved in this disease of the small cerebral vessels remain poorly understood. This is because of the absence of a good animal model on which they can be studied. Recently, a Franco-German collaboration has been able to remedy this shortfall by obtaining a transgenic mouse model which develops the same lesions as those relating to CADASIL syndrome. Anne Joutel and her team at Inserm Unit 740, "Genetics of the vascular diseases", have recently published their work in the *Journal of Clinical Investigation* on 1st February 2010.

Small cerebral vessel diseases are responsible for lesions in the white matter of the brain and for multiple, major cerebral infarctions. They are the major cause of 20% of strokes and are the second most common cause of dementia after Alzheimer's disease. CADASIL syndrome is a hereditary form of this type of disease, characterised by the presence of specific vascular deposits (known as GOM or Granular Osmiophilic Material) and the gradual degeneration of the smooth muscle cells which make up the blood vessel wall. "This disorder is considered to be rare, with only 500 families recorded worldwide. However, it would seem that its prevalence has been greatly underestimated" explains Anne Joutel, a researcher from Inserm Unit 740, "Genetics of vascular diseases". The first clinical symptoms of the disease appear between the ages of 40 and 45. However, magnetic resonance imaging (MRI) of the brain can detect the disease from age 30, via lesions in the white matter. Its development leads to a bed-ridden state and to death of the patient when aged between 60 and 65 years old.

Although these diseases of the small cerebral vessels are frequent, the exact mechanisms involved are very poorly understood, primarily because of the absence of a good animal model in which the precise chronology of the lesions could be studied. For this reason, no specific treatment currently exists. After several unfruitful attempts, Anne Joutel and her collaborators have now obtained a genetically modified mouse model which develops similar cerebral lesions with age to those which are observed in patients suffering from CADASIL syndrome.

Several years ago, research revealed that CADASIL syndrome was caused by mutations of the Notch3 gene. A part of the Notch3 protein, which results from this mutated gene, accumulates abnormally in the smooth muscle cells of the blood vessels and in the pericytes of the capillaries (cells which have long cytoplasm prolongations and which have the capacity to regulate the blood flow through the vessels which they surround).

[1] CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy



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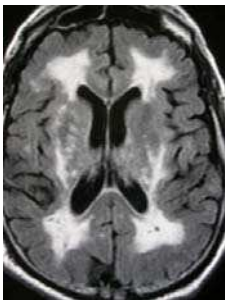
An immuno-stained Notch3 showing the accumulation of Notch3 (red) in a capillary (green) marked with an anti-collagen IV.



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Cerebral MRI of a patient afflicted with CADASIL illustrating the white matter lesions.

Using their new in-vivo model the researchers have been able to observe, from the age of five months in the transgenic mice expressing the mutated Notch3 protein, the characteristic vascular lesions of the disease, namely the abnormal accumulation of the Notch3 protein and of GOM. From the age of 12 months, these mice developed lesions of the cerebral white matter which are associated with a reduction in cerebral perfusion similar to that observed in patients suffering from CADASIL. By using immunohistological and functional analyses of the cerebral vessels, the scientists have demonstrated that the lesions of the brain in CADASIL do not form from a destruction of the smooth muscle cells of the cerebral arteries, but from the combination of a dysfunction of the vessels and a reduction in the microcirculation within the cerebral white matter.

This new murine model offers multiple and very significant possibilities for CADASIL syndrome and, more generally, for vascular dementias. It constitutes a tool of choice for improving understanding of the mechanisms involved with cerebral lesions in small cerebral vessel diseases and to test therapeutic solutions aimed at preventing or slowing their appearance.

Further information:
Interview with A. Joutel and video on the *Inserm-Actualités* website

Source:

Cerebrovascular dysfunction and microcirculation rarefaction precede white matter lesions in a mouse genetic model of cerebral ischemic small vessel disease.

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