Press release

Cerebral cavernomas: a possible pharmacological alternative to neurosurgery

A team of scientists at IFOM and the University of Milan has identified a potential therapeutic approach to treating cerebral cavernomas, a congenital or sporadic malformation that can lead to cerebral hemorrhaging and, until now can only be cured through neurosurgical removal.
The discovery published today in *Nature* identifies an anti-inflammatory and anti-tumor therapy that may cure this little-known disease, which is much more common than one might imagine: potentially affecting at least one person in 500.

Milan, June 9, 2013 - This familial or sporadic cerebral vessel malformation is characterized by the formation of clusters of abnormally dilated and fragile blood vessels, called "cavernomas", which can manifest as intracerebral hemorrhages, neurological deficits, seizures or recurrent headaches.
Cerebral cavernomas have a shape similar to a raspberry, constituted by a dense agglomeration of bubbles engorged with blood and encased in a very thin and fragile endothelial wall. The type and severity of symptoms depend on their location in the brain and size, which can range from a few millimeters to several centimeters. The number of lesions may vary from one, in cases of sporadic disease, to a twenty or more in the hereditary form.
It is estimated that the probability of developing cerebral cavernomas affects more than one person in 500, but most cases (70-80%) remain asymptomatic for the entire life of the subject. The malformation can be sporadic – i.e., present in only one family member - or hereditary, with an autosomal dominant mode of transmission. Whether the malformation is present from birth or develops later in life, the onset of clinical symptoms occurs mainly in adulthood, after age 20. Cerebral cavernomas are difficult to diagnose in the absence of hereditary link; often they are discovered fortuitously, during examinations conducted for other reasons. The symptoms are nonspecific and may be incorrectly attributed to other cerebral diseases.
Once diagnosed by MRI, the only treatment currently available for cerebral cavernomas is surgical removal via craniotomy, which is only necessary for symptomatic or expanding disease.
Although the safety of neurosurgical removal is improving, thanks to the precision of microsurgical methodology, this operation can be critical: especially if the patient is a child or if the cavernoma is located in a sensitive brain area or in the spinal cord, because the intervention is likely to damage surrounding healthy structures.
A better understanding of the molecular mechanisms underlying cavernoma formation seems to point the way to alternative, less invasive and more decisive therapeutic approaches.
It is already known that Cerebral Cavernous Malformations (CCM) are caused by absence of one of three proteins that form the CCM complex. These are encoded by the genes CCM1, CCM2 and CCM3. However, until now, many questions remained unresolved: which molecular factors initiate the pathology? What mechanisms are involved in the alterations that lead to the development of abnormal blood vessels?
The study published today in the authoritative scientific journal *Nature* has made decisive steps toward understanding the molecular basis of CCM and identifying a therapy for it. Elisabetta Dejana conducted this research in the IFOM laboratories in Milan. Dejana has distinguished herself recently for her contributions to our understanding of the mechanisms regulating vascular development in tumors.
"In fact, cavernomas are similar to benign tumors, where progressive and uncontrolled multiplication of cells remains circumscribed in a specific area in the tissue." explains Elisabetta Dejana, head of the IFOM research program *The Vascular System of Cancer* and Professor of General Pathology in the Department of Biosciences at the University of Milan. "As in tumors, the endothelial cells are transformed and become more mobile and invasive, causing the uncontrolled vascular growth that leads to the development and expansion of cavernomas."
"We have focused our research on the CCM1 gene, responsible for the onset of 40% of cavernomas - continues the researcher - and we observed that inactivation of this gene resulted in the loss of endothelial cell-specific functional characteristics and transformation into mesenchymal cells." This process is known as

"endothelium-mesenchymal transition", and is typically seen in tumors and in inflammatory diseases, wherein endothelial cells acquire more migratory and invasive properties.
"In cavernomas - explain Luigi Maddaluno and Noemi Rudini, both first authors on this paper - we noticed that this change of function is mediated by *bone morphogenetic protein 6* (BMP6), a factor that is produced abnormally in endothelial cells that lack the CCM1 protein. BMP6 makes these cells very sensitive to inflammatory factors that may be present in high concentrations in the brain, such as *transforming growth factor beta* (TGF-b), which plays a crucial role in many inflammatory diseases and in tumors. Next, we conducted experiments using inhibitors of BMP6 or of TGF-b and observed a highly significant protection against the development of vascular lesions in the brain."
These drugs have already been developed and are currently under investigation for use in blocking tumor proliferation or in inflammatory diseases. Therefore, this discovery opens the door to possible therapeutic applications that are not far removed from clinical practice: "Having identified an alternative therapeutic approach to neurosurgery - Dejana states - is an important turning point for research but also for these patients." Cavernomas are not uncommon in children, where surgery can damage brain development, or in areas of the adult brain that are inoperable.
"Now we hope to have the support necessary to initiate a preliminary clinical study", concludes the researcher.

The research conducted by Dejana was supported by grants from the Italian Association for Cancer Research (AIRC) and other agencies including the Fondation Leducq, an organization engaged in research on cardiovascular diseases.

Editorial details

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Authors: **Luigi Maddaluno, Noemi Rudini**, Roberto Cuttano, Luca Bravi, Costanza Giampietro, Monica Corada, Luca Ferrarini, Fabrizio Orsenigo, Eleanna Papa, Gwenola Boulday, Elisabeth Tournier-Lasserve, Françoise Chapon, Cristina Richichi, Saverio Francesco Retta, Maria Grazia Lampugnani & **Elisabetta Dejana**