Novel diagnostic and therapeutic perspectives for CCM disease prevention and treatment

An **international cooperation** between researchers of the **University of Utah** (Salt Lake City, UT, USA), coordinated by prof. Dean Li, and two research units of the **CCM_Italia multidisciplinary research network** (Torino [1] and L'Aquila [2]), coordinated by prof. Francesco Retta, has led to the demonstration that compounds endowed with antioxidant properties, including cholecalciferol (**Vitamin D_3**) and **tempol** (a scavenger of superoxide), are effective in rescuing major phenotypes associated with loss-of-function of CCM genes in both human endothelial cells and a mouse model of CCM disease, suggesting that these two known drugs might be **repurposed to treat CCM disease**.

The relative paper is currently *in press* and will be soon available online. Further work is ongoing to determine whether the reported findings will translate to humans with CCM disease.

Notably, while supporting and strengthening the **original discovery** that **oxidative stress may play a critical role in CCM disease** (Goitre et al., 2010 [3]; Goitre et al., 2012 [4]; Guazzi et al., 2012 [5]; Goitre et al., 2014 [6]), leading to concrete **therapeutic perspectives**, the novel findings strongly support immediate amendment of research protocols on human patients with CCM to include measurements of both **Vitamin D_3** [25(OH)D3] and relevant **biomarkers of oxidative stress**. Indeed, whereas low levels of Vitamin D_3 might constitute a potential **risk factor** for CCM disease progression and severity, blood tests for measuring levels of Vitamin D_3 and biomarkers of oxidative stress may have **diagnostic and prognostic value** for the early assessment of high-risk groups of patients with CCM disease, thus facilitating clinical decision-making and prompt initiation of adequate therapy. Consistently, there is some evidence suggesting that CCM-related symptoms increase during the winter months, which would be consistent with seasonal **variation in Vitamin D** or the **increased oxidative stress** associated with inflammation due to typical winter infections such as influenza. On the other hand, the **accessibility of Vitamin D_3**, which is inexpensive and widely available in supplement form, freely available outdoors to those with exposed skin, and has a wide safety margin, and the **various clinical trials underway** in the United States **for tempol** in a variety of conditions suggest that one or both of these drugs could be rapidly applied to the treatment of CCM disease.

What is CCM disease?

Cerebral Cavernous Malformations (**CCM**; OMIM 116860) (also known as **cavernous angioma** or **cavernoma**) are major vascular malformations having a raspberry-like appearance and consisting of closely clustered, **abnormally dilated and leaky capillary**

channels (caverns) lined by a thin endothelium layer devoid of normal vessel structural components (*Rigamonti 2011*).

CCM disease has been recognized as **a common clinical entity**, having a **prevalence of 0.3%-0.5%** in the general population, and accounting for approximately 24 million people worldwide with a major impact on quality of life. It can occur as **single or multiple lesions** (even hundreds) ranging in size from a few **millimeters** to a few **centimeters** and, depending on the size and location, can be clinically silent or give rise to serious clinical symptoms such as **headaches**, **neurological deficits**, **seizures**, **stroke**, and **intracerebral hemorrhage** that can result in death.

Symptomatic disease typically begins in the third through fifth decades of life, although lesions have been described in all age groups, including young children, with no sex predominance. **Diagnosis** is commonly made by routine magnetic resonance imaging (MRI) screening, although detection is far more likely via gradient-echo (GRE) or susceptibility-weighted imaging (SWI), which can unmask small lesions. Generally, approximately 30% of people with CCM lesions eventually will develop clinical symptoms.

CCM disease in Italy

Symptomatic CCM disease is estimated to hit a number of Italian people ranging from 15,000 to 80,000. Specifically, it has been estimated that the **sporadic** (sCCM) and **familial** (fCCM) forms of CCM disease affect a number of Italian people ranging from 10,500 to 56,000 (2-9 cases per 10,000 inhabitants) and from 4,500 to 24,000 (0.75-4 cases per 10,000 inhabitants), respectively.

Despite CCM disease goes up to the Italian breaking news and headlines when it hits famous people, including recently the football player of the Roma soccer team **Leandro Castan**, its **knowledge and risk awareness** is generally poor within the society and **very low even among medical doctors**. Furthermore, while medications are available to treat some clinical symptoms caused by CCM lesions, including seizures and headaches, to date there are **no direct therapeutic approaches** for CCM disease, **besides surgical removal** of accessible lesions in patients with recurrent hemorrhage or intractable seizures. In particular, **novel pharmacological strategies** are required for preventing CCM disease progression and severity in susceptible individuals.

Italian researchers from the CCM Italia network have provided original and fundamental insights into the understanding of molecular mechanisms underlying CCM pathogenesis and the definition of novel pharmacological approaches for **CCM disease prevention and treatment**, including the recent important findings described above. However, it is worth, and sad, to point out that these contributions arise exclusively from the **tireless passion** of young researchers, whose **work** is **neither recognized nor supported** not only by Italian health and biomedical research institutions but often even by the general population.

Francesco Retta

See also:

Altered Redox Signaling and Oxidative Stress: the Emerging Faces of CCM Disease [7]

La gioia del ritorno in campo [8]

References:

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For updated information on this topic, please visit CCM Italia and Associazione Italiana Angiomi Cavernosi [19] (AIAC) websites.

Lingua
Italiano

Links
[1] http://www.ccmitalia.unito.it/content/unità-di-ricerca-di-torino
[2] http://www.ccmitalia.unito.it/content/unità-di-ricerca-di-laquila
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