

Press release

When stability runs through your veins

A key mechanism that ensures that blood vessel cells live in harmony, and as a consequence, stabilises the vascular system, has recently been discovered in Italy. This discovery has important implications for the treatment of cancer, as well as heart disease, stroke and inflammatory diseases: the research was published in *Nature Cell Biology*.

Who sets the rules by which blood vessel cells live together? Who conveys to them a sense of self, as well as an awareness of their neighbouring cells? Who controls their capacity to form cohesive and compact interactions? Who ensures that they communicate efficiently with one another to generate a harmonious community in which every cell knows its place and respects its boundaries?

The answer is a protein called VE-Cadherin.

VE-Cadherin was first identified over 10 years ago by Elisabetta Dejana (head of the Angiogenesis program at the IFOM [FIRC Institute of Molecular Oncology] Foundation) during an in depth study on the development of the vascular system. It was initially characterised as an important adhesion factor for blood vessel cells and, therefore, was recognised as a potential therapeutic target for the inhibition of tumour angiogenesis, i.e. tumour-induced blood vessel formation, required for tumour growth and survival.

Recent research by Dejana's group, now reported in the prestigious international scientific journal, *Nature Cell Biology*, has revealed other important aspects of VE-Cadherin function: not only does VE-Cadherin glue endothelial cells together (these cells line the inside walls of blood vessels), but it also allows them to "sense" their position, it regulates cell-to-cell contacts, controls growth, defines boundaries and, above all, transmits signals to their nuclei, which results in the active cooperation of endothelial cells in blood vessel stabilisation. In particular, the group has identified the pathway by which VE-Cadherin induces the production of Claudin-5, a protein that literally "seals" blood vessels from external infiltrations.

This important research, which originally began as basic cancer research, now opens the way for the identification of new therapeutic targets to fight, not only cancer, but also other diseases such as stroke, heart disease, certain hereditary diseases and inflammatory conditions.

"Nowadays, scientific research tends to be "highly focused" on one specific problem (disease) – comments Dejana – however, our results underline the interdisciplinary impact of basic research. The study of basic biological mechanisms can lead to discoveries that have far reaching implications for multiple, apparently unrelated, areas of research, and allow the development of novel therapeutic strategies for different diseases that share the same underlying molecular causes."

This research, directed by Dejana, is the result of an intense study, lasting nearly 4 years, that was financed by the 'Associazione Italiana per la Ricerca sul Cancro (AIRC)' and other funding bodies including Fondation Leducq, an organisation involved in research into cardiovascular disease.

VE-CADHERIN AND VASCULAR STABILISATION: RESULTS AND POTENTIAL THERAPIES

Elisabetta Dejana is head of the Angiogenesis program at the IFOM (FIRC Institute of Molecular Oncology) Foundation and Full Professor of General Pathology at the Department of Biomolecular Sciences and Biotechnology, within the Faculty of Mathematical, Physical and Natural Sciences at the University of Milan. In recent years, she has gained wide recognition by the international scientific community and the public, for her important contributions to research on the development of the vascular system.

The characterisation of VE (Vascular-Endothelial) -Cadherin as an "adhesive" protein that "zips" tissue endothelial cells together, dates back to the end of the 1990s. VE-Cadherin, through its ability to stabilise vascular structures, was found to play a key role in tumour vascularisation; hence, it represents an important therapeutic "target" for the inhibition of tumour angiogenesis. Indeed, inactivation of the gene encoding VE-

Cadherin inhibits tumour blood vessel formation and starves tumours of their blood supply, without compromising normal tissue vascularisation. The starved tumours regress and become more susceptible to targeted therapies.

However, recent research by Dejana's group has uncovered a more significant role of VE-Cadherin in vascular development. Andrea Taddei (first author of the research paper), who has been working on VE-Cadherin since he joined IFOM as a new graduate at the age of 23, explains: "we have discovered that the role of VE-Cadherin in vascular stabilisation is more complex than initially thought. In addition to being directly responsible for gluing cells together, VE-Cadherin activates a 'virtuous circle' inside the cell, by imparting signals to the nucleus that direct the cell to express a 'team' of vascular stabilisation genes.

Thanks to an innovative experimental methodology that combines DNA Affymetrix microarrays (gene expression analysis) and Real Time PCR (a quantitative, snapshot of the expression of genes within cells) the specific molecular pathway through which VE-Cadherin activates gene expression in endothelial cells has been uncovered. By binding to intracellular molecules, VE-Cadherin triggers a signalling cascade that instructs the nucleus to activate a gene encoding a protein that plays a crucial role in vascular stabilisation: Claudin-5.

Claudin-5 is a crucial component of vascular endothelial tight junctions, conferring a barrier property to these junctions (N.B. claudin comes from the latin claudere = to close), which protects blood vessels against the infiltration of soluble molecules from the extracellular space.

Dejana's group confirmed, by in vitro and in vivo experiments, that inhibition of VE-Cadherin causes a reduction in Claudin-5, leading to a destabilisation of the vascular system, with blood vessels becoming more fragile and permeable.

The characterisation of how VE-Cadherin on the endothelial cell surface communicates with the nucleus inside the cell opens the way for the identification of novel therapeutic targets: the destabilisation of vascular structures is a common feature of many diseases. In all cases, a dysfunctional VE-Cadherin causes an imbalance in Claudin-5 production. This explains, for example, the rupture of blood vessels in the brain haemorrhages, which may be prevented by novel therapies that enhance the stability of blood vessels. In contrast, for cancer, which is characterised by the overproduction of blood vessels, agents that destabilise blood vessels can be used to "cut the supply of nutrients" to the tumour and arrest tumour growth.

Milan, August 2008

EDITORIAL DETAILS

Publication: Nature Cell Biology, August 2008

Title:

Endothelial adherens junctions control tight junctions by VE-cadherin-mediated upregulation of claudin-5

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