Press Release

New perspectives for cancer research: stabilization of blood vessels in tumours may render cancers more sensitive to treatment

Milan, 15 June 2010 – A team of researchers led by Elisabetta Dejana (Head of the Angiogenesis Research Program at IFOM) have identified a novel mechanism underlying the abnormal development of the vascular system in tumours, a distinctive and dangerous feature of cancer. The discovery has important implications: it opens the way for new therapeutic approaches that could complement and enhance existing anticancer therapies that block the blood supply to tumours. In the near future, the researchers will test the effectiveness of the new therapeutic approach in cancers such as melanoma, breast cancer and pancreatic cancer. The study was published online today in the renowned scientific journal, *Developmental Cell*.

A crucial phase in the development of cancer is the **formation of new blood vessels**, a process called **angiogenesis**. Soon after the formation of a tumour, new vascular structures, originating from those of the host organism, are formed in the tumour. These structures provide the tumour with its own supply of oxygen and nutrients. They also act as "highways" through which cancer cells can enter the body's bloodstream and disseminate around the body, resulting in **metastases** in distant organs. Thus, an obvious strategy for attacking cancer is to prevent the formation of blood vessels in tumours. This should inhibit, on the one hand, tumour growth and on the other, the formation of metastases at sites, distinct from that of the primary tumour.

This strategy, although effective in the laboratory, has so far achieved only limited results in the clinic. "Several recent studies have shown that you need to consider not only the quantity, but also the **quality of the vessels** within the tumour," says Elisabetta Dejana, Head of the Angiogenesis Research Program at IFOM (FIRC Institute of Molecular Oncology) and Full Professor of Pathology at the Dept. of Biomolecular Sciences and Biotechnology, under the Faculty of Mathematical, Physical and Natural Sciences, at the University of Milan. "When new blood vessels penetrate the tumour", - explains Dejana – "their normal characteristics change: they become very irregular and develop an altered vessel lumen (enlarged or reduced), making it very difficult to distinguish between arteries and veins. **Tumour blood vessels are very fragile and permeable**, and, as a consequence, bleeding or the leakage of fluids into the tumour tissue occurs frequently, causing swelling and the build-up of pressure. Under these circumstances, blood flow in the tumour is impaired, leading to necrosis in areas of the tumour and hindering the delivery of chemotherapy drugs inside the tumour mass. If you think of a river" - continues Dejana – "when the banks are high and fortified, flooding is prevented and the land can be irrigated in a controlled manner; however, when the banks are weak and irregular, it is more likely that flooding will occur and that irrigation will be altered. In addition, the river bed can now be easily accessed from the banks. In a similar fashion, irregular and highly permeable blood vessels in tumours not only cause bleeding, but also offer very little resistance to the infiltration of cancer cells, which can then circulate around the body".

Until now, the mechanism responsible for the formation of abnormal vascular structures in tumours was unclear: the new discovery made by Elisabetta Dejana's research team represents a significant step forwards in the identification of the guilty players in this process. "We identified a family of factors" - explains Dejana – "that controls the formation of new blood vessels. When these factors are not properly controlled, their associated signalling pathways become permanently activated, causing the formation of abnormal and fragile blood vessels". The factors in question belong to the **Wnt protein family**. Under normal conditions, these factors regulate various processes during embryonic development; however, Wnt proteins are also produced at high

concentrations by many tumours and it has been observed that **their uncontrolled activity is largely responsible for the abnormal organization of the tumour vasculature**.

Dejana's research team started off by studying the functions of Wnt proteins, but their results have gone far beyond. "We have characterized the mechanism by which Wnt factors affect vasculature. The mechanism involves another important communication system used by cells, the Notch signalling pathway. The deregulation of these two molecular pathways causes vascular abnormalities typical of those observed in cancer", explains Monica Corada, first author of the paper and researcher at IFOM.

The discovery may have very significant practical consequences. According to Dejana, "The identification of key molecules involved in the formation of an abnormal vascular system, as occurs in cancer, will allow us to identify **specific therapeutic targets that can be inhibited to allow vascularisation to return to normal".** Therapies that block tumour vascularisation remain, however, valid and are being tested in clinical trials. Their effectiveness, however, is still only partial. "Not only is it important to reduce the number of tumour blood vessels" – explains the researcher – "but it may also be important, particularly in advanced cancers, to stabilize and normalize tumour blood vessels, in order to facilitate the diffusion of drugs within the tumour and to prevent metastasis. Thus, future research, based on this initial discovery, will focus on developing new tools to complement existing ones, in order to improve cancer treatment".

In the near future, Dejana's team will focus their research on cancers that display a highly altered expression of Wnt proteins; for example, melanoma, which is a particularly aggressive cancer, as well as other types of cancer, such as breast and pancreatic cancer. The researchers aim to interfere with the production and/or activity of Wnt factors, in order to reduce tumour growth and inhibit metastasis. "The goal" – concludes Dejana – "is to identify the ideal combination of treatments, in order to specifically target different types of cancer depending on their particular characteristics and their stage of progression."

The study was conducted with the support of AIRC (the Italian Association for Cancer Research), the Italian Ministry for Health, the Cariplo Foundation, the Italian National Institute of Health, the European Community, the Leducq Foundation, the Transatlantic Network of Excellence, and the Association for International Cancer Research.

Elisabetta Dejana has been working in the field of angiogenesis for many years and has received many prestigious scientific and civil awards, the most recent being an honorary degree conferred by the University of Helsinki on June 2, 2010. Her new research, which appears online today in the journal Developmental Cell, represents a significant contribution to the identification and characterization of proteins involved in vascularisation in normal and tumour cells. It also is an important step forward in the identification of new molecular targets for the development of novel anti-cancer drugs.

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