DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

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Human Vascular System in Mice

Researchers of the German Cancer Research Center are studying in mice how tumors manipulate the human vascular system

To survive, tumors use the body's blood system for their own purposes: They stimulate the growth of blood vessels that supply the tumor. Medical treatment blocks this process in order to restrain tumors. Scientists of the Joint Research Division "Vascular Biology" of the Mannheim Medical Faculty of the University of Heidelberg and the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), collaborating with colleagues in Freiburg, have developed a method for producing a complex human vascular system in mice. Thus, they can study the effect of tumors on the intact human vasculature and test therapeutic agents.

The formation of new blood vessels, or angiogenesis, is an Achilles' heel of tumor growth, because tumors depend on the supply of oxygen and nutrients for survival. Therefore, for some years now substances called angiogenesis inhibitors have been used in cancer treatment to suppress this process. In order to advance this new research field, a team of researchers headed by Professor Hellmut Augustin has developed a method to create a complex human vascular system in mice, which stays functional even after several months.

The method is based on the observation that isolated cells of the vessel walls, called endothelial cells, congregate spontaneously in cell cultures to form aggregates known as spheroids. "Individual endothelial cells floating in suspension are doomed to die – the association in spheroids stabilizes them," says Hellmut Augustin. The scientists Abdullah Alajati and Anna Laib have been able to inject such spheroids, embedded in a gel matrix, under the skin of mice and to stimulate the formation of a network of human blood vessels by means of growth factors. The mice were genetically modified in such a way that their immune system was unable to reject the foreign cells. "The newly formed blood vessels are made exclusively of human endothelial cells," explains Anna Laib, a young researcher at the DKFZ. "At the matrix borders the human endothelial cells establish contact with those of the mouse. In this way, the transplanted human vasculature gets connected to the blood circulation of the mouse."

The method provides experimental freedom and may deliver answers to various questions of vascular biology research. Scientists can genetically manipulate the endothelial cells before transplantation in order to investigate the formation of vascular networks. In addition, it is possible to test the effect of pharmacological substances; the Freiburg-based company ProQinase GmbH, which is involved in the study, is already conducting such experiments. "The method is even interesting for the production of artificial tissues," Hellmut Augustin says. "So far, one difficulty with the use of artificial replacement tissues has been to create a functioning vascular system that sufficiently supplies the tissue constructs."

Figure captions

Fig. 1: Three-dimensional reconstruction of a vascular system made of human endothelial cells in mice 20 days after injection of the spheroids. Image taken with a confocal microscope, stained green.

Fig. 2: The three-dimensional analysis of blood vessels formed shows that growth factors such as fibroblast growth factor (FGF)-2 effectively promote the coating of the newly formed

blood vessels (stained green) with smooth muscle cells (stained red). Image was taken with a confocal microscope.

Abdullah Alajati, Anna M Laib, Holger Weber, Anja M Boos, Arne Bartol, Kristian Ikenberg, Thomas Korff, Hanswalter Zentgraf, Cynthia Obodozie, RalphGraeser, Sven Christian, Günter Finkenzeller, G Björn Stark, Mélanie Héroult & Hellmut G Augustin: Spheroid-based engineering of a human vasculature in mice. Nature Methods, April 2008, DOI: 10.1038/nmeth.1198

Das Deutsche Krebsforschungszentrum hat die Aufgabe, die Mechanismen der Krebsentstehung systematisch zu untersuchen und Krebsrisikofaktoren zu erfassen. Die Ergebnisse dieser Grundlagenforschung sollen zu neuen Ansätzen in Vorbeugung, Diagnose und Therapie von Krebserkrankungen führen. Das Zentrum wird zu 90 Prozent vom Bundesministerium für Bildung und Forschung und zu 10 Prozent vom Land Baden-Württemberg finanziert und ist Mitglied in der Helmholtz-Gemeinschaft Deutscher Forschungszentren e.V.

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