Dual effect on tumor blood vessels

May 31 2012

Angiogenesis is considered to be a major target of new cancer treatments. Angiopoietin-2 (Ang-2) is one of the key regulators of angiogenesis. Scientists of the German Cancer Research Center and Medical Faculty Mannheim, Heidelberg University, have now discovered that Ang-2 even has a dual effect on angiogenesis: Firstly, it affects the sprouting of new capillaries and, secondly, it impacts the maturation of the newly formed vessels. Therapies targeting Ang-2 might therefore attack angiogenesis from two angles at once.

As soon as they have grown to pinhead size, tumors rely on the formation of new blood vessels - a process which is scientifically called angiogenesis. Interfering with this process (antiangiogenesis) is considered to be a promising approach in cancer medicine. However, those drugs that are already available for preventing the sprouting of new blood capillaries have failed to fulfill the high expectations placed on them.

Medical researchers hope to increase the efficacy of antiangiogenic therapies by attacking angiogenesis from several angles. Currently available antiangiogenic drugs are directed against the VEGF growth factor, which induces the sprouting of new blood vessels. However, other important players in angiogenesis include two signaling molecules called angiopoietin-1 and angiopoietin-2. Ang-1 is responsible for vascular maturation, while Ang-2 is a functional antagonist of Ang-1. Both signaling molecules bind to the same receptor, Tie-2, on the surface of endothelial cells.

"There are already studies showing that Ang-2 is a suitable target of new therapies directed against the blood supply of tumors. Combinations with already approved antiangiogenic drugs are regarded as particularly promising," says Prof. Dr. Hellmut Augustin, whose working groups are located at DKFZ and at Medical Faculty Mannheim of the University of Heidelberg. "However, as the role of Ang-2 was not entirely clear yet, we first needed to gain a better understanding of its molecular mechanism of action."

The scientists in Augustin's group have now found out that epithelial cells at the tip of sprouting capillaries produce large amounts of Ang-2, but not its known receptor, Tie-2. Nevertheless, these cells respond to the signaling molecule. This has prompted researchers to conclude that Ang-2 may also be able to mediate signals to epithelial cells via other surface molecules than Tie-2.

Indeed, the team of vascular experts found in the tip cells of newly sprouting capillaries that Ang-2 can use what are called integrins as alternative receptors. Integrins are membrane proteins common in many cell types, which are involved in many intercellular signaling processes.

"That means that we are dealing with two independent effects," Hellmut Augustin explains. "On the one hand, the already known function as an antagonist of Ang-1 in epithelial cells which produce the Tie-2 receptor and, on the other, the integrin-dependent effect on the capillary tip cells which do not have Tie-2. This also explains why experimental therapies targeting Ang-2 are more successful than those targeting its known receptor, Tie-2. This finding shows that it is double worthwhile to further develop therapies against Ang-2. Thus, we can attack the formation of blood vessels in the tumor from two angles at once."

More information: Moritz Felcht, Robert Luck, Alexander Schering, Philipp Seidel, Kshitij Srivastava, Junhao Hu, Arne Bartol, Yvonne

Kienast, Christiane Vettel, Elias K. Loos, Simone Kutschera, Susanne Bartels, Sila Appak, Eva Besemfelder, Dorothee Terhardt, Emmanouil Chavakis, Thomas Wieland, Christian Klein, Markus Thomas, Akiyoshi Uemura, Sergij Goerdt and Hellmut G. Augustin: Angiopoietin-2 differentially regulates angiogenesis through TIE-2 and integrin signaling. *Journal of Clinical Investigation* 2012, DOI: 10.1172/JCI58832