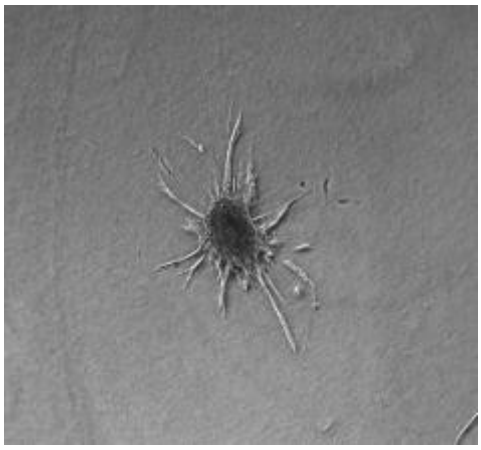
Healthcare industry BW

What makes blood vessels sprout?

Calcified arteries or capillaries – this is often associated with blood stasis, reduced oxygen supply, and subsequent cardiac strain that compensates these deficiencies. Dr. Sebastian Grundmann from the Department of Cardiology and Angiology at the University Medical Centre Freiburg and his team are investigating how the growth of blood vessels is triggered, and potentially find ways to naturally deviate the site of congestion.

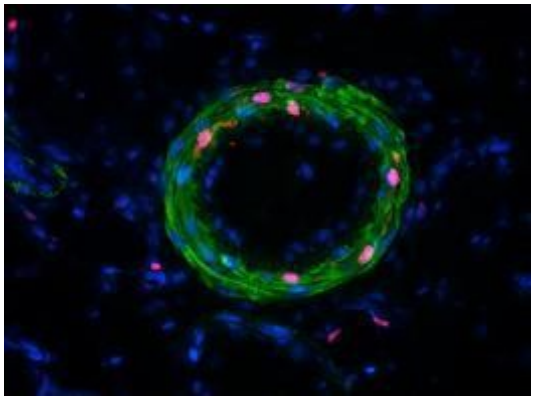
Main branches, side branches, a network of twigs – this is not a tree, it is the human blood vessel system. It transports nutrients such as sugar or oxygen to peripheral parts of the body; it removes degradation products and CO2 from the tissue. In patients with coronary heart disease, individual blood vessels are constricted as a result of arteriosclerosis, the reduced supply of oxygen to the heart causes a great deal of pain, and in the worst case scenario, leads to cardiac infarction. Cardiac catheters or bypass surgery can sometimes be the answer. "But about 20 percent of patients are not suited to any of the operations that are currently available," said Dr. Sebastian Grundmann (MD), a post-doctoral scientist in Dr. Martin Moser's team in the Department of Internal Medicine III at Freiburg University Hospital. "Therefore, we are investigating ways to induce endogenous blood vessel growth."

Experimental model: Intermittent claudication



Sometimes arteries calcify so slowly that new vessels are generated naturally, taking over the activity of the original ones. Which mechanisms lead to the generation of new blood vessels? It is known that this process involves cells of the vascular walls - the endothelial cells and smooth muscle cells - as

well as stem cells or mobile cells such as monocytes. Secondary messengers induce genetic programmes in these cells, which subsequently divide and migrate to other areas. Some of them develop into blood vessel cells and contribute to arterial and capillary growth. Grundmann and his team are currently investigating the molecular players that direct this process. They are particularly interested in the forkhead box transcription factor P1. They are also investigating microRNAs that have been shown to have numerous regulatory functions in other experiments carried out in recent years.



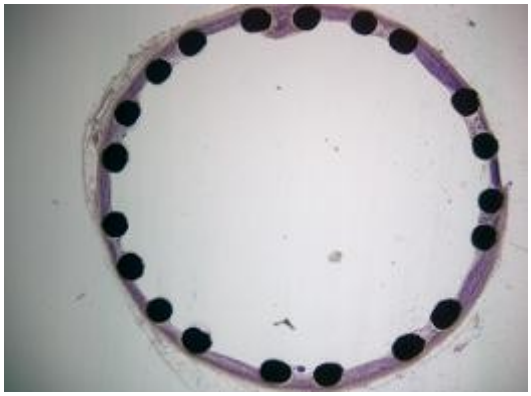
Grundmann and his team of researchers became interested in the forkhead box transcription factor P1 a few years ago when they induced artificial constrictions in the blood vessels of the legs of mice. This manipulation leads to intermittent claudication caused by peripheral arterial disease. The cells in the animals' vascular walls produced larger quantities of P1 than normal. The researchers have since been able to inhibit the generation of P1 in different cell types using molecular genetics methods. They found that such cells divide considerably slower than non-manipulated ones. In addition, the cells displayed a reduced migration activity and did not generate so many new vessels.

Working with colleagues from the Department of Nephrology in Freiburg, Grundmann and his team have been able to show in the zebrafish model that the blood vessel system of embryos fails to develop correctly when the P1 transcription factor is lacking. "The molecular network involving this transcription factor is still unknown. We also do not know which genes it influences," said Grundmann adding that his team is currently working on finding this out.

Potent small molecules

The scientists have come up with similar results for some microRNAs. These molecules are able to inhibit the messenger RNA of certain genes. This results in the reduced production of important proteins that might also play a role in angiogenesis. Grundmann and his team found several dozen small RNAs in the aforementioned mouse model, which were suddenly produced in greater quantities and also appeared to have a role in natural vascularisation. The researchers carried out experiments with cells in which they either inhibited or stimulated the production of potential RNA candidates and, as a result, found that there were some RNAs that regulate the division and migration of blood vessel cells. The researchers have plans to test whether the inhibition of such small RNAs in living mice also impedes the growth of arteries and capillaries.

A project carried out by Grundmann during his postdoctoral period in Holland between 2005 and 2007 shows that basic research results gained in the field of angiogenesis (growth of blood vessels) can be turned into clinical applications. Back then, Grundmann was working in cooperation with the stent manufacturer Metronic to develop a stent coated with TGF-ß1. Another of Grundmann's colleagues had previously shown that this secondary messenger induced the growth of blood vessels.



The stents, tubes of only a few millimetres in size, are inserted into the blood vessels where they release the substance into the blood and locally induce angiogenesis. "The prototype is currently being tested. Preclinical studies have already shown that the principle works," said Grundmann.

Further information:

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