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Inhibition of microRNAs can stimulate the growth of new blood vessels

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This is the result of a recent experimental study carried out at the University Hospital Freiburg in Germany and funded by the German Research Foundation. In an animal model of peripheral artery disease, blood flow to the lower leg was significantly improved after treatment with the so-called "antagomir"-inhibitor.

MicroRNAs are a class of recently discovered molecules that can bind to other RNAs and thereby regulate the expression of several genes at once. More than 1000 microRNAs exist in humans and recent studies have shown an important function of these small regulators in many aspects of cardiovascular disease, from atherosclerosis to heart failure. It is estimated that more than 30% of all genes are affected by microRNAs.

Researchers from Freiburg describe for the first time the changes in microRNA-expression that occur if a major artery is occluded and new blood vessels develop as a compensatory mechanism. "We then selected the microRNAs with highest change in expression for further analysis", research lead, Dr. Sebastian Grundmann, explains. "The levels of microRNA-100, which is highly expressed in resting blood vessels, rapidly decreased if small vessels had to proliferate to compensate for the occluded artery. However, in patients this adaptive growth often remains insufficient to bring enough blood to the tissue at risk."

The additional pharmacologic inhibition of microRNA-100 with a new "antagomir"-inhibitor could be used to stimulate this natural adaptive mechanism. "In the treatment group, blood flow increased by almost

30%", Dr. Grundmann summarizes the main result of the study, "and we could show that an increase in the microRNA-100 target mTOR was responsible for this effect".

mTOR (mammalian target of rapamycin) is a central signal transduction molecule with an important function in cell proliferation, blood vessel growth and metabolic regulation. Inhibitors of mTOR are currently used for the prevention of in-stent re-stenosis and evaluated in several other cardiovascular and oncologic disease states. The discovery that microRNA-100 acts as an endogenous mTOR-modular extends the possible function of this small RNA beyond the regulation of blood vessel growth.

Since microRNA-100 and mTOR are not specific for blood vessels, potential side effects of its inhibition are also a concern. Indeed, first results from the Freiburg group demonstrate that the microRNA-100-inhbibitor also affects inflammatory processes, an unwanted effect in cardiovascular disease. "Together with expert collaborators, we are currently investigating microRNA-100 and its inhibitor in several other disease models, where we already know that mTOR is critical", Dr. Grundmann explains. "Our results on microRNA-100 in blood vessel show that microRNAs are attractive targets for future therapy of cardiovascular disease."

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