MicroRNAs could increase the risk of amputation in diabetics

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New research has found one of the smallest entities in the human genome, micro-RNA, could increase the risk of limb amputation in diabetic patients who have poor blood flow.

The study by Dr Andrea Caporali and colleagues in Professor Costanza Emanueli's research group in the Regenerative Medicine Section of the School of Clinical Sciences at the University of Bristol was funded by the Medical Research Council and is published online in *Circulation: Journal of the American Heart Association*.

The research group have shown in an experimental cell study that conditions mimicking diabetes and a lack of blood supply to a tissue increased a particular miRNA (miRNA-503) and impaired the ability of endothelial cells, which line the interior surface of blood vessels. Micro-RNAs (miRNAs) are small sections of ribonucleic acid (RNA) that can inhibit many genes.

Alternatively, slowing down miRNA-503 improved the capability of endothelial cells to duplicate and form into networks of small blood vessels. The researchers showed that microRNA-503 reduces cell growth and prevents the formation of blood vessels by direct binding and inhibition of cyclin E1 and Cdc25 mRNA.

Costanza Emanueli, Professorial Research Fellow in Vascular Pathology & Regeneration, said: "Because each miRNA can regulate many genes, they represent an exciting new target to correct diseases that have

complex underlying mechanisms, like diabetes, rather than trying to target one specific gene. Our study is the first to provide evidence for a role of miRNAs in diabetes-induced defects in reparative angiogenesis."

The team subsequently investigated miR-503 and target gene expression in muscular specimens from the amputated ischaemic legs of diabetic patients. As controls, calf biopsies of non-diabetic and non-ischemic patients undergoing saphenous vein stripping were used. In diabetic muscles, miR-503 expression was remarkably higher, and plasma miR-503 levels were also elevated in the diabetic subjects.

Finally, using mouse models of diabetes and limb ischaemia, the researchers found that inhibition of the miRNA-503 (using a "decoy miRNA") could restore-post-ischaemic blood flow recovery. The findings of this study highlight important clinical implications of miR-503 in diabetes-associated vascular complications.

In early diabetes, high blood glucose levels damage blood vessels leading to lack of blood flow (ischaemia). Such ischaemic complications are the leading cause of disease and death in diabetic patients. In limbs, lack of blood flow can result in non-healing ulcers and, in diabetic patients, the ischaemic disease follows an unalterable course and limb amputation is too often the eventual remedy.

Tissues can recover from lack of blood flow by new blood vessel growth (angiogenesis), which restores blood supply to the tissue (reperfusion). However, diabetes harms the restoration of the flow of blood to a previously ischemic tissue, by mechanisms that are not fully understood, and so a better understanding of the molecular mechanisms underpinning diabetes-associated vascular complications is urgently needed to improve therapeutic options.

More information: Deregulation of microRNA-503 contributes to

diabetes-induced impairment of endothelial function and reparative angiogenesis after limb ischemia, Andrea Caporali, Marco Meloni, Christine Völlenkle, Desiree Bonci, Graciela B Sala-Newby, Roberta Addis, Gaia Spinetti, Sergio Losa, Rachel Masson, Andrew H Baker, Reuven Agami, Carlos le Sage, Gianluigi Condorelli, Paolo Madeddu, Fabio Martelli, Costanza Emanueli, *Circulation*, published online January 10, 2011.