

Insight into mechanisms of diabetes-induced microvascular disease reveals new therapies

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New findings from Bristol scientists could lead to future treatments to prevent lower limb amputations in diabetes - which currently affect 100 people a week in the UK (source Diabetes UK).

The research from the University of Bristol is published online in *Circulation Research* and was funded by the British Heart Foundation (BHF) and the European Vascular Genomic Network of Excellence (EVGN).

Diabetes can have serious complications like gangrene and skin ulcers due to a restriction of blood supply to and healing capacity of the affected areas and this causes the dysfunction of cells lining the blood vessels. Legs and feet are often severely affected, and, after blood supply is obstructed or injury, the tissue seems to be unable to heal itself by growing new blood vessels making the situation much worse. If gangrenous wounds fail to heal amputation may be the only option.

Dr Costanza Emanuelli, BHF Reader at Bristol University and colleagues at the Bristol Heart Institute have previously found that a group of growth factors - known as neurotrophins - play a role in the vascular system. Growth factors act on two completely different types of cellular receptors. One type, trk, mediates positive actions, such as survival and growing new blood vessels and the other, p75NTR, has not been comprehensively characterised.

In healthy blood vessels, the cells that line the blood vessels do not

possess the p75NTR receptor, and the development of new blood vessels and healing of the obstructed blood supply and wounds is rapid. However, diabetes causes the cells lining the blood vessels to produce the p75NTR receptor, and prevents the growth of new blood vessels necessary for blood supply and healing of damaged tissue.

Dr Emanuelli's group found that if they put the receptor gene into healthy blood vessel cells, the cells became dysfunctional. Equally, injecting the gene into healthy muscle and then restricting blood supply caused impaired healing following the injury identical to that seen in diabetes.

The final proof was to inhibit the p75NTR receptor in diabetic mice before restricting the blood supply to one of their "limbs". The researchers found that p75NTR inhibition enabled the limb to recover from the restricted blood flow and be well supplied with blood.

p75NTR acts by depressing the cell's normal signalling mechanisms that are necessary to stimulate the growth of new blood vessels. In its absence, this process proceeds normally.

Dr Emanuelli said: "Our findings demonstrate the importance of understanding the individual factors responsible for such diabetes-induced complications. The data reveal that by suppressing the action of one particular gene, we can improve recovery of tissues following inadequate blood flow, and this opens up new avenues for its use to combat diabetes-induced vascular disease."

Source: University of Bristol

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