**LAY Abstract - Original**

**Background**

Rarefaction of peritubular capillaries (PTC) is a key determinant of progressive chronic kidney disease following ischemia-reperfusion injury (IRI). Renal IRI induces apoptosis of PTCs, leading to the release of apoptotic exosomes (ApoExos), a distinct type of extracellular vesicles. These ApoExos carry mRNA coding for PCSK5, a serine protease from the proprotein convertase family. In turn, neighboring endothelial cells (EC), take up ApoExos which induces increased expression of PCSK5.

**Objectives**

To determine the impact of ApoExos and their cargoed PCSK5 mRNA on endothelial function, specifically regarding proteolysis, migration, and angiogenesis.

**Methods**

ApoExos were isolated by ultracentrifugation from serum-free media conditioned by primary human EC. EC were transfected with pLX302-PCSK5 plasmid and PCSK5 siRNA to respectively increase and inhibit PCSK5 expression. Apoptosis, wound closure and angiogenic activity were monitored by in vitro caspase-3/7 activity, scratch and tube formation assays respectively. Unilateral hind limb ischemia, a model of persistent vascular injury, was surgically induced by femoral arteriectomy. Mice were injected intravenously with ApoExos or intramuscularly with PCSK5 plasmid. Blood flow recovery and capillary density were assessed by laser Doppler and CD34 immunohistochemistry respectively.

**Results**

Both ApoExos and PCSK5 inhibited apoptosis of EC and promoted endothelial wound closure and tube formation. Silencing of PCSK5 expression in endothelial cells in vitro decreased angiogenic activity while showing no impact on cell migration. Both ApoExo- and PCSK5-injected mice exhibited enhanced blood flow recovery. Capillary density was increased in the ApoExo- injected group.

**Conclusion**

These results suggest that PCSK5, the predominant mRNA found in endothelial ApoExos, may play a crucial role in facilitating the recovery of the microvasculature after severe vascular injury. These findings offer new insights into microvascular restoration mechanisms of potential use for preventing microvascular rarefaction.

 **LAY Abstract – Edited**

Dre. Marie-Josée Hébert's research team discovered that certain little pieces of cells excreted by dying cells in the tiny blood vessels of diseased kidneys contain a molecule that actually helps repair blood vessels after injury. The loss of blood vessels is a serious problem strongly associated with progressive chronic kidney disease that occurs after kidney transplantation. Using this molecule to prevent the loss of the kidney’s blood vessels could mean less people suffering from chronic kidney disease, and ultimately, less people needing dialysis after an unsuccessful transplant.

The kidney doesn't receive enough blood during transplantation surgery, and without the oxygen and nutrients delivered by that blood, small blood vessel cells inside the kidney die. This releases cell fragments into the bloodstream that contain a helpful “healing” molecule. These fragments are then transported to neighbouring cells to help maintain the health of the blood vessels not yet severely damaged. Laboratory experiments with cells show that these cellular fragments, together with the “healing” molecule inside them, promote resistance to cell death, increase cellular movements that encourage repair, and increase the formation of new blood vessel structures. All of which are key to rebuilding the kidney’s blood vessel network.

The beneficial effect on the growth of new blood vessels was also validated in mice. Blood flow to their hindlimb was blocked and then the cellular fragments or the “healing” molecules were injected into the mice. The research team found that these injections led to a significant increase in the return of the blood flow to the hind limbs. Blood vessels were also counted to examine their regrowth, and it was shown that the mice injected with the cellular fragments had a higher density of blood vessels. All in all, these findings show that these newly characterized cellular fragments have beneficial effects on vascular growth. Of interest, the molecule found in abundance inside them could be used therapeutically to preserve optimal vascular health after injury. How? By preventing the loss of blood vessels, a severe complication of transplantation.