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DIABETIC NEPHROPATHY

Lipid toxicity drives renal disease

> VEGF-B-mediated lipid accumulation in podocytes drives DKD development

Diabetic kidney disease (DKD) is often considered to be a consequence of hyperglycaemia. However, Ulf Eriksson and colleagues now report that lipid accumulation in podocytes drives the development of this disease.

The finding that improved glycaemic control in patients with diabetes mellitus has not resulted in decreased DKD prevalence indicates that other mechanisms must be involved and a role for renal lipotoxicity has been suggested. Eriksson's research group previously showed that vascular endothelial growth factor B (VEGF-B) promotes lipid uptake into muscle, leading to insulin resistance. "In our recent study we wanted to investigate whether we could affect lipid uptake in the kidney by antagonizing VEGF-B signalling and if so, prevent renal disease progression," explains Eriksson.

In mouse models of type 2 diabetes (that is, *db*/*db* mice or wild-type mice fed a high-fat diet), the researchers show that inactivation of VEGF-B signalling by *Vegfb* knockout or by administration of an anti-VEGF-B antibody, led to reduced lipid accumulation in podocytes, fewer signs of DKD-like kidney injury and improved renal function compared with diabetic mice with functional VEGF-B signalling. Pharmacological VEGF-B inhibition in a mouse model of type 1 diabetes had similar outcomes.

"Our most significant finding is that lipid accumulation in podocytes seems to be a driving mechanism underlying the development of DKD," claims Eriksson. "We have not found evidence that hyperglycaemia drives disease progression, which is in sharp contrast to the prevailing paradigms."

Lipid accumulation was mainly observed in podocytes, which were also the source of VEGF-B. In fact, podocyte-specific overexpression of *Vegfb* in mice showed that podocyte-derived VEGF-B is sufficient to impair renal function. When fed a high-fat diet, these mice showed a more considerable increase in renal lipid accumulation and injury as well as compromised kidney function compared with control mice. Thus, the researchers conclude that VEGF-B-mediated lipid accumulation in podocytes drives DKD development.

Molecular analysis indicated that increased VEGF-B signalling likely promotes lipid accumulation in podocytes through upregulation of fatty acid transport proteins. Lipid accumulation, combined with increased insulin resistance, leads to podocyte loss, which contributes to renal impairment. By contrast, VEGF-B inhibition re-sensitizes podocytes to insulin, thereby improving their survival.

Of note, the researchers' gene and protein expression analysis showed that renal VEGF-B signalling was activated in mice and patients with DKD, suggesting that this pathway is an attractive target for treatment. Eriksson comments that CSL Limited (Melbourne, Australia) plan to start a phase 1 clinical trial to test the safety and tolerability of a novel anti-VEGF-B antibody towards the end of 2017. In the meantime, his research group is trying to gain a better understanding of the changes in VEGF-B levels during disease progression and their correlation with established parameters of kidney function in humans.

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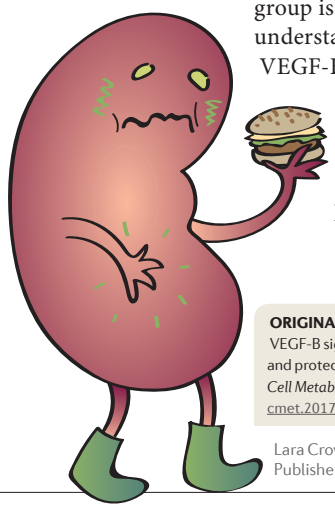

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