The role of ADAMTS5 in extracellular matrix remodelling in diet-induced insulin resistance

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Changes in the extracellular matrix (ECM) have been linked to diet-induced insulin resistance. Recently we have demonstrated that genetic deletion of ADAMTS5, an ECM remodelling enzyme, results in a greater level of diet-induced insulin resistance in male, but not female mice. Our aim was to elucidate whether gender specific changes in ECM components in skeletal muscle and liver explain the difference in diet induced insulin resistance observed between male and female ADAMTS5 deficient mice.

Methods: Male and female ADAMTS5 knock out ($ADAMTS5^{-/-}$; KO) and littermate wild type control ($ADAMTS5^{+/+}$; WT) mice (n=9-10 in each group) were fed a chow (CHOW) or high fat diet (HFD) for 13 weeks. Mice were humanely killed *via* cervical dislocation. Hind limb skeletal muscle and liver were collected and analysed for total collagen using a hydroxyproline assay, and collagen isoform specific gene expression using a reverse transcription polymerase chain reaction. Gene expression levels of versican, an ECM proteoglycan and key ADAMTS5 substrate, was also measured.

Results: In male mice, skeletal muscle total collagen was not different in WT and KO mice, in both CHOW and HFD conditions. However, in male mice isoform specific Col1a, Col3a, and Col4a gene expression was increased (p<0.05, main effect genotype) in KO compared to WT, whilst Col4a gene expression was also further elevated (p<0.05, main effect diet) in HFD compared to CHOW. In contrast, in female mice, skeletal muscle total collagen and Col1a, Col3a and Col4a gene expression was similar between all treatment groups. In skeletal muscle of male mice, versican gene expression was elevated (p<0.05 main effect diet) in HFD compared to CHOW mice, and was further elevated (p<0.05 main effect genotype) in KO compared to WT. In female mice, skeletal muscle versican gene expression was higher (p<0.05 main effect diet) in HFD compared to CHOW mice, but there was no effect of genotype.

In the liver, in male mice total collagen was lower (p<0.05 main effect diet) in HFD compared to CHOW. In contrast, gene expression for all collagen isoforms were higher (p<0.05 main effect diet) in HFD compared to CHOW; and there was no effect of genotype, expect Col4a levels were reduced (p<0.05 main effect genotype) in KO compared to WT. In female mice, total collagen in KO mice was lower (p<0.05) in HFD compared to CHOW; whilst in HFD conditions, Col1a and Col4a gene expression levels were lower (p<0.05) in KO compared to WT. In the liver of male mice, versican gene expression was elevated (p<0.05 main effect genotype) in KO compared to WT. In female mice, liver versican gene expression was higher (p<0.05) in KO compared to WT mice under HFD conditions.

Conclusion: Taken together these findings show that elevated gene expression levels of specific collagen isoforms and versican in skeletal muscle of male KO mice are associated with greater diet-induced insulin resistance when compared to ADAMTS5 deficient female mice. However, ongoing analysis will determine whether these changes observed in gene expression translate to changes in protein expression.