**Genetic mapping of the morphological and proteomic landscapes of adipose tissue reveals novel ECM – adipocyte interactions**.

*Aim:*

The adipose tissue is a highly plastic organ that can expand its energy storage capacity by either increasing adipocyte size (hypertrophy) or adipocyte number (hyperplasia). Adipocyte hypertrophy is a hallmark of adipose tissue dysfunction and drives systemic insulin resistance. We aimed to clarify mechanisms regulating the hypertrophy – hyperplasia axis.

*Method:*

We measured the average adipocyte size of inguinal white adipose tissue (iWAT) histological stains in 412 Diversity Outbred Australia (DOz) mice. DOz mice capture immense genetic and phenotypic diversity that mimic that of the human population making them a powerful tool for genetic mapping. In a subset of 282 mice, we conducted iWAT proteomics.

*Results:*

Genetic mapping yielded 4 adipocyte size quantitative trait loci (QTLs) and over 2700 protein QTLs (pQTLs). Each adipocyte size QTL had one or more overlapping pQTLs indicating a gene – protein – trait link. Further single nucleotide polymorphism (SNP) analysis identified rs46563785, a variant specific to the NZO mouse strain, which associated with smaller adipocytes and increased expression of the iWAT protein arylsulfatase B (ARSB). ARSB removes sulphate from chondroitin sulphate glycosaminoglycans (GAGs) which are bound to extracellular proteoglycans. Proteoglycans maintain structural support and act as an extracellular matrix (ECM) – adipocyte signalling hub where the degree of sulphation affects binding of proteins such as growth factors. To further characterise the relationship between ARSB and adipose tissue GAGs, we performed glycomics in iWAT across several inbred mouse strains and diets. Notably, NZO mice exhibited distinctly lower total chondroitin sulphate GAGs, and decreased sulphation in-line with greater ARSB activity.

*Conclusion:*

Together, these results suggest that ARSB plays a crucial role in ECM proteoglycan remodelling regulating adipocyte size.