The diabetes risk gene TCF7L2 regulates human adipose progenitor cell biology.

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Background and aims: Dysfunctional adipose tissue *e.g.* as seen in obesity or lipodystrophy is associated with insulin resistance (IR) which predisposes to type 2 diabetes (T2D) and cardiovascular disease (CVD). Nonetheless, the risk of T2D and CVD is not uniform in similarly obese subjects. The adipose tissue (AT) response to chronic caloric overload (hypertrophy *vs.* hyperplasia) is a major determinant of susceptibility to IR. TCF7L2 is a key transcription factor involved in WNT signalling, a developmental pathway, which has a central role in AT biology. A common SNP in TCF7L2 (rs7903146) is the strongest genetic determinant of T2D risk in humans with the risk being higher in lean *vs.* obese subjects. We hypothesised that TCF7L2 modulates T2D risk partly *via* effects on AT biology.

Materials and methods: *In vitro* functional studies in primary and immortalised human adipose progenitor cells (APCs) and AT phenotyping in rs7903146 risk variant carriers.

Results: *Ex vivo TCF7L2* expression was higher in APCs compared to mature adipocytes (mADs) ($p<0.001$, n=35-49) and adipose endothelial cells ($p<0.01$, n=5-6) in both abdominal and gluteal depots. *Ex vivo TCF7L2* expression corelated positively with BMI in abdominal ($p=0.001$, $R^2=0.28$, n=35-50) and gluteal ($p=0.04$, $R^2=0.12$, n=35-50) APCs but not in mADs. Stable TCF7L2 knockdown (KD) with two independent shRNAs (low and high efficiency) in immortalised human abdominal APCs led to impaired proliferation ($p<0.01$) and a dose-dependent increase in WNT signalling ($p<0.001$) both basally and following WNT3a treatment. Notably, adipogenesis was enhanced ($p<0.001$) with low efficiency TCF7L2 KD whilst being impaired ($p<0.001$) with high efficiency TCF7L2 KD in both immortalized and primary human abdominal APCs. AT phenotyping showed reduced *ex vivo* TCF7L2 mRNA ($p=0.015$, n=15-29) and protein ($p=0.04$, n=5-10) levels *selectively* in abdominal APCs of T2D risk allele (T) carriers. Accordingly, *in vitro* reporter assays for *cis*-regulatory activity at rs7903146 revealed that the T2D risk allele (T) abrogates a weak enhancer in abdominal APCs (C *vs.* T, $p<0.001$). Lastly, compared with homozygous carriers of the C allele, individuals homozygous for the T2D risk allele (T) displayed altered adipocyte size distribution in abdominal AT ($p<0.001$, n=9-25).

Conclusion: These results implicate TCF7L2 in human adipose progenitor biology, AT plasticity and susceptibility to T2D.

Funding/Support: This work was supported by Oxford-Novo Nordisk Postdoctoral Research Fellowship (MV).

Keywords (Category): 33 Adipose tissue biology and adipocytokines

Disclosure: This work was supported by Oxford-Novo Nordisk Postdoctoral Research Fellowship (MV). The funders had no role in study design, analysis or reporting of the current work.