Co-activator-associated arginine methyltransferase 1 (CARM1) is overexpressed in type 2 diabetes.

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Background

Type 2 diabetes (T2DM) is on the rise worldwide but the causes for this epidemic remain to be ascertained. While several genetic markers were described, their contribution to the total risk of developing T2DM appears minimal. On the other hand, urbanisation has driven dramatic changes in lifestyle and may increase risk factors for T2DM via epigenetic mechanisms.

Objective

Over the years, our research interest has focused on identifying the dimensions involved in lifestyle changes in people with T2DM. As part of an ongoing study, we investigated the differential expression of a panel of histone modulating enzymes in T2DM patients and non-diabetic controls.

Patients and Methods

Patients (n=21) with T2DM, aged 40-70, treated by diet and/or oral glucose-lowering agents and with at least 1-year attendance in the clinic were randomly selected. Exclusion criteria were current insulin treatment, known psychiatric conditions, cancer or other conditions with potential impact on the epigenetic machinery. Clinical, blood chemistry, epigenetic, inflammatory cytokines and endocrine variables were measured in the patients and in 21 non-diabetic controls matched by age and sex. Peripheral blood leukocytes were separated and total RNA and DNA isolated. The isolates were retro-transcribed to evaluate the expression of a panel of 84 histone modifying enzymes by Real-Time PCR. A panel of 22 cytokines and 10 hormones involved in metabolism were measured in serum by specific ELISA or by Bio-Plex Multiplex Immunoassay System.

Chi-square test or Fisher exact test were performed to compare groups of categorical data, and the Mann-Whitney U test to compare continuous data. A discrete Bayesian Network was built to explore the relationships between all variables. Normality of distribution of continuous variables was tested by the Shapiro-Wilk test and, since it was not satisfied, Hartemink's Information-Preserving Discretization was carried out. Power analysis showed that 21+21 samples allowed a statistical power of 81% to detect a 25% difference in CARM1 expression with alpha=5% and a Bonferroni correction for 100 multiple tests.

Results.

BMI, plasma glucose and serum glucagon were higher in the patients. These were all on metformin and 10 on pioglitazone, both insulin-sensitizers, and most were on statins and/or other lipid-lowering drugs, which may account for why the controls had higher total and LDL cholesterol, while serum insulin and HOMA-IR index did not differ between the groups. Of the 84 histone-modifying enzymes checked, only CARM1 showed a 5-fold higher median value in the patients ($p<0.001$), who also had significantly higher levels of GIP, IL-4, IL-7, IL-13, IL-17, FGF basic, G-CSF, IFN γ and TNFα, and decreased levels of IP-10. Bayesian network analysis showed that the dichotomy health/diabetes was independently linked to plasma glucose, CARM1 and leptin. A second independent node proceeded from IL-1b to IL-6, TNFα and IFN- γ. TNFα also clustered with IL-7, IL-4 and IL-17.

Conclusions.

This is the first report on increased expression of CARM1 in patients with T2DM, independent of known hormonal and inflammatory pathways. CARM1 enhances transcriptional activation of nuclear receptors by interacting with coactivators p160 and CBP and methylation of histone H3 at arginine 17. In particular, it is a coactivator of nuclear factor-kB and a possible key regulator of glucose-induced insulin secretion and glucose metabolism in the liver. Further studies will need to elucidate the conditional dependence of CARM1 expression on the presence/absence of T2DM