Results: Genomic DNA methylation analysis identified 813 DMPs, including 279 hypomethylated and 534 hypermethylated. Functional classification of these methylated genes revealed associations with biological processes and pathways related to clinical phenotype, including immune response, adhesion, oxidative stress and vascular signaling. Correlation and association studies showed that the methylation levels of genes related to antigen-presenting cells were associated with the CV-risk score, aGAPPS (CCFR2, TXLN8, GLIPFR), type of thrombosis (SIGLEC11, COLEC16, LRRCA16A, AHSA1, TRIL) and aPL titers (CLEC4G, RGS4, HLA-DPA1, B2F6, RAET1E, HLA-G, HLA-DPA1, HLA-H, TXLN8). Besides, methylation levels of DMPs related to vascular signaling and adhesion processes were associated with the presence of thrombotic recurrences (VEGFA, MAPK14, ITGA8, EPCAM, PCDH26, DLG1) as well as with prevalent CV-risk factors such as hypertension and dyslipidemia (ITGA11, DSCAM, CLEC4F, CD44, LTBP2, PCDHB14). In addition, methylation levels of DMPs related to oxidative stress (GP2, PGD, ADH1) were associated with microvascular endothelial dysfunction. An altered mRNA expression of some of these genes with aberrant methylation and related to increased CV-risk and thrombotic recurrences in APS was also identified. Both, abnormal methylation and transcription levels of several genes were further associated with a pathological increase of the CIMT. Finally, in vitro studies supported the role of aPLs as key players in the altered methylation and transcriptomic profiles of APS patients.

Conclusion: APS patients showed an impaired methylation profile in monocytes of genes associated with clinical features of the disease, including aPL titers, CV risk, thrombotic recurrences, endothelial dysfunction and early atherosclerosis. These results offer a map to the monocytes methylome and shed light on the pathophysiology of APS, paving the way for the development of new, more effective biomarkers and therapeutics.

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Figure 1. Plots are shown for CpGs in CD4+ T cells that were found to be either (A) hyper-variable or (B) hyper-variable in rheumatoid arthritis patients, with equivalent B cell plots again depicting (C) rheumatoid arthritis hypo-variable and (D) hyper-variable positions. $\Delta T_q$ = Bartlett’s $\tau$-value, a false discovery rate adjusted measure of group differences in DNA methylation variance. $T_q = T$-test $p$-value, applied to test for differences between the group means of any positions found to exhibit differential variance between cases and controls in the Bartlett’s test ($q < 0.001$).

Conclusion: We highlight a role for altered variability in DNA methylation during the molecular pathogenesis of RA, and emphasise the importance of its study in relevant cell subsets.

References: