

The Atypical Cadherin FAT1 in Atherosclerosis

Phenotypic modulation of smooth muscle cells (SMCs) promotes atherosclerosis, and the transition from a quiescent to a proliferative state is a key feature of SMC plasticity. How SMCs meet higher demands for energy and biomass imposed by increased proliferation is largely unknown. We showed that FAT1 limits SMC growth, in part by restraining the mitochondrial electron transport chain, and restricts neointima formation upon injury. We hypothesize that 1) FAT1 affects SMC metabolism by restraining metabolic pathways that support cell division, and 2) SMC FAT1 limits atherosclerotic plaque formation. We performed a metabolomics analysis of SMCs lacking FAT1—which proliferate more—and found by clustering and principal component analyses that FAT1-deficient SMCs have a distinct metabolomic profile compared to controls. Pathway analysis identified prominent effects on glutamine metabolism and aerobic glycolysis due to FAT1 loss. Flux analysis showed a higher extracellular acidification rate (ECAR) in FAT1 deficient SMCs, also suggesting increased glycolysis. Moreover, loss of FAT1 increased SMC lactate dehydrogenase activity. Assays of substrate utilization by mitochondrial metabolism showed that SMCs lacking FAT1 are more adept than controls at using glutamine, glutamate and alpha-ketoglutarate, consistent with increased glutaminolysis. In vivo, we found FAT1 expression in human and mouse atheromas. Notably, SMC-selective deletion of FAT1 in ApoE KO mice resulted in increased SMC content, fibrous cap thickness, and plaque size. Altogether, FAT1 limits SMC aerobic glycolysis and glutaminolysis, key metabolic pathways that support cell proliferation, and reduces SMC content and size of atheromas.