Abstract – Daniel Karl Glatzel

„Acetyl-CoA Carboxylase 1 (ACC1) Regulates Endothelial Cell Migration by Shifting the Membrane Lipid Composition"

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The enzyme acetyl-CoA carboxylase (ACC) plays a fundamental role in the fatty acid metabolism. It regulates the first and rate limiting step in the biosynthesis of fatty acids by catalyzing the carboxylation of acetyl-CoA to malonyl-CoA and exists as two different isoforms, ACC1 and ACC2. In the last few years, ACC has been reported as an attractive drug target for treating different diseases, such as insulin resistance, hepatic steatosis, dyslipidemia, obesity, metabolic syndrome and nonalcoholic fatty liver disease. An altered fatty acid metabolism is also associated with cancer cell proliferation. In general, the inhibition of ACC provides two possibilities to regulate the fatty acid metabolism: It blocks the *de novo* lipogenesis in lipogenic tissues and stimulates the mitochondrial fatty acid β-oxidation. Surprisingly, the role of ACC in human vascular endothelial cells has been neglected so far. This work aimed to investigate the role of the ACC/fatty acid metabolism in regulating important endothelial cell functions like proliferation, migration and tube formation.

To investigate the function of ACC, the ACC-inhibitor soraphen A as well as an siRNA-based approach were used. This study revealed that ACC1 is the predominant isoform both in human umbilical vein endothelial cells (HUVECs) and in human dermal microvascular endothelial cells (HMECs). Inhibition of ACC *via* soraphen A resulted in decreased levels of malonyl-CoA and shifted the lipid composition of endothelial cell membranes. Consequently, membrane fluidity, filopodia formation and the migratory capacity were attenuated. Increasing amounts of longer acyl chains within the phospholipid subgroup phosphatidylcholine (PC) were suggested to overcompensate the shift towards shorter acyl chains within phosphatidylglycerol (PG), which resulted in a dominating effect on regulating the membrane fluidity.

Most importantly, this work provided a link between changes in the phospholipid composition and altered endothelial cell migration. The antimigratory effect of soraphen A was linked to a reduced amount of PG and to an increased amount of polyunsaturated fatty acids (PUFAs) within the phospholipid cell membrane. This link was unknown in the literature so far. Interestingly, a reduced filopodia formation was observed upon ACC inhibition *via* soraphen A, which presumably caused the impaired migratory capacity.

This work revealed a relationship between ACC/fatty acid metabolism, membrane lipid composition and endothelial cell migration. The natural compound soraphen A emerged as a valuable chemical tool to analyze the role of ACC/fatty acid metabolism in regulating important endothelial cell functions. Furthermore, regulating endothelial cell migration *via* ACC inhibition promises beneficial therapeutic perspectives for the treatment of cell migration-related disorders, such as ischemia reperfusion injury, diabetic angiopathy, macular degeneration, rheumatoid arthritis, wound healing defects and cancer.