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## **Human adipose stromal cells resist the detrimental effects of hyperglycaemic modified extracellular matrix in contrast to human retinal pericytes**

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Diabetic retinopathy, the leading cause of blindness in the Western world, is characterized by an early loss of pericytes accompanied with thickening of the basement membrane and changes of the extracellular matrix (ECM) of connected endothelial cells. In models of diabetic retinopathy, adipose stromal cells acquired pericyte features and provided retinal microvascular support, suggesting functional replacement of pericytes. In contrast to pericytes, ASC appear to be refractory to hyperglycemic conditions. To address this, we first tested the effects of hyperglycemia on basic ASC features and second assessed whether high-glucose conditioned extracellular matrix affects adhesion and growth of ASC.

First, human ASC were isolated and expanded in normal (NG, 5.6 mmol/l) or high glucose (HG, 28 mmol/l) containing medium. Proliferation, differentiation and immunomodulatory capacities were compared. Second, human ASC and human retinal pericytes (HRP, primary and Bmi-1 immortalized) were seeded on ECM produced by human umbilical vein endothelial cells (HUVEC) under varying glucose conditions: NG, HG, or intermittent phases of hyperglycemia (every 3h during daytime). Adhesion and cell confluency on the ECM were monitored using kinetic live cell imaging. Apoptotic events were assessed using a fluorescent caspase 3 substrate.

ASC functional features were not affected by HG, supporting notions that ASC are refractory to hyperglycemia. Also, in contrast to HRP, they resisted the detrimental effects of constant hyperglycemic modified ECM of endothelial cells (ECM<sub>NG</sub> ASC and HRP =100%, ECM<sub>HG</sub> ASC=in average 110% and ECM<sub>HG</sub> HRP 85%,  $p \leq 0.05$ ). Only intermittent phases of hyperglycemia affected the adhesion and growth of ASC (95% versus ECM<sub>NG</sub> 12-16hours after seeding). The higher sensitivity of HRP to hyperglycemic-modified ECM was apparent by the occurrence of apoptotic events, rarely seen in ASC.

Our data document that ASC, in contrast to HRP, resist the detrimental effects of constant hyperglycemia. Thus they may serve as corrective against hyperglycemia-induced pericyte death or dysfunction reducing microvascular complications. Whether the angiogenic, secretory and immunomodulatory properties of ASC contribute further to prevent/treat diabetic complications is a matter of current studies.