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Title: The correction of monocyte-derived neohepatocytes from alpha1 antitrypsin deficient patients

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Body: This study explores the culture of monocyte-derived neohepatocytes from PiZ alpha1 antitrypsin deficient (α_1ATD) patients and homologous replacement using small DNA fragments (SDFs) to correct the Z defect. Monocytes from 6 patients were de-differentiated with MCSF and IL3 and then differentiated into neohepatocytes with FGF-4. Albumin, urea and α_1AT were measured. SDF enclosing the normal sequence at the PiZ mutation site was generated from genomic DNA of a healthy volunteer. SDFs were transfected into neohepatocytes and cDNA checked for the M or Z message. No albumin was detected from monocytes. Neohepatocytes secreted 250±50 mg/dL albumin/72h. Monocytes secreted both urea (5±2 µg/dL) and α_1AT (272±42 µg/ml) over 72h. Neohepatocytes secreted 103±30 µg/dL urea and 311±34 µg/ml α_1AT. Neohepatocytes produced PCR products from Z primers. M SDF treated neohepatocytes generated bands using M primers, indicating the generation of a corrected transcript. Neohepatocytes transfected with a monocyte transfection kit but no DNA control produced 163 ± 42µg/ml α_1AT in 24h, whereas 20µg M SDF significantly increased secretion (173 ± 41µg/ml/24h, p=0.046, n=3). Using a hepatocyte transfection kit caused further increases in the amount of α_1AT released. Control transfected neohepatocytes produced 322µg/ml/24h α_1AT and 20µg M SDF significantly increased secretion (590 ± 104µg/ml/24h, p=0.026, n=3). Moreover, 50 µgM SDF caused more α_1AT production (886 ± 298µg/ml/24h). Neohepatocytes can be generated from α_1ATD monocytes. The defective gene can be corrected and is associated with an increase in α_1AT secretion. Development of this technique could be beneficial and protect both the liver and lungs.