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Titel des Beitrags:
Decrease of Global Methylation Improves Significantly Hepatic Differentiation of Ad-MSCs: Possible Future Application for Urea Detoxification.

Abstract:
Hepatocyte transplantation is considered to be an alternative to orthotopic liver transplantation. Cells can be used to bridge patients waiting for a donor organ, decrease mortality in acute liver failure, and support metabolic liver diseases. The limited availability of primary human hepatocytes for such applications has led to the generation of alternative hepatocyte-like cells from various adult stem or precursor cells. The aim of this study was to generate hepatocyte-like cells from adipose-derived mesenchymal stem cells (Ad-MSCs) for clinical applications, which are available "off the shelf." Epigenetic changes in hepatocyte-like cells were induced by 5-azacytidine, which, in combination with other supplements, leads to significantly improved metabolic and enzymatic activities compared to nontreated cells. Cells with sufficient hepatic features were generated with a four-step protocol: 5-azacytidine (step 1); epidermal growth factor (step 2); fibroblast growth factor-4, dexamethasone, insulin-transferrin-sodium-selenite, and nicotinamide (step 3); and hepatocyte growth factor, dexamethasone, insulin-transferrin-sodium-selenite, and nicotinamide (step 4). Generated differentiated cells had higher phase I (CYP1A1/2, CYP2E1, CYP2B6,
CYP3A4) and phase II activities compared to the undifferentiated cells. A strong expression of CYP3A7 and a weak expression of 3A4, as well as the important detoxification markers α-fetoprotein and albumin, could also be detected at the mRNA level. Importantly, urea metabolism (basal, NH4-stimulated, NH4- and ornithine-stimulated) was comparable to freshly isolated human hepatocytes, and unlike cryopreserved human hepatocytes, this activity was maintained after 6 months of cryopreservation. These findings suggest that these cells may be suitable for clinical application, especially for treatment of urea cycle disorders.