Role of sortilin-1 in hepatocellular carcinoma proliferation and adipocyte differentiation

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Background

Sortilin-1 is a sorting receptor that acts as an alterative receptor for LDL. Sortilin-1 is normally highly expressed in adipocytes and is abnormally high in hepatocellular carcinoma (HCC). The uptake of LDL impacts the expression of the cholesterol-sensitive sterol regulatory element-binding proteins (SREBPs). SREBPs regulate the cell cycle through miR33, which is contained within an intron of SREBP-2. SREBPs are also part of the transcription factor network behind adipocyte differentiation.

Aims/Hypothesis

We assessed how sortilin-1 knockdown impacted proliferation of hepatocellular carcinoma (HCC) cell lines and adipocyte differentiation.

Methods

LDL was isolated from 6 healthy subjects. To assess sortilin-1's role in HCC, HUH7 cells were treated with LDL and proliferation was measured using flow cytometry. HUH7 cells containing shRNA to sortilin-1 were then treated with lipoprotein depleted serum followed by treatment with LDL. Using microRNA extraction and RT-PCR the miR33 expression of these cells versus controls was assessed. To investigate sortilin-1's role in adipocyte differentiation, 3T3-L1 cell lines were brought through a standardized protocol to induce differentiation into adipocytes. 3T3-L1 cell lines with and without shRNA to sortilin were harvested at various days of differentiation. Expression of sortilin-1 and known markers of adipocyte differentiation was measured in the cell lysates using Western blot analysis. Differentiation and lipid accumulation in shortilin-1 knockdown lines were measured using Oil Red O staining.

Results

LDL was found to have a variable and relatively small affect on HUH7 cell proliferation. Sortilin-1 knockdown also did not alter LDL suppression of miR33 expression in HUH7 cells. Sortilin-1 knockdown did decrease expression of FABP4 and PPARγ in 3T3-L1 cells over the course of differentiation. Sortilin-1 knockdown also decreased lipid accumulation in 3T3-L1 cells.

Conclusion

Based on our results, sortilin-1 does not appear to contribute to dysregulation of the cell cycle in HCC by the suppression of miR33 via increased uptake of LDL. However, our study did indicate that sortilin-1 plays a necessary role in the differentiation of adipocytes.

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