MiR-15/16 play an important role in liver development and hepatocyte differentiation, but the mechanisms by which these miRNAs regulate their targets and downstream genes to influence cell fate are poorly understood. In this study, we showed up-regulation of miR-15/16 during HGF- and FGF4-induced hepatocyte differentiation from amniotic epithelial cells (AECs). To elucidate the role of miR-15/16 and their targets in hepatocyte differentiation, we investigated the roles of miR-15/16 in both the MAPK and Wnt/β-catenin pathways, which were predicted to be involved in miR-15/16 signaling. Our results demonstrated that the transcription of miR-15/16 was enhanced by c-Fos, c-Jun, and CREB, important elements of the MAPK pathway, and miR-15/16 in turn directly targeted adenomatous polyposis coli (APC) protein, a major member of the β-catenin degradation complex. MiR-15/16 destroyed these degradation complexes to activate β-catenin, and the activated β-catenin combined with LEF/TCF7L1 to form a transcriptional complex that enhanced transcription of hepatocyte nuclear factor 4 alpha (HNF4α). HNF4α also bound the promoter region of miR-15/16 and promoted its transcription, thereby forming a regulatory circuit to promote the differentiation of AECs into hepatocytes. Endogenous miRNAs are, therefore, involved in hepatocyte differentiation from AECs and should be considered during the development of an effective hepatocyte transplant therapy for liver damage [1)].

1)

Bai C, Zhang H, Zhang X, Yang W, Li X, Gao Y. MiR-15/16 mediate crosstalk between the MAPK and Wnt/β-catenin pathways during hepatocyte differentiation from amniotic epithelial cells. Biochim Biophys Acta Gene Regul Mech. 2019 Feb 9. pii: S1874-9399(18)30359-6. doi: 10.1016/j.bbagrm.2019.02.003. [Epub ahead of print] PubMed PMID: 30753902.