Abstract

Transdifferentiation induces chromatin reconstructions and epigenetic changes that affect gene expression spectum and cause cell remodeling in general. Direct conversion of mature somatic cell line into another mature cell type occures during the transdifferentiation thereby differences betweeen individual germ layers are eliminated. The aim of the master thesis is transdifferentation of mesenchymal cells - mouse embryonic fibroblast into endodermal cells - hepatocytes *in vitro*, using combination of transcripion factors *Hnf4α* and *Foxa1*. Detection of fibroblasts transformation has been initiated immediately after retroviral transduction and final generation of induced hepatocyte culture was confirmed by morphological and function analysis. The population of mouse induced hepatocytes served as a possible model for human liver disease in case of a pacient whose liver proteins could not be detected immunohistochemically. Genome editing of induced hepatocytes was realized by CRISPR/Cas9 technology which is based on cooperation of guideRNA and Cas9 nuclease followed in addition to generation of DNA-specific double strand breaks. These specific breaks in the *Tight junction protein 2* gene were repaired via homologous recombination that induced a missense mutation with amino acid changes in the target protein. This master thesis is a part of bigger project which has a goal to reduce the amount of biopsies and another painful surgical interventions by utilization of transdifferentiation and also facilitate to develop approprite therapeutic methods via genome editing and modeling of clinical relevant diseases.

Key words: Conversion of somatic cells, Hnf4α, Foxa1, induced hepatocytes, mutation in *Tjp2*, intrahepatic cholestasis, CRISPR/Cas9