論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	Mougina Kamaleldin Hussein Eltahir
論文題名 Title	**Pharmacotherapy alleviates pathological changes in human direct reprogrammed neuronal cell model of myotonic dystrophy type 1** (筋強直性ジストロフィー1型のヒト直接再プログラム化ニューロン細胞モデルの病理学的変化を軽減する薬物療法)

論文内容の要旨

〔目　的(Purpose)〕

Myotonic dystrophy type 1 (DM1) is a trinucleotide repeat disorder affecting multiple organs. However, most of the research is focused on studying and treating its muscular symptoms. On the other hand, despite the significant impact of the neurological symptoms on patients' quality of life, no drug therapy was studied due to insufficient reproducibility in DM1 brain-specific animal models. The aim of this study is to use direct reprogramming approach for the first time to generate DM1 human neurons from patients' fibroblasts to model and effectively treat the phenotypic brain abnormalities and aberrant splicing of gene transcripts reported previously in the literature by drug therapy.

〔方法ならびに成績(Methods/Results)〕

To establish DM1 neuronal model, human skin fibroblasts were directly converted into neurons by using lentivirus expressing small hairpin RNA (shRNA) against poly-pyrimidine tract binding protein (PTBP). We found faster degeneration in DM1 human induced neurons (DM1 hiNeurons) compared to control human induced neurons (ctrl hiNeurons), represented by lower viability from 10 days post viral-infection (DPI) and abnormal axonal growth at 15 DPI. Nuclear RNA foci were present in most of DM1 hiNeurons at 10 DPI. Furthermore, DM1 hiNeurons modelled aberrant splicing of *MBNL*1 and 2, *MAPT*, *CSNK1D* and *MPRIP* at 10 DPI. We tested two drugs that were shown to be effective for DM1 in non-neuronal model and found that treatment of DM1 hiNeurons with 100 nM or 200 nM actinomycin D (ACT) for 24 h resulted in more than 50% reduction in the number of RNA foci per nucleus in a dose dependent manner, with 16.5% reduction in the number of nuclei containing RNA foci at 200 nM and treatment with erythromycin at 35 μM or 65 μM for 48 h rescued mis-splicing of *MBNL*1 exon 5 and *MBNL* 2 exons 5 and 8 up to 17.5%, 10% and 8.5%, respectively. Moreover, erythromycin rescued the aberrant splicing of *MAPT* exon 2, *CSNK1D* exon 9 and *MPRIP* exon 9 to a maximum of 46.4%, 30.7% and 19.9%, respectively.

〔総　括(Conclusion)〕

These results prove that our model is a promising tool for detailed pathogenetic examination and novel drug screening for the nervous system.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

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This research is worth being granted a doctoral degree (Medicine).