Therapeutic Methods, Treatment of Genetic Diseases

AB063. Development of a fusion protein combined alpha-galactosidase A and insulin-like growth factor 2 for treatment of Fabry disease

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Background: Fabry disease (FD) is an X-linked inherited disease with estimated incidence of 1/50,000 but was reported at especially high frequency in Taiwan, approximately 1/1,000. FD is caused by deficiency of an enzyme, alpha-galactosidase A (GLA), involved in catalyzing the breakdown of globotriaosylceramide (Gb3). Reduce or absence of GLA activity results in the accumulation of Gb3 in cells and further induces cell damages and defects in organ functions. The most effective therapy so far is enzyme replacement therapy (ERT). At present, only two protein drugs for FD treatment have been approved, Agalsidase alfa (Replagal®, Shire) and Agalsidase beta (Fabrazyme®, Sanofi), respectively. However, the cost is very expensive. Development of a new treatment strategy to increase efficiency and improve long-term administration is highly demanded.

Methods: We have constructed a fusion protein contained a partial insulin-like growth factor 2 (IGF2) peptide and GLA. This fusion protein is overexpressed in GLA knock-out cell. Enzyme activity, uptake efficiency and the clearance of Gb3 accumulation were examined to investigate its therapeutic effect in treatment to FD. We first generated a GLA-deficient HEK293 cell lines using CRISPR/Cas9 technique. Second, we constructed different forms of fusion proteins and determined the most active form by measuring enzyme activity.

Results: Our results showed that enzyme activity in GLA-deficient cells is significantly increased after GLA-IGF2 treatment. Moreover, the accumulation of intracellular Gb3 in FD fibroblasts was found to be cleared efficiently using immunofluorescent staining. We further found out that GLA-IGF2 fusion protein can be uptake by cells more efficiently compare to recombinant GLA, showing by cellular level of GLA become comparable to normal cell at lower dosage and shorter time treatment.

Conclusions: We were able to demonstrate that GLA-IGF2 fusion protein is a functional and may become a feasible approach for cardiac type FD patients.

Keywords: Fabry disease (FD); alpha-galactosidase A (GLA); enzyme replacement therapy (ERT)

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