S21-1 Development of new enzyme replacement therapy for Fabry disease utilizing molecular designing

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Fabry disease is a genetic disease caused by a deficiency of alpha-galactosidase A (GLA), resulting in renal and cardiovascular involvement. Two different recombinant GLAs have been developed for enzyme replacement therapy (ERT) for this disease. But these drugs are unstable in blood, and they are not well incorporated into target organs, including the kidneys and heart. Furthermore, repeated injection of the drugs frequently results in an allergic reaction and development of antibodies against the recombinant GLAs sometimes decreases the effects of the enzymes. In this study, we paid attention to alpha-N-acetylgalactosaminidase (NAGA), which is similar to GLA in protein structure but the substrate specificity being different. We designed a modified NAGA exhibiting catalytic activity as GLA by making structure-based amino acid substitutions and produced the enzyme in CHO cells. The new enzyme is more stable in blood than the recombinant GLAs and it has many mannose 6-phosphate residues which are essential for the incorporation of the enzymes into cells. The modified NAGA injected into Fabry model mice was successfully incorporated into the organs and improved the Fabry pathological changes. There was no immunological cross-reactivity between the modified NAGA and GLA, and the modified NAGA did not react to serum from a patient with Fabry disease recurrently treated with a recombinant GLA. The new enzyme is highly promising as an effective and safe enzyme for ERT for Fabry disease.