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ORPHAN DRUG DEVELOPMENT FOR DUCHENNE MUSCULAR DYSTROPHY BY PROTEIN CRYSTALLIZATION IN SPACE

Abstract

Duchenne muscular dystrophy (DMD) is one of the most common types of muscular dystrophy, affecting about 1 out of 3,500 boys. DMD is a severe X-linked muscle disease characterized by progressive skeletal muscle atrophy and caused by mutations in the gene of dystrophin, a cytoskeletal protein. There is still no cure for this disastrous disease. We found that grouped necrotic muscle fibers in patients with DMD expressed hematopoietic prostaglandin (PG) D2 synthase (H-PGDS), which catalyzes the biosynthesis of PGD2, an allergic and inflammatory lipid mediator. We obtained very high quality crystals of human recombinant H-PGDS in complexes with a variety of inhibitors, whose half maximal inhibitory concentrations (IC50s) were in the sub micro-molar range, by the counter-diffusion method onboard the ISS. We determined the detailed three-dimensional structures of H-PGDS/inhibitor complexes by X-ray diffraction analysis of the microgravity-grown crystals using an intense X-ray at SPring-8 synchrotron facility. Based on the fine structure of the inhibitor within the catalytic pocket of human H-PGDS, novel potent inhibitors TFC-007 and TAS-205 were developed, whose IC50 value was 20 nM. Both compounds prevented the expansion of muscular necrosis and muscle atrophy without any side effects by chronic treatment of genetically dystrophin-deficient mdx mice. Clinical trials of TAS-205 for treating DMD patients have begun sponsored by Taiho Pharmaceutical Co. Ltd. at National Center of Neurology and Psychiatry in Japan from Sept in 2014. Phase 1 study of single and multiple doses of TAS-205 in 21 patients was successfully finished to confirm the safety of this drug (see the entry in clinicaltrials.gov, NCT02246478). This is a real milestone to establish drug therapy for DMD patients. We believe that TAS-205 is able to slow down the progression of DMD boys remarkably. The fine structure of the drug-binding pocket of human H-PGDS is very useful to theoretically and inexpensively develop follow-up compounds, whose chemical structures and metabolism are different from TAS-205. Those drugs are also useful for the treatment of other PGD2-related inflammatory diseases in muscular or nervous tissues. In 2014, we started a new project entitled “Research Base Formation of Space Science of High Quality Protein Crystallization Technology” funded by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.