Towards Developing Patient-Specific Induced Pluripotent Stem Cell Based Assays for Disease Modeling and Drug Screening

Kuwait-MIT Center for Natural Resources and the Environment

Project Outcomes Report
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The aims of this research project was to identify patients in Kuwait with rare autosomal recessive forms of muscular dystrophy (MD) such as α-dystroglycanopathies and limb-girdle muscular dystrophies (LGMDs), that are expected to be overrepresented in the Middle East and to collect tissue samples from these patients (aim 1). The samples would then be transferred to MIT to generate patient-specific induced pluripotent stem cell (iPSCs) lines (aim 2) that have the ability to self-renew and differentiate into any specialized type of cell, thus supplying scientists with large quantities of hard-to-access disease-relevant cell types, complete with the individual's genetic makeup with the intent of eventually utilizing these iPSC lines to develop patient-specific cell-based disease models to screen for therapeutic drugs (future aim 3).

Upon the initiation of this project, little data was available on the incidence and prevalence of autosomal recessive MDs in the region. One of the major outcomes of this study was that results of the genetic testing we performed on suspected MD patients shed some light on the incidence of these disorders in Kuwait. Of the suspected MD patients that were recruited for this study, 7 patients were genetically diagnosed with different autosomal recessive forms of limb-girdle muscular dystrophy (LGMD: 4 LGMD2A, 1 LGMD2B, & 2 LGMD2I) a genetically and clinically heterogeneous group of rare MDs that predominantly affect the hip and shoulder muscles. Two of these 7 patients were diagnosed with LGMD2I (a mild form of α-dystroglycanopathy) and 2 additional patients possessed very rare unreported genetic variants in known LGMD genes (suspected LGMD2D and LGMD2I).

All LGMD patients were requested to donate their skin samples to generate iPSCs and 3 patients gave consent: one LGMD2I subject, one LGMD2A, and one suspected LGMD2D subject possessing an unreported genetic variants in the α-sarcoglycan gene (SGCA). iPSC lines were successfully generated from the primary fibroblasts of these 3 subjects by repeated transfection with mRNA encoding the four reprogramming factors OCT4, SOX2, cMYC and KLF4 and pluripotency was characterized by the expression of pluripotency markers at the protein level (Oct-4 and Tra1-60). The generation of these dystroglycanopathy and LGMD iPSC lines provides a platform to develop patient-specific cell-based disease models to probe the cellular and molecular processes underlying the disease, validate new targets, and screen for therapeutic drugs in the future (future aim 3).