Human pluripotent stem cells: from disease modeling to for drug discovery

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The lack of existing models of pathologic tissues has rendered many important questions in disease pathogenesis inaccessible. Human embryonic stem cells derived from affected embryos during a pre-implantation diagnostic (PGD), as well as the technical development to obtain human induced pluripotent stem cells generated from patients, offer the unique opportunity to have access to a large spectrum of disease-specific cell models. Disease-specific pluripotent stem cells capable of differentiation into the various tissues affected in each condition could undoubtedly provide new insights into the pathological mechanisms by permitting analysis in a human system. These new disease-specific cell models are applicable for a wide systemic mechanistic analysis ranging from functional studies at the cellular level to a large-scale functional genomics screening.

As a proof of principle, we demonstrated that PGD-derived hES cells and derivatives which, express the causal mutation implicated in the Myotonic Dystrophy type 1 (DM1), may mimic molecular defects associated to the pathology, such as the nuclear aggregation of mutant RNA. By taking advantage of this pertinent cellular model, we identified, through a genome-wide analysis, two early developmental defects in genes involved both in myogenesis as well as in neurite formation and establishment of neuromuscular connections. These neuropathological mechanisms may bear clinical significance as related to the functional alteration of neuromuscular connections associated with DM1.

In parallel to these functional pathological studies, we developed two different approaches to identify new therapeutic strategies. The first one was based on a high content screening approach. A pilot drug screening experiment has been successfully conducted in order to identify new molecules which, due to their ability to disrupt the nuclear mutant RNA aggregation, might represent new therapeutic strategies. The second strategy used a genomics screening based on gene knockdown approach. This analysis allowed the identification of a potentially druggable target protein, inhibition of which tends to normalize molecular defects associated to DM1 leading to the development of a clinical trial.