2D and 3D human iPSC-based models to reveal new therapeutic targets for Duchenne muscular dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) is caused by mutations in the X-linked Dystrophin gene that cause progressive muscle disorder where respiratory and cardiac failures are the major causes of premature death. Many efforts have focused on providing cutting-edge stem cell-based models and therapies, hoping to ultimately cure this devastating disease. The contribution of stem cells combined to microfluidic technology, "organ-in-a-dish" and 3D bioprinting to DMD medical research is enormous, however, several hurdles still have to be overcome, including functional muscle maturation of stem cell progenitors, stringent manufacturing guidelines, immune rejection, and tumorigenicity (1). In addition, single cell analysis and genetic correction of Dystrophin deficiency through CRISPR/Cas9 editing are crucial tools to better interpret the models and for deciphering pathological mechanisms and drug discovery. Chemically defined induced pluripotent stem cell-derived mesodermal progenitors (cdMiPs) are able to contribute to myotube formation and differentiate into cardiomyocytes, both in vitro and in vivo (2). Moreover, the addition of valproic acid increases the potential of the cdMiPs to contribute to myotube formation without compromising their ability to differentiate towards cardiomyocytes (CMs). Nevertheless, CMs differentiated from DMD iPSCs showed significantly elevated intracellular reactive oxygen species (ROS) concentrations and high NADPH oxidase 4 (NOX4) protein levels that contribute to premature cell death. Thus, targeting ROS production and prevent the detrimental effects of NOX4 on dystrophic CMs need to be further explored as new therapeutic solutions for the treatment of DMD cardiomyopathy.

Bibliography

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