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MODELLING SATELLITE CELL DYSFUNCTION TO UNDERSTAND PATHOGENESIS OF NEUROMUSCULAR DISORDERS

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Muscle maintenance and regeneration depend on satellite cells, the resident stem cells of skeletal muscle. Impaired satellite cell function is increasingly recognized as a key contributor to many neuromuscular disorders. Through a multimodal discovery approach integrating transcriptomic profiling of satellite cell activation, regulation by the master transcription factor PAX7, and comparative analysis of neuromuscular disease models, we have defined Satellite cell-opathies: a class of disorders in which satellite cell dysfunction drives pathogenesis (1,2). To extend this concept to human disease, we generated transcriptomic datasets from human muscle cells expressing PAX7, revealing novel PAX7-regulated genes potentially underlying additional satellite cell-opathies. I will discuss our recent modelling of an ultra-rare PAX7-related myopathy. We identified two missense variants in PAX7 in a patient presenting with an FSHD-like phenotype (3). Functional studies in patient-derived myoblasts and engineered cell models demonstrated that these variants disrupt PAX7-dependent transcriptional programs, alter splicing factor expression, increase mitochondrial oxidative stress, and reduce cell proliferation, highlighting defective satellite cell function as the pathogenic mechanism (4). Together, this work expands the clinical and molecular spectrum of Satellite Cell-opathies and underscores the importance of muscle stem cell biology in understanding and treating inherited myopathies. These findings also provide a framework for assessing genotype–phenotype relationships in rare neuromuscular disorders and identifying novel therapeutic targets for regenerative interventions.

Keywords: *Myopathy, stem cell, satellite cell, neuromuscular disorders.*