Doctoral research proposal

Title of the project: *3D co-culture model for idiopathic inflammatory myopathies*

Description of the research project

Inclusion body myositis (IBM) is a neuromuscular disease that occurs predominantly in men over the age of 50 and is categorised as an idiopathic inflammatory myopathy (synonym: myositis)[1]. In muscle biopsies from these patients, evidence of inflammatory and degenerative processes as well as mitochondrial damage can be found[2,3]. The pathogenesis of IBM is currently still the subject of scientific research. Unlike other forms of myositis, IBM does not respond sufficiently to treatment with immunomodulatory therapies, meaning that there is currently no effective therapy available for patients[4]. The basis for the development of such therapy options is a better understanding of the pathogenesis of the disease.

The Neuromuscular Diseases research group in Göttingen is investigating these relationships in the cell culture model of myositis. Pro-inflammatory cytokines are used to induce an inflammatory environment in human muscle cells in order to examine the influence on cellular structures and molecular biological signaling pathways[5,6]. Up to now, these investigations have generally been carried out in 2D cell culture models, which, however, causes limitations in the investigation of functional aspects of skeletal muscle, such as contraction force. Furthermore, we are also at the beginning of establishing co-culture systems for this disease and already have experience with the cultivation of T-cells in our 2D system.

The **main aim** of our study is to investigate the growth behaviour of human muscle cell cultures in a 3D model in combination with T-cells in a newly developed (and rewarded: Innovation price of lower Saxony) cell culture chamber system in collaboration with the Faculty of Physics at the University of Göttingen.
Muscle cell cultures of other cell lines have already been successfully cultivated in 3D in the corresponding chambers and analysed in terms of cell migration and growth behaviour using high-resolution life cell imaging methods, as well as investigating their contractility [7].

The aim of this project is to translate this experience into the well-established cell culture model of myositis and to investigate the influence of pro-inflammatory cytokines on the growth and migration behaviour of muscle cells. Experiments are planned to investigate the contractility of the muscle cell construct, analyses of the ultrastructure and molecular biological investigations after completion of the live cell experiments to further characterise the influence of the proinflammatory cytokine environment on the muscle cells.

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Project-relevant publications from the lab

- **Zschüntzsch J**, Meyer S, Shahriyari M, Kummer K, Schmidt M, Kummer S, Tiburcy M. The Evolution of Complex Muscle Cell In Vitro Models to Study Pathomechanisms and Drug Development of Neuromuscular Disease. Cells. 2022 Apr 5;11(7):1233. doi: 10.3390/cells11071233.
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- De Paepe B, **Zschüntzsch J**. Scanning for Therapeutic Targets within the Cytokine Network of Idiopathic Inflammatory Myopathies. Int J Mol Sci. 2015 Aug 11;16(8):18683-713. doi: 10.3390/ijms160818683.
- Muth IE, **Zschüntzsch J**, Kleinschnitz K, Wrede A, Gerhardt E, Balcarek P, Schreiber-Katz O, Zierz S, Dalakas MC, Voll RE, Schmidt J. HMGB1 and RAGE in skeletal muscle inflammation: Implications for protein accumulation in inclusion body myositis. Exp Neurol. 2015 Sep;271:189-97. doi: 10.1016/j.expneurol.2015.05.023.
- **Zschüntzsch J**, Voss J, Creus K, Sehmisch S, Raju R, Dalakas MC, Schmidt J. Provision of an explanation for the inefficacy of immunotherapy in sporadic inclusion body myositis: quantitative assessment of inflammation and β-amyloid in the muscle. Arthritis Rheum. 2012 Dec;64(12):4094-103. doi: 10.1002/art.37692.

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Disease. Cells. 2022 Apr 5;11(7):1233. doi: 10.3390/cells11071233.
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