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Idiopathic Inflammatory Myopathies - Lessons Learned from Animal Models

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Idiopathic Inflammatory Myopathies (IIM) encompass a rare group of (auto)immune mediated muscle diseases characterized by muscle weakness and mononuclear muscle cell infiltrates. Since its first description, research has focused on describing effector and target cell interaction [1-4]. The immunobiological capacity of muscle cells has become increasingly clear over the last few decades. Skeletal Muscle Cells (SkMCs) are perfectly suited to function as non-professional Antigen-presenting Cells (APCs) by expressing MHC I/II and costimulatory molecules as well as secreting soluble molecules like cytokines and chemokines [5]. However, there is an ongoing debate about the role of SkMCs in the pathophysiology of IIMs.

Research in the field of immunology has gained fundamental insights into pathophysiological processes on the basis of experimental animal models. In the context of neuroimmunological diseases like Multiple Sclerosis (MS), immunological animal models have helped to pave the way for novel therapeutic approaches [6]. In IIMs, there is still a lack in an animal model mimicking phenotypical, histopathological and immunological features of IIMs. Although genetically, infectious or immunologically induced models have been already proposed, all of these were only partially able to represent certain aspects of IIMs [7].

Genetically induced models have highlighted the role of non-immune mechanisms in the pathophysiology of IIMs. Especially for Spontaneous Inclusion Body Myositis (sIBM), conditional Knock-out Models (KO models) with in-tracellular deposits like Amyloid Precursor Protein (APP) or phosphorylated tau were able to resemble phenotypical features of myopathies [8-12]. Similar results were obtained from a Major Histocompatibility Complex (MHC)-I KO-model accompanied by increased levels of endoplasmic reticulum stress markers [13-14]. Up to now, most of the genetically induced models lack of histopathological signs of mononuclear cell infiltrates, which is an important finding in IIMs [7]. Infectious mediated murine models resemble an acute monophasic systemic syndrome consist-ing of myositis, tendinosis and myocarditis with a critically severe disease course and a high mortality rate [7]. In contrast, immunologically mediated models induced by immunization with muscle homogenates or a muscle spe-cific protein showed histopathological aspects of IIMs like infiltrating CD8+ T cells and muscle fiber surrounding cytokines or chemokines creating an immunological microenvironment. However, up to now clinical signs of myo-pathy were absent in those models [7].

Since our group has gained experience in Experimental Autoimmune Encephalomyelitis (EAE), the established animal model for MS, we put effort in establishing an immunological model fulfilling all the aforementioned fea-tures of IIMs [6-7]. On the example of Sugihara and colleagues and their C-protein Induced Model (CIM) [15], we are immunizing mice with fragments of the C-protein in order to resemble phenotypical and histopathological signs of IIMs [7]. This will be a critical step in order to test potential molecules in the context of this model.

During the last decade, our group has focused on two-pore domain potassium channels (K2P-channels), a certain family of potassium channels formerly termed as "leak channels", in the context of neuroimmunological disease like MS. We were able to show a modulating effect of certain K2P-channels in the disease course of EAE by influ-encing effector functions of CD4+ and CD8+ T cells or target cells like endothelial cells [16-18]. Recently, we were able to show that different K2P-channels are functionally expressed in SkMCs with an impact on muscle cell differ-entiation and electrophysiological parameters like potassium current, resting membrane potential and consequently calcium influx [19]. In the context of IIMs, we are interested in the influence of K2P-channels on the aforemen-tioned immunobiological functions of SkMCs with a tendency of anti-inflammatory properties (data not pub-lished). Established immunological models are critically necessary to prove this hypothesis with the aid of K2P-KO mice.

However, there is still a long way to go until these goals can be achieved. Gladly, research on IIMs has become more popular

over the last few decades [7]. Feature investigations should take putative approaches like humanized animal models [20-21] or the concept of exercise/injury induced muscle immunology [22-24] into account in order to pave the way to enlighten the pathophysiology of IIMs and enable putative pharmacological treatments.

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