Editorial on EMC 2017 special issue

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Characterization of the basic mechanisms of sarcomere function is one of the major aims of the European Society for Muscle Research (ESMR). Since the first description of the sliding filament theory our knowledge on myofilament function has been strikingly expanded. Over the past decades the ESMR has also broadened its focus towards translational aspects of muscle research and the development of novel treatment options of striated muscle diseases. However, despite the rapid progress towards these aims it is important to not forget that important key mechanisms of myofilament function and homeostasis are yet unresolved. In this years Annual Meeting of our society, the 46th European Muscle Conference (EMC), Wolfgang Linke has put together an inspiring program with a strong focus on basic myofilament structure and function, and a particular spotlight on the giant sarcomere protein titin. The EMC highlighted the recent advances on single sarcomere mechanics and intersarcomere dynamics, and provided a perfect platform to discuss novel findings regarding the contribution of the thin and thick filaments, as well as of titin and associated proteins to contractile function and force development. Our classic view considered titin being (only) a structural filament protein that acts as a blueprint for sarcomere assembly, centers myosin in the sarcomere, and may serve as a signaling node and important determinant of myofilament passive tension. However, we may have to rethink the view on titin as a passive contributor to myofilament function, as emerging evidence suggests an additional role of titin in contributing to active force development (Rivas-Pardo et al. 2016).

In this EMC-dedicated special issue of the Journal of Muscle Research and Cell Motility Tesi and Stehle address another still not entirely understood topic (Stehle and Tesi 2017, in this issue), by composing a thorough review on the current theories on the cross bridge cycle. In particular, the authors demonstrate that the precise mechanisms underlying

the coupling of phosphate release and the rate-limiting transition for de novo force generation and the uncoupling of the force-generating step and phosphate release for force re-generation still need to be resolved.

Importantly, the article highlights that working towards a unifying concept combining turnover and recovery kinetics and fully understanding the cross-bridge cycle is not purely of academic interest but may be essential for developing drugs targeting the kinetics of skeletal and cardiac muscle contraction (Stehle and Tesi 2017, in this issue).

Another traditionally well-represented topic at the EMC is the development and functional consequence of cardiomyopathy. Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease and characterized by left-ventricular and septum hypertrophy, myocyte disarray and fibrosis. In the past decades, extensive efforts have been made to identify and understand the genetic causes of HCM and the mechanisms involved in disease development and progression. It is commonly recognized that mutations in MyBPC3 encoding for myosin binding protein C, and in the MYH7 gene encoding for β -myosin heavy chain account for 50% of all diagnosed HCM cases (Burke et al. 2016). Other sarcomeric HCM mutations mainly affect thin filament proteins such as troponin I and T, tropomyosin and actin. However, progression and severity of HCM varies, even among patients carrying the same mutation. One explanation for the different disease penetrance and outcome is the relative amount of mutant mRNA and protein expression. In this issue Montag et al. compared the expression of the MYH7 alleles in non-HCM donors and in HCM-patients with different heterozygous MYH7-missense mutations and determined allelic imbalances at the mRNA and protein level (Montag et al. 2017, in this issue). The authors provide evidence that allelic expression of MYH7 and its pathological variants is intrinsically regulated by transcriptional and post-transcriptional mechanisms. While such allelic imbalance would not affect non-HCM individuals with both alleles intact, it could well be a major determinant of disease severity in HCM patients and may thus provide a plausible

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explanation for the different outcome of patients sharing identical heterozygous HCM-mutations.

Approximately 3% of all cardiomyopathies are caused by variations in cardiac genes involved in cardiomyocyte signaling and Ca^{2+} -handling. In this issue Ehsan et al. (2017) review the current knowledge on pathogenic variants in Titin, FHL1, MLP/Crsp3, Filamin C and Phospholamban, and discuss how signalling pathways involved in the detection and adaptation to increased load can be disturbed by such pathogenic variants and may contribute to long-term cardiomyopathic effects. In light of the recent advances in CRISPR/Cas9 genome-editing technologies, future studies will likely identify a large number of novel pathogenic variants in cardiomyocyte genes, and it will be a major challenge to confidently assign a causal role of these variants in disease development and progression.

The use of induced pluripotent stem cell (iPSC)-derived cardiomyocytes provides a promising tool to test the functional relevance of such disease gene candidates and to explore the patho-mechanisms of cardiomyopathies. Along this line, the possibility to generate patient-specific iPSCs, e.g. from patients carrying rare HCM-related mutations has great scientific potential as it allows detailed molecular analyses and maybe even personalized drug screening. Recent advances in this rapidly developing research field have been presented and discussed at this year's EMC (see EMC meeting abstracts).

Our current view on HCM development is based on observations showing that HCM-related mutations often lead to myocyte hypercontractility associated with excessive energy use and general changes in myocardial energetics (Watkins et al. 2011). Hypercontractility and increased ventricular load in the setting of acute or chronic cardiac dysfunction pose a major functional challenge to the myocytes and therefore requires high myofilament turnover and effective repair. The mechanisms involved in the concerted regulation of these adaptive processes are not entirely resolved. Analyses of muscle metabolism and energetics, especially in the HCM setting, have therefore gained further attention in this year's EMC, which is also reflected by an increasing number of scientific contributions in this field.

A major challenge of muscle homeostasis is the physiological demand for a precise and simultaneous regulation of sarcomeric protection, regulated protein turnover and maintenance of basic muscle function. The delicate and sometimes contradicting nature of these processes has recently been demonstrated in myofibers from skeletal myopathy patients. Recently, Unger et al. demonstrated that chaperone-binding to the titin springs prevents sarcomeric protein aggregation and thereby protects the structural integrity of the myofibers, but at the same time, by increasing titin-based passive tension, the chaperone association is detrimental for sarcomere function (Unger et al. 2017). This study again

underlines the need for more work to increase our understanding of the processes involved in sarcomere assembly and disassembly, myofilament metabolism and muscle repair in the context of striated muscle disease.

A less commonly focused muscle-related disorder is clinically described as muscle contractures that derive from injury to the central nervous system. Cerebral palsy (CP) describes a subset of this disease with early childhood onset. Unlike spastic muscles, CP-related muscle contractures are characterized not by enhanced active contraction, but a gradual increase in passive muscle stiffness. This eventually results in complete fixation of the joints and significantly affects patients' quality of life. In this issue, Pingel and Suhr discuss the current literature on mechanosensitive muscle regulators involved in development of CP-related muscle contractures (Pingel and Suhr 2017, in this issue). The review discusses previous work on altered Ca^{2+} -handling and cellular metabolism as causes for muscle contractures, but also highlights recent observations strengthening the hypothesis that mechanically sensitive substructures of skeletal muscle fibers, specifically the extracellular matrix and Costameres, are involved in CP-related contractures and their phenotype progression.

One main focus at every EMC is the presentation and discussion of novel methodological approaches that may eventually lead to the development of therapeutic tools but also help basic research. In this year's meeting this aim was very well presented by contributions on stem cell-derived myocytes, muscle tissue engineering and experimental genome editing.

Optogenetic technologies present another upcoming tool that has profoundly impacted neuroscientific research over the last decade and is currently entering the cardiovascular field. Optogenetic stimulation of cells is based on genetically encoded light-controllable proteins that can be used for fast modulation membrane potential, intracellular signaling cascades or translocation of proteins by illumination with local precision and high temporal resolution. Optogenetic approaches are now about to enter the field of skeletal muscle research, which is reflected by a growing number of publications. In this issue, van Bremen et al. summarize the current knowledge about the use of this technology for directly, non-neuronal control of skeletal muscle function (van Bremen et al. 2017, in this issue). The high temporal flexibility of using light pulses to precisely modulate the membrane potential of muscle fibers within the intact muscle allows new stimulation patterns to investigate skeletal muscle physiology. The authors highlight the advantage of the high spatial precision of focused illumination for selective stimulation of distinct nearby antagonist muscle groups, and discuss the hypothesis that cell-type specific expression of light-sensitive effector proteins in muscle fibers will allow pain-free stimulation. Finally, the review discusses

the potential of optogenetics to be applied in the clinics, e.g. as laryngeal pacemaker in patients with bilateral recurrent nerve paralysis.

Taken together, the articles of this special issue reflect the main messages of this year's EMC, in that the European Society of Muscle Research should continue the successful analyses of basic mechanisms in myofilament and myocytes function, and should also feel encouraged to adopt novel methods and follow promising paths in order to translate basic research finding to the clinics.

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