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EDITORIAL

Introducing a special edition of the Journal of Muscle Research and Cell Motility on tropomyosin: form and function

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The Journal of Muscle Research and Cell Motility aims to serve its readers both by publishing original research on muscle and motility and by informing readers of the state of the art in muscle and cell motility research and to promote discussions.

With this aim in mind, we present the second of our occasional series of topical special issues that combine original research with review articles related to an individual protein important for muscle and motility. The first special edition was devoted to Myosin Binding Protein-C (May 2012), and this edition is devoted to tropomyosin.

In the last year, we have also published special issues on Lifestyle and Ageing in Muscle Disease (August 2012) and A Tribute to the Life and Science of Michael and Kate Bárány (December 2012). Further topical issues are planned, and we would welcome ideas for themes to be covered in the future.

Tropomyosin was first isolated from striated muscles by Bailey (1948). For many years, it was regarded as an archetypal coiled-coil protein with no known function, mainly of interest to X-ray "diffractionists", and it was several decades before its location in the muscle sarcomere and its function were discovered. The key findings were the determination that tropomyosin was a component of the muscle thin filament, based on the electron microscopy and X-ray studies of Huxley, Hanson and Lowy (Hanson and Lowy 1963; Moore et al. 1970), and the discovery that tropomyosin was a component of the Ca^{2+} dependent regulatory complex of striated muscle (Ebashi 1963).

By 1972, when the celebrated Cold Spring Harbour Symposium on muscle was published, tropomyosin had come of age. Tropomyosin, in concert with troponin, was shown to regulate the activity of the thin filament in response to Ca^{2+} (Ebashi and Endo 1968), to confer cooperativity to thin filament regulation (Bremel et al. 1972; Bremel and Weber 1972). It was discovered that tropomyosin formed a continuous strand that was wound round the actin helix and changed its position in response to Ca^{2+} or myosin head binding, and as a result, the steric blocking hypothesis of regulation was born (Huxley 1972; Moore et al. 1970; Parry and Squire 1973). Skeletal tropomyosin was sequenced (Hodges et al. 1972; Sodek et al. 1972) and the sites of interaction with actin were mapped out (McLachlan et al. 1975).

The molecular biology revolution of the 1980s revealed that although tropomyosin is one of the most highly conserved proteins and is present in all eukaryocytes, it is extremely diverse: in vertebrates there are 4 tropomyosin genes (TPM 1–4) and each gene can generate many tissue-specific isoforms by alternative splicing of exons (Vrhovski et al. 2008). Indeed, tropomyosin has been a favoured model for studying the mechanisms of exon splicing (Gooding et al. 1994; Gooding and Smith 2008). The study of the function of tropomyosin outside of the muscle sarcomere has also become important (Lin et al. 1985) especially in the context of altered actomyosin cell motility in cancer cells (Choi et al. 2012; Franzén et al. 1996; Helfman et al. 2008; Stehn et al. 2013), and extrapolation of these results suggests that the development of compounds directed against specific classes of malfunctional tropomyosins could also be possible in striated muscle.

An admirable review of tropomyosin by Sam Perry was published in the Journal of Muscle Research in 2001 (Perry 2001), and the articles in this issue bring tropomyosin studies fully up to date. The structure of tropomyosin and

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its formation into dimers is described by Janco et al. (2013) and the structure of tropomyosin incorporated into the thin filament is described by Lehman et al. (2013). The article by Colpan et al. (2013) describes the end-capping of thin filaments by tropomodulin. Reconciliation of functional studies on tropomyosin's role in muscle regulation with the structural models, as represented by the steric blocking hypothesis has been controversial since the seminal study of Chalovich et al. (1981): a forthcoming article by El-Mezgueldi will describe the dynamics of tropomyosin and how they contribute to its role in thin filament regulation.

Tropomyosin has been considered to be a phosphorylated protein for many years, but until recently, these studies have not attracted much interest: the history of tropomyosin phosphorylation in striated muscles is described by Heeley (2013) and the possibilities of phosphorylation playing a modulatory role in cardiac muscle is described by Schulz and Wieczorek (2013). Three papers tackle the question of what is the level of tropomyosin phosphorylation and the isoforms expressed in human heart and in eye muscles (Marston et al. 2013; Peng et al. 2013; Bicer and Reiser 2013).

In recent years, mutations in skeletal muscle tropomyosin have been identified as causative of some forms of congenital skeletal myopathy, and mutations in alpha tropomyosin have been found as a rare cause of both hypertrophic cardiomyopathy and dilated cardiomyopathy. The articles by Memo and Marston (2013) and by Ochala and Iwamoto (2013) consider the molecular mechanisms by which skeletal muscle mutations cause myopathy. Redwood and Robinson review current understanding of tropomyosin mutations causing cardiomyopathies, and Kawai et al. (Bai et al. 2013) present functional studies on the effect of tropomyosin mutations in reconstituted cardiac muscle fibres.

Finally, the roles of tropomyosin outside the sarcomere are discussed. Vindin and Gunning (2013) make the case for cytoskeletal tropomyosins as choreographers of actin filament functional diversity, whilst Chase et al. (2013) describe the possible roles of tropomyosin in the nucleus.

In summary, the tropomyosin molecule, as a predominantly coiled-coil parallel dimer with 284 amino acids (245 in non-muscle systems), is deceptively simple. It interacts only with itself, by end-to-end linkages, and with actin, troponin T and tropomodulin- yet, its cooperative and allosteric interactions are vital in muscle regulation and have now been found to play a role in many other cellular processes. There is much that can be learned from studying tropomyosin. Its multiplicity of isoforms exquisitely tune the structure and function to the requirements of different tissues in ways that are not yet understood. On the other hand, advances in structural, functional and genetic studies are approaching the point where a complete description of the role of tropomyosin in the muscle thin filament may be achieved and point to the possibility of sarcomeric proteins as viable drug targets.

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