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Ciclo XXXV Tutor Marco Linari / Marco Caremani

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Title of the research: The molecular mechanism of regulation in striated muscle

Regulation of contraction in striated muscle is due to mechanisms on both thin and thick filaments. Ca^{2+} binding to troponin C in the thin filament leads to a structural change in tropomyosin (Tm) that makes the actin sites available for the interaction with the myosin motors; mechano-sensing in thick filament switches ON motors from the energy saving OFF state in relation to the load. Biochemical and structural evidence suggest that the actin sites availability is modulated by motor attachment to actin, which could also be responsible for the spread of activation along the thin filament, under a cooperative mechanism (still poorly defined) that determines the steepness of the sigmoidal force-pCa relation (estimated by the Hill coefficient n_H). My research project is aimed at clarifying the mechanisms responsible for cooperativity in thin filament activation using fast sarcomere-level mechanics in demembranated fibres from soleus muscle of rabbit. During the first year the force-pCa relation and the half sarcomere stiffness were determined with protocols in which the force generated by the myosin motor was modulated by either temperature or addition of 1 μM of the β /slow myosin activator omecamtiv mecarbil (OM). In the second year the experiments were extended to 0.1-10 μM OM and to the definition of the temperature dependence of OM action (range 12-35°C). It was found that (i) 1 μM OM reduces the average force per myosin motor from 1.82 ± 0.08 pN (control) to 0.93 ± 0.07 pN (OM) at 12°C and from 2.73 ± 0.07 pN to 1.95 ± 0.13 pN at 35°C; ii) the OM concentration for half-maximum effect at saturating pCa increases with temperature from 0.5 (12°C) to 1.3 μM (35°C); iii) n_H , increases with temperature from 2.00 ± 0.08 (12°C) to 3.02 ± 0.22 (35°C) in control, while in the presence of OM (1 μM) it remains constant (0.88 ± 0.11). These results indicate that the cooperativity in thin filament activation depends on the stress induced along the thin filament by the attached myosin motor.

• Abstracts e partecipazione a congressi e corsi: autori, titolo della presentazione, nome e date del congresso:

- Reconditi M, Caremani M. Linari M, **Marcello M**, Morotti I, Narayanan T, Lombardi V, Piazzesi G. (2021). Thick filament regulation in cardiac muscle. Virtual European Muscle Conference (September 20-22, Warsaw operated).

- Ricerche bibliografiche e open access & science (07/05/2021);
- Diritto dei brevetti (10/05/21, 13/05/21 e 11/05/2021);
- Spin Off e Start up della ricerca: l'ecosistema di innovazione a supporto di start up (17/05/2021);
- Spin Off e Start up della ricerca: il modello di business e i regolamenti (18/05/2021);
- Creating value from large archive and big data (25/05/2021);

- How to exploit your research idea: a quick introduction to EU project design and management (26/05/2021 e 27/05/2021);
- I rapporti tra scienza e società: tra persistenze e cambiamenti (03/05/2021);
- Soft skills per fare ricerca nelle organizzazioni (07/06/2021);
- Analisi della risposta immunitaria alla vaccinazione e all'infezione: dalla fase di sperimentazione a quella di analisi dati tramite un approccio di systems biology (08/06/2021);
- Spin off e Start up della ricerca: L'ecosistema di innovazione a supporto delle start up (15/06/2021);
- Lavoro editoriale per l'editoria scolastica e universitaria (scienze e lettere) (17/06/2021);
- Comunicare in ricerca (28/06/2021);
- Possibili percorsi formativi post PhD (02/07/2021).

- Eventuali soggiorni in altri laboratori italiani o esteri:

Nel periodo 20-27 giugno 2021 ho partecipato a esperimenti combinati di meccanica e diffrazione a raggi X presso la linea di luce ID02 del sincrotrone europeo ESRF di Grenoble (Francia) per investigare il meccanismo molecolare della regolazione del filamento spesso nel cuore, utilizzando singole trabecole isolate dalla parete interna del ventricolo di ratto.