

Dottorato di Ricerca in Medicina Molecolare
Relazione attività di ricerca (primo anno)

Attività scientifica svolta nel 1° anno di Dottorato, Anno Accademico 2019/2020

Al collegio docenti del Dottorato in Medicina Molecolare

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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 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; motors on the thick filament are switched ON from the energetically convenient OFF state in relation to the load by thick filament mechano-sensing. Biochemical and structural evidence suggests that the removal of the block of Tm on the actin sites depends on motor attachment. Myosin binding is likely responsible also for the spread of activation along the thin filament, with a cooperative mechanism (still to be defined) that in skinned fibres determines the steepness of the sigmoidal force-pCa relation estimated, according to Hill equation, by the coefficient n_H .

My research project is aimed at clarifying this mechanism using fast sarcomere-level mechanics in demembranated fibres from soleus muscle of rabbit. The force-pCa relation and the stiffness of the half sarcomere were determined in protocols where the force generated by the myosin motor was modulated by either temperature (range 12-35 °C) or addition 1 μM omecamtiv mecarbil (OM). OM is known to (i) suppress the force of the motors while remaining strongly bound to actin and (ii) increase Ca^{2+} sensitivity of thin filament shifting the force-pCa relation toward larger pCa while reducing its steepness n_H (Governali *et al. Nat Commun* 11:3405, 2020).

It has been found that i) the force per myosin motor (F_0), determined by using the half-sarcomere compliance analysis on pCa -modulated force, ranges, under the action of the various modulators, from 0.81 ± 0.08 pN (1 μM OM, 12°C) to 3.17 ± 0.27 pN (control, 35°C), and ii) n_H of the corresponding force-pCa relation is linearly related to F_0 . These results suggest that the cooperativity in thin filament activation depends on the local stress induced by the attaching motor.

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

- Partecipazione a corsi:
- Comunicare in ricerca (03/06/2020)
- Spin Off e Start up della ricerca: concetti introduttivi e presupposti per la nascita di un'impresa (08/06/2020);
- Spin Off e Start up della ricerca: il modello di business e i regolamenti (09/06/2020);
- Spin Off e Start up della ricerca: l'ecosistema di innovazione a supporto di start up (18/06/2020);
- Nuovi strumenti per l'analisi della risposta immunitaria alla vaccinazione e all'infezione tramite un approccio si "Systems Biology" (11/06/2020);
- Lavoro editoriale per l'editoria scolastica e universitaria (16/06/2020);

- La ricerca dell'informazione di ambito scientifico su Internet (25/06/2020);
- Scientific Writing and Presentation (08/09/2020 e 09/09/2020);

- Pubblicazioni scientifiche autori, titolo della pubblicazione, nome e numero della rivista, anno di pubblicazione

- Eventuali soggiorni in altri laboratori italiani o esteri: nessuno.