X-ray diffraction studies of the molecular mechanism of muscle contraction: use of mammalian muscle opens new research horizons.

M. Reconditi[1], E. Brunello[1], M. Caremani[1], M. Linari[1], M. Dolfi[1], M. Fernandez-Martinez[2], T. Narayanan[2], D. Gore[3], T. Irving[3], G. Piazzesi[1], M. Irving[4], V. Lombardi[1]

[1]University of Florence, Florence, Italy
[2]ESRF, Grenoble, France
[3]IIT, Chicago, IL, USA
[4]Kings' College London, London, UK

Muscle contraction is due to the proteins myosin and actin that are organised in quasi-crystalline filament arrays, allowing the study of the molecular mechanism of contraction in single cells or whole muscle by small-angle X-ray scattering (SAXS). Combining time-resolved SAXS and fast mechanics in single cells dissected from the skeletal muscle of the frog, we were able to determine the load dependence of the amplitude and the speed of the working stroke in the myosin motor (Reconditi et al., *Nature* 428:578, 2004; Piazzesi et al., *Cell* 131:784, 2007), the mechanism of muscle braking in response to stretch (Brunello et al., *PNAS USA*, 104:20114, 2007) and the conformational change in the myosin motors during muscle activation and the development of isometric force (Reconditi et al., *PNAS USA*, 108:7236-7240, 2011). Recently we extended this approach to mammalian muscle, using either demembranated fibres from rabbit psoas, in which the biochemical milieu can be controlled, or the whole mouse muscle, in which an adequate signal to noise is achieved for the weaker X-ray reflections that carry fundamental information about the structural changes in the filaments. This has enabled a new programme of research, linking the structural and mechanical changes in the myosin motor to the steps of the ATP hydrolysis cycle that fuels contraction. In future the combination of SAXS with transgenics and transfection of mouse muscles will allow the investigation in intact muscle cells of the structural and functional consequences of specific molecular changes relevant to human diseases.