Unlocking the secrets of heart muscle structure

Seminar by:

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Time: 14:30 - 15:30
Venue: Seminar room L4E01

Abstract

Sarcomeres are force-generating and load-bearing devices of muscles. A precise molecular picture of how sarcomeres are built underpins understanding their role in health and diseases. The Raunser group has determined the molecular architecture of native skeletal and cardiac sarcomeres and structures of sarcomeric proteins using cryo-focused-ion-beam milling (cryo-FIB) and electron cryo-tomography (cryo-ET). Their three-dimensional reconstruction of the sarcomere reveals molecular details in the A-band, I-band and Z-disc and demonstrates the organisation of the thin actin and thick myosin filaments and their cross-links [1,2]. Their reconstruction of the thick filament reveals the three-dimensional organization of myosin heads and tails, myosin-binding protein C (MyBP-C) and titin, elucidating the structural basis for their interaction during muscle contraction [2]. Using sub-tomogram averaging, the Raunser group has determined an *in situ* structure of the thin filament at 4.5 Å, revealing the structure of nebulin and the molecular mechanism underlying its role as a "molecular ruler", in stabilising thin filament and in regulating myosin binding [3]. They also determined single particle cryo-EM structures of F-actin at unprecedented resolutions, offering a direct visualization of water molecules and allowing atomic insight into ATP hydrolysis and phosphate release [4,5]. In their latest study, they elucidated the molecular mechanism of actin filament elongation by formins [6]. Taken together, the Raunser group's cryo-EM studies provide deep insights into muscle structure, actin filament aging and the interaction between actin and myosin and their associated proteins, which form the basis of muscle contraction and regulation.

References

[1] Wang Z, Grange M et al. (2021), **Cell**. 184, 2135-2150.613
[2] Tamborrini D et al. (2023), **Nature**, 623(7988):863-871
[3] Wang Z, Grange M et al. (2022), **Science**. 375, eabn1934
[4] Oosterheert W et al. (2022), **Nature**, 611(7935):374-379
[5] Oosterheert W, Blanc F et al. (2023), **Nat Struct Mol Biol.** 30(11):1774-1785
[6] Oosterheert W, Boeiro Sanders M et al. (2024), **Science**, 384(6692):eadn9560

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