Investigating mitochondrial complex I assembly as a factor for disease

Supervisory team:
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Project description:
Mitochondria are prominent in the public domain, with breaking news stories often reporting on newly discovered links between mitochondrial function and their primary role - harnessing the energy stored in food to provide the power for cell survival in the form of ATP. There is increasing evidence that relates mitochondrial dysfunction with ageing and neurodegenerative disorders, such as Parkinson's disease.

The respirasome is a massive molecular machine that carries out cellular respiration in the mitochondrial inner membrane. It is comprised of four complexes (I–IV), which transfer electrons from NADH and succinate to molecular oxygen. Energy gained through this process is used to pump protons across the inner mitochondrial membrane, leading to a membrane potential that is used to generate ATP.

Approximately 50% of all mitochondrial disorders affecting energy metabolism can be traced back to mutations in one of the subunits of complex I. In exciting new data, we have discovered that an accessory protein of complex I plays a key role in the stability of the respirasome. Knock-down of this protein shows additional deleterious effects on respiration, production of reactive oxygen species (ROS) and reduction of the inner membrane potential. By cutting-edge imagining techniques, we have also observed that mitochondrial morphology is perturbed, which likely has additional consequences on network formation and the structure of protein complexes in the inner membrane.

In this multi-disciplinary project, state-of-the-art imaging methods including fluorescence light microscopy and high-resolution electron cryomicroscopy (cryoEM), will be used to investigate the break-down of mitochondrial networks and the consequence on protein structures in our complex I mutants. This will be combined with biochemical experiments to explore the structural and functional integrity of the electron transfer apparatus. These will include analysis of the assembled state of the respiratory super-complexes alongside their electron transfer, proton-pumping and oxygen uptake activities. Their ability to restrict excessive (and damaging) production of ROS will also be evaluated. Knowledge gained will be used to shed light on, and guide the further study of, diseases associated with complex I dysfunction. In summary, this will provide an excellent training opportunity in modern methods at the frontier of biological sciences research.