Role of HIGD1A and Cytochrome c Proteins in Mitochondrial Respiratory Chain Supercomplexes

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Recently, cryo-electron microscopy was used to elucidate the structure of the respirasome, a mitochondrial supercomplex containing complexes I, III and IV (CI, CIII and CIV, respectively)[1,2]. Despite having been developed at high resolution, the model lacks membrane proteins HIG1 domain family 1A and 2A (HIGD1A and HIGD2A), which have been identified as supercomplex adaptors. Indeed, HIGD2A is necessary for the assembly of the respirasome, whereas HIGD1A has been recognised as a positive regulator of cytochrome *c* oxidase (from CIV), with an impact on cell survival and tumour growth[3]. In addition, new studies suggest a putative stabilization of the CI/CIII and CIII/CIV supercomplexes by mobile carriers coenzyme Q and cytochrome *c* (C*c*), respectively[4,5].

The pro-survival activity of HIGD1A is related to the inhibition of C*c* release and the decrease in caspase activation[6]. This effect is dependent on the soluble N-terminal, 26-amino-acid-long domain of HIGD1A, which is oriented towards the mitochondrial intermembrane space[6]. The C*c*/N-term HIGD1A interaction was characterized by combining measurements obtained through isothermal titration calorimetry and nuclear magnetic resonance, revealing transient C*c*/N-term HIGD1A contacts in the supercomplex context. Further experiments will be carried out using the full-length HIGD1A bound to GFP to improve solubility.

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