

Unravelling the molecular architecture of the Commander assembly

Michael Healy¹

¹*Institute for molecular biosciences*

michael.healy@uq.edu.au

The Commander complex is a conserved regulator of intracellular trafficking. This ancient complex consists of 15 core components as well as a number of associated proteins that can be subdivided into three (3) categories: the COMMD/Coiled coil domain containing proteins, the Retriever complex (a distant relative of the Retromer complex) and a number of associated proteins. Functionally Commander couples to Sorting Nexin 17 (SNX17) to facilitate the recycling of over 100 cell surface proteins including key receptors such as, LDLR, LRP1, p-Selectin and the amyloid precursor protein. In addition, Commander dysfunction has been linked to various disease pathologies including X-linked intellectual disability. It is therefore crucial to understand the structure, mechanism and function of this complex, an understanding that has remain largely elusive to date.

The development of the machine learning algorithm Alphafold2, has greatly accelerated our understanding of this complex. Using this program we have successfully modelled all 10 COMMD proteins, this revealed the precise arrangement of the paralogues and as well as a striking decameric structure (see Figure 1). Using this we created a polycistronic E.coli expression vector that allowed us to express all 10 COMMD proteins simultaneously and despite been unable to reconstitute the decamer we were able to identify four stable tetramers that had the same arrangement predicted by Alphafold2. In addition to this we were able to resolve a 3.3 Å crystal structure of a COMMD subcomplex containing Commd5-7-9-10. Revealing an intimately assembled heterotetramer, with interfaces along the β -strands of the highly conserved COMM domain and more subunit specific interactions between the loops on the COMM domain and the more variable helical N-terminal domain (See Figure 2). Again this structure was in agreement with the model predicted by Alphafold2. Overall, this work provides the first glimpse into the structural organisation of the conserved and essential Commander assembly.