Towards an integrated approach to structural biology.

Macromolecular complexes involved in DNA replication: a case study

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Although protein crystallography is a very powerful technique to understand biological processes at the atomic level, many important cellular machines are often large and polymorphic and exist in a variety of functional states, making them a challenging target for crystallization. There is therefore the need for alternative methods that are able to cope with the size, complexity and flexibility of large macromolecular systems. Single particle electron microscopy and small-angle X-ray scattering provide useful techniques to visualise such complexes. Data from these techniques can be combined with crystallographic atomic structures to get a three-dimensional picture of the complex architecture.

I will present an examples derived from our own work aimed at unravelling the structural and functional aspects of eukaryotic DNA replication, focusing on the structure of the replicative CMG helicase [1-2]. The 11 proteins that make up this complex are present only in proliferating cells and are highly expressed in malignant human cancer cells and pre-cancerous cells undergoing malignant transformation. Therefore, these proteins are ideal diagnostic markers for cancer and possibly targets for anti-cancer drug development.

References:

[1] B. Medagli, P. Di Crescenzio, M. De March and S. Onesti, *Structure and activity of the Cdc45-Mcm2-7-GINS (CMG) complex, the replication helicase* in *The initiation of DNA replication in eukaryotes*, Springer (2016).

[2] S. Onesti and S.A. MacNeill, *Structure and evolutionary origins of the CMG complex,* Chromosoma **122**, 47 (2013).