A CRYPTIC MOTIF IN BRCA2 TRIGGERS OLIGOMERIZATION OF THE MEIOTIC HSF2BP, AS CHARACTERIZED BY NMR, X-RAY CRYSTALLOGRAPHY AND CRYO-ELECTRON MICROSCOPY

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BRCA2 is one of the most studied cancer predisposition genes. The protein encoded by this gene, BRCA2, is large (more than 3000 amino acids), and is mutated along its entire length in patients with breast, ovarian and prostate cancers. The absence of BRCA2 also causes a fertility defect in men. BRCA2 is essential for homologous recombination, a process central to DNA repair and meiosis. In particular, BRCA2 recruits the RAD51 protein to DNA, in order to search for sequence homologies between two strands and allow their exchange. A team from the ERASMUS Medical Center (Rotterdam, The Netherlands) has recently identified a new BRCA2 partner, HSF2BP, which is widely expressed in meiotic cells. Mutations in HSF2BP are implicated in fertility problems: in particular, loss of HSF2BP prevents homologous recombination during spermatogenesis.

In order to determine whether HSF2BP is involved in the localization of BRCA2 at homologous recombination sites during meiosis, we solved the 3D structure of the interacting domains of BRCA2 and HSF2BP by X-ray crystallography, in collaboration with Synchrotron Soleil (Ghouil et al., Nat Commun 2021). From a molecular point of view, BRCA2 is mostly predicted as disordered, as characterized by NMR, which makes its structural analysis particularly complex (Julien et al., Biomolecules 2021). We identified a disordered repeated motif in BRCA2 capable of binding two HSF2BP domains and showed that two BRCA2 fragments bind simultaneously to four HSF2BP domains, leading to a very high affinity between the two partners and to the formation of a tetramer of HSF2BP domains. Deletion of the first repeat of the motif strongly decreases the affinity between BRCA2 and HFS2BP and prevents tetramerization of the HSF2BP domain. However, this deletion does not reproduce the HFS2BP loss phenotype in mice. Further in vitro analysis of the complex between the repeated motif of BRCA2 and full-length HSF2BP revealed the assembly of a large oligomer of 900 kDa, whose 3D structure is now being characterized by cryo-electron microscopy. A fragment of BRME1, a HSF2BP partner, inhibits the formation of this oligomer. The meiotic function of the complex between BRCA2 and HSF2BP and its inhibition by BRME1 will be discussed.

References:

Ghouil R, et al. Nat Commun. 2021 Jul 29;12(1):4605.

Julien M, Ghouil R, et al. Biomolecules. 2021 Jul 20;11(7):1060.

3D structure BRCA2 peptide/HSF2BP Armadillo domain