INSTITUTIONEN FÖR KEMI OCH MOLEKYLÄRBIOLOGI

Identification of novel BRCA2-binding proteins that are essential for meiotic homologous recombination

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Abstract

Meiotic recombination is a molecular process in which the induction and repair of programmed DNA double-strand breaks (DSBs) creates genetic exchange between homologous chromosomes and thus increases genetic diversity and ensures chromosome segregation.

Breast cancer susceptibility gene 2 (*BRCA2*) is a potent cancer suppressor and is required for DSB repair by homologous recombination (HR) in mitosis. However, due to the embryonic lethality of the *Brca2* knockout (KO) mice, the role of BRCA2 in meiotic HR is less well defined.

In our work, we have identified two novel meiosis-specific proteins, MEILB2 (meiotic localizer of BRCA2) and BRME1 (BRCA2 and MEILB2-associating protein 1) that form a ternary complex with BRCA2 and shed light on BRCA2 and its co-factors' roles during meiotic HR.

In *Meilb2* KO male mice, the localization of the recombinases RAD51 and DMC1, which catalyze the homology-directed repair of DSBs, is almost totally abolished, leading to errors in meiotic DSB repair and subsequent sterility. Moreover, MEILB2 binds directly to BRCA2 and is responsible for BRCA2 localization at the meiotic DSBs.

BRME1 functions as a stabilizer of MEILB2 by binding to the α-helical N-terminus of MEILB2 and preventing MEILB2 self-association. In *Brme1* KO mice, the BRCA2-MEILB2 complex is destabilized, leading to defects in DSB repair, homolog synapsis, and crossover formation. Persistent DSBs in *Brme1* KO spermatocytes reactivate the somatic-like DNA-damage response (DDR), which repairs DSBs but cannot complement the crossover formation defects. Further, MEILB2-BRME1 is activated in many human cancers, and somatically expressed MEILB2-BRME1 impairs mitotic HR.

Finally, we solved the crystal structure of the MEILB2-BRCA2 complex and showed that disruption of the MEILB2-BRCA2 interface compromises the recruitment of both MEILB2 and BRCA2 to recombination sites in mouse spermatocytes, thus demonstrating their inter-dependent localization mechanism in meiosis.

Taken together, our results show that the meiotic BRCA2 complex plays a central role during meiotic HR, and its misregulation is implicated in human infertility, miscarriage, and cancer development.

Keywords: meiosis, DSB, cancer, BRCA2, HR, MEILB2, BRME1, RAD51, DMC1, DDR