DNA DAMAGE RESPONSE

Higher-order BRCA1 complexity

> “…identification of a new component of a BRCA1-containing complex…”

The breast cancer susceptibility gene 1 (BRCA1) protein forms complexes with other protein components to regulate the cellular response to DNA damage. Three studies now report the identification of a new component of a BRCA1-containing complex that is integral to its stability and is required for DNA damage resistance and G2–M checkpoint control.

Using an affinity purification approach, Feng *et al.* and Shao *et al.* identified a protein, which they named MERIT40 (mediator of RAP80 interactions and targeting 40 kDa), that exists in a BRCA1 complex with RAP80 (which contains ubiquitin-binding motifs), CCDC98 (a coiled-coil domain-containing protein also known as FAM175A or Abraxas), BRCC36 (a deubiquitylating enzyme) and BRE (an adaptor protein also known as BRCC45). Wang *et al.* also identified this protein, which they named NBA1 (new component of the BRCA1 A complex), from a screen for resistance to ionizing radiation (IR), and showed that it exists in the same BRCA1-containing complex.

Even though the three studies report conflicting data on which components of the BRCA1 complex the protein called MERIT40 or NBA1 interacts with, the consensus view is that MERIT40/NBA1 is essential for the integrity of the complex. The components of the complex are thought to be interdependent and may bind cooperatively to CCDC98, which interacts with all members of the complex. In turn, a stable complex is required for localization of the complex — and, consequently, recruitment of BRCA1 — to sites of DNA breaks. Depletion of any non-BRCA1 component compromised the formation of DNA damage-induced BRCA1 foci. By contrast, BRCA1 depletion does not affect the localization of the other components of the complex, which suggests that it functions downstream of the other components.

The three teams further demonstrated that depletion of MERIT40/NBA1 results in defective G2–M checkpoint control and increased sensitivity to IR. BRCA1-containing complexes are known to be recruited to polyubiquitylated chromatin at double-strand breaks (DSBs) following DNA damage. Depletion of RAP80 resulted in decreased amounts of MERIT40/NBA1 at DSBs, which led Shao *et al.* to conclude that recruitment of the BRCA1 complex to sites of DNA damage may be mediated by RAP80. These authors also showed that the deubiquitylating activity of BRCC36 is essential for both the G2–M checkpoint and IR resistance responses.

Bioinformatics analysis carried out by Wang *et al.* further revealed that the BRCA1-containing complex resembles the lid complex of the 26S proteasome. They also showed in *in vitro* binding assays that several other components of the BRCA1-containing complex (in addition to RAP80) have the ability to bind polyubiquitin chains. Although the functional significance of these observations remains to be determined, the combined findings from the three studies suggest that MERIT40/NBA1 connects BRCA1 complex integrity, DSB recognition and ubiquitin chain activities to the DNA damage response.

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ORIGINAL RESEARCH PAPERS Feng, L. *et al.* MERIT40 facilitates BRCA1 localization and DNA damage repair. *Genes Dev.* **23**, 719–728 (2009) | Wang, B. *et al.* NBA1, a new player in the Brca1 A complex, is required for DNA damage resistance and checkpoint control. *Genes Dev.* **23**, 729–739 (2009) | Shao, G. *et al.* MERIT40 controls BRCA1–Rap80 complex integrity and recruitment to DNA double-strand breaks. *Genes Dev.* **23**, 740–754 (2009)