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Review Article

The MRE11 complex: An important source of stress relief

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Introduction

To prevent the accumulation of DNA lesions, cells activate a DNA damage response that orchestrates cell cycle checkpoint responses, the recruitment of DNA repair complexes and the regulation of cell fate decisions, including programmed cell death (apoptosis) and senescence [1]. Defects in the DDR can result in chromosome instability that can contribute to a broad spectrum of human pat-

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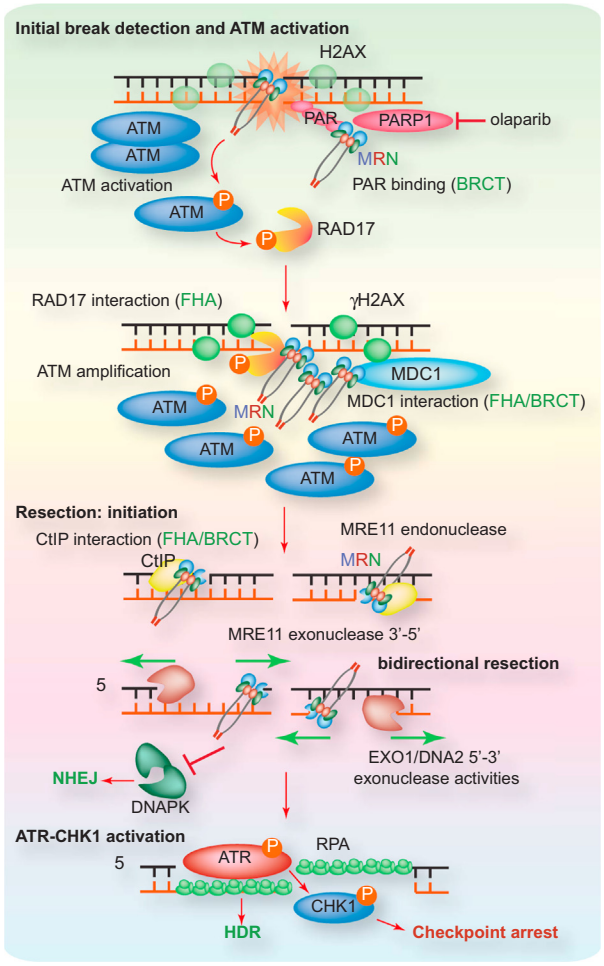

Fig. 1 – Summary model of MRE11 complex recruitment and resection at DNA breaks. Following break detection, initial MRN retention (green) is facilitated by NBS1-BRCT binding to PAR, leading to rapid ATM activation and phosphorylation of RAD17 and H2AX. Phospho-dependent interactions between RAD17 and the NBS1-FHA domain recruit additional MRN and amplify ATM activation (yellow). MDC1 interactions with NBS1 and H2AX facilitate further retention of MRN at breaks. Resection is initiated by MRE11 and/or CTIP endonuclease activity followed by bidirectional resection, preventing DNAPK mediated NHEJ (pink) and facilitating RPA binding and ATR-CHK1 activation (blue). For the sake of brevity, many key regulators are omitted.

hologies. The MRE11 complex (or MRN), composed of MRE11, RAD50 and NBS1 (Xrs2 in yeast), is a sensor of DNA double-strand breaks (DSBs) [2]. Following DSB detection, the MRE11 complex plays diverse roles in the DDR to promote DNA repair and prevent the accumulation of potentially pathological chromosome breaks and rearrangements.

Critical for many of its roles in the DDR, the MRE11 complex exhibits several enzymatic activities including 3′–5′ exonuclease activity and endonuclease activity of MRE11 and ATPase and adenylate kinase activity of RAD50 (we refer readers to a detailed review of the enzymatic activities in this issue [3]). In addition, the RAD50 protein contains a zinc hook domain that is essential for MRE11 complex functions and faciliates multimerization of the holocomplex. NBS1, the least conserved complex member, is not believed to have enzymatic activities, but promotes nuclear localization of the holocomplex and regulates its activities by influencing protein–protein interactions and structure [2,4–7]. The N-terminus of NBS1 contains a Forkhead associated domain (FHA) and tandem BRCA1 C-terminal domains (BRCT) that together mediate phospho-specific protein–protein interactions that influence the subcellular localization of the complex [5,8–11]. The C-terminus of NBS1 contains domains that facilitate regulatory interactions with both MRE11 and the ATM kinase [12–15].

The precise stoicheometry of the holocomplex and its range of structural conformations *in vivo* remains unclear, but the core holocomplex consists of 2 RAD50 subunits, 2 MRE11 subunits and likely 2 or more subunits of NBS1 [4,16]. The multimerization of the MRE11 complex has been demonstrated *in vitro* and requires the zinc hook domain of RAD50 that is located at the apex of 2 stretches of antiparallel coiled coil motifs [17]. The integrity of the zinc hook domain is important for MRE11 complex stability and function, as mutations in its zinc coordinating residues lead to complex destabilization and a null phenotype [18,19].

The MRE11 complex acts as a sensor of DSBs and governs the activation and activity of the central transducing kinases Ataxia telangiectasia mutated (ATM) and ATM and RAD3 related (ATR) [20–23]. The MRE11 complex both promotes the activation of ATM and ATR and acts as a mediator, regulating their ability to phosphorylate a yet unknown fraction of their hundreds of substrates, which include key regulators of cell cycle checkpoints, DNA repair and transcriptional activities [24–28]. The influence of the MRE11 complex on the activation of ATM, as well as its mediator functions, are required for efficient checkpoint induction in the S and G2 phases of the cell cycle, as well as apoptosis in lymphoid cells [14,15,27].

The DDR promotes the repair of DSBs through one of two major pathways, non-homologous end-joining (NHEJ) or homology-directed repair (HDR) [29]. In mammals, the MRE11 complex is primarily involved in promoting HDR where it plays structural, enzymatic and signaling roles [2,3]. The capture of dsDNA ends by the MRE11 complex promotes their 5′–3′ resection to generate ssDNA overhangs. These overhangs can prevent the binding of the DNA dependent protein kinase (DNA-PK: composed of the Ku70, Ku80 and DNA-PKcs subunits) which would facilitate their repair by NHEJ. While the precise roles of the MRE11 complex in resection remain an area of intense investigation, the emerging model based on data from several systems is that the endonuclease activity of MRE11 or its interacting protein, CTIP, initiates resection by nicking upstream from the DNA end [30–32]. This is followed by bidirectional resection that involves the 3′-5′ exonuclease of the MRE11 complex acting towards the broken end and the 5′-3′ exonuclease activities of either EXO1 or DNA2, potentially in conjunction with the BLM helicase, carrying out more extensive resection away from the end [31–40]. Collectively, these activities generate ssDNA overhangs that promote strand invasion and facilitate HDR (Fig. 1). In addition, these overhangs are a potent activator of the ATR and CHK1 kinases that are essential for cell cycle arrest in S and G2 phases [41,42]. (We refer the reader to recent reviews for a more detailed description of end resection mechanisms in different systems [3,43]).

The identification of mutations in *MRE11*, *NBS1* and *RAD50* in Ataxia-telangiectasia like disease (ATLD), Nijmegen Breakage Syndrome (NBS) and NBS like disease (NBSLD) respectively, has linked defects in MRE11 complex function to human disease, as these