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Signalling around DNA breaks – new tricks for old dogs!

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Of the myriad of different lesions inflicted on DNA, double-stranded breaks (DSBs) are, arguably, the most toxic. Their detection and repair is achieved through a complex cascade of events that requires the timely recruitment of a large number of proteins and complexes at and around the damage site. Key to many of these processes is the Mre11/Rad50/Nbs1 (MRN) complex that plays a number of roles in repair of the break and a plethora of signalling events that are, by and large, rather poorly understood. The MRN, in complex with the ATM kinase, is one of the first complexes recruited to the break site. It is then progressively sequestered into megabase regions of chromatin distal to the break through a constitutive, casein kinase II-dependent interactions of the FHA and BRCT-repeat phospho-specific interaction domains of Nbs1 with multiple di-phosphorylated motifs within the mediator/scaffold molecule Mdc1. Mdc1 is, in turn, tightly secured to a subset of H2AX-containing nucleosomes that have been phosphorylated on their extreme C-termini by ATM, generating binding sites for the Mdc1 BRCT-repeat domain. Although disruption of the Nbs1-Mdc1 interaction is known to result in a number of defective DDR phenotypes, the structural mechanism of Mdc1-dependent MRN recruitment remains largely obscure. I will present updates on recent progress with structural and biochemical characterisation of Nbs1 function in the DDR with a particular focus on FHA and BRCT-repeat domain specificity and multi-site interactions with both Mdc1 and other binding partners.

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