MRN complex

The MRN complex, also known as the MRE11-RAD50-NBS1 complex, is a crucial protein complex involved in the DNA damage response and repair mechanisms within cells. It plays a central role in sensing and processing DNA double-strand breaks (DSBs), one of the most severe types of DNA damage that can occur in cells.

The MRN complex consists of three core components:

MRE11: MRE11 (Meiotic Recombination 11) is a nuclease and endonuclease enzyme that possesses 3' to 5' exonuclease and 3' to 5' endonuclease activities. It binds to DNA ends at sites of DSBs and acts as a sensor of DNA damage.

RAD50: RAD50 is a protein with ATPase activity that binds to MRE11 and forms the structural core of the MRN complex. It is involved in tethering and stabilizing the complex at DNA break sites.

NBS1 (Nijmegen Breakage Syndrome 1): NBS1, also known as nibrin, is a protein that interacts with MRE11 and RAD50 and serves as a mediator between these two proteins. It plays a critical role in facilitating the activation of the DNA damage response and repair pathways.

Functions of the MRN complex:

DNA damage sensing: The MRN complex recognizes DNA DSBs and recruits other DNA damage response proteins to the site of damage.

DNA end processing: The MRE11 nuclease activity is involved in resecting DNA ends at the DSB site, creating single-stranded DNA overhangs. This step is essential for the activation of DNA repair pathways.

Activation of ATM kinase: The MRN complex promotes the activation of the ATM (ataxia-telangiectasia mutated) kinase, a key regulator of the DNA damage response. ATM activation triggers a signaling cascade that leads to cell cycle arrest, DNA repair, and apoptosis if necessary.

Homologous recombination repair: The MRN complex is involved in the initiation of homologous recombination repair, a precise and error-free DNA repair pathway that utilizes an undamaged sister chromatid as a template for repair.

Non-homologous end joining (NHEJ): The MRN complex is also involved in NHEJ, a DNA repair pathway that directly rejoins broken DNA ends, albeit with the potential for introducing mutations.

Defects or mutations in the MRN complex components can lead to genomic instability, impaired DNA repair, and an increased risk of developing cancer and other genetic disorders. For instance, mutations in the NBS1 gene are associated with Nijmegen Breakage Syndrome, a rare autosomal recessive disorder characterized by microcephaly, growth retardation, immunodeficiency, and an increased susceptibility to cancer. Dysfunction of the MRN complex can also contribute to various human diseases and conditions linked to defective DNA repair mechanisms.

Hypomorphic mutations in MRN complex genes are frequently found in cancer, supporting their role as oncosuppressors. However, unlike canonical oncosuppressors, MRN proteins are often

overexpressed in tumor tissues, where they actively work to counteract DSBs induced by both oncogene-dependent RS and radio-chemotherapy. Moreover, at the same time, MRN genes are also essential genes, since the constitutive KO of each component leads to embryonic lethality. Therefore, even though it is paradoxical, MRN genes may work as oncosuppressive, oncopromoting, and essential genes. In this review, we discussed how alterations in the MRN complex impact the physiopathology of cancer, in light of our recent discoveries on the gene-dosage-dependent effect of NBS1 in Medulloblastoma. These updates aim to understand whether MRN complex can be realistically used as a prognostic/predictive marker and/or as a therapeutic target for the treatment of cancer patients in the future [1].

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Petroni M, La Monica V, Fabretti F, Augusto M, Battaglini D, Polonara F, Di Giulio S, Giannini G. The Multiple Faces of the MRN Complex: Roles in Medulloblastoma and Beyond. Cancers (Basel). 2023 Jul 13;15(14):3599. doi: 10.3390/cancers15143599. PMID: 37509263; PMCID: PMC10377613.