Abstract

DNA double strand breaks are the most dangerous type of DNA damage. The MRN complex and 53BP1 have essential functions in the repair of DNA double strand breaks and are therefore important for maintaining genomic stability and preventing cancer. DNA double strand breaks are repaired by two main mechanisms - homologous recombination and non-homologous end joining. The MRN complex senses DNA double strand breaks and activates a cascade of posttranslational modifications that activates and recruits other effector proteins. In addition MRN mediated resection is important for removing adducts in non-homologous end joining and creating single stranded DNA required for homologous recombination. 53BP1 is recruited to DNA double strand breaks by site specific ubiquitinations and inhibits DNA resection, thereby promoting non-homologous end joining at the expense of homologous recombination. In this thesis we show that MRE11 binds to the R2TP chaperone complex through a CK2 mediated phosphorylation. Knockdown of R2TP or mutating the MRE11 binding site leads to decreased MRE11 levels and impaired DNA repair. Similar phenotype has been observed in cells from patients with ataxia-telangiectasia-like disorder (ATLD), containing MRE11 deletion mutation which is missing the R2TP complex binding site. Based on R2TP complex function as a molecular chaperone, we conclude, that R2TP complex is important for MRN complex assembly/quality control. Moreover, we explored the processes important for regulating localisation of DNA repair protein 53BP1 to the nucleus and DNA damage site. We investigated PLK1 and CDK1 mediated phosphorylations in 53BP1 ubiquitin binding domain and discovered that they inhibit 53BP1 recruitment to the DNA damage site in mitosis. Finally we discovered the sequence of 53BP1 localisation signal and explored regulatory mechanisms of 53BP1 nuclear localisation by post translational modifications. In conclusion, we deepened our understanding of MRN complex assembly and pathophysiology of a specific MRE11 mutation leading to ATLD. In addition we found new ways of regulation of 53BP1 localization and function.