Abstract

RAD18 is an E3 ubiquitin ligase that prevents the replication forks from collapsing caused by damaged DNA. As an important factor controlling replication, its dysregulation was shown to be associated with some human tumours. However, the clinical relevance of this finding is unknown. The aim of the thesis was evaluation of selected *RAD18* variants that had been identified in breast and ovarian cancer patients. This work revealed functional defects of RAD18 variants not only in replication fork protection but also in repair of DNA double-strand breaks. This unconventional role of RAD18 is known to be dependent on upstream ubiquitination events, however, its contribution to the repair per se is not understood. This work aimed to elucidate the function of RAD18 in DNA double-strand break repair by homologous recombination focusing especially on its relationship with 53BP1. Data presented here show that RAD18 effectively disrupts 53BP1 accumulation in the repair foci by competition for the same binding partner and thus promotes resection of DNA ends. This antagonistic function of RAD18 is restricted both spatially (to the vicinity of the repair centre) and temporarily (to S phase). Moreover, it seems to be regulated by existence of RAD18 in two distinct complexes. Potential models for this regulation are discussed at the end of this work.

Keywords: RAD18, DNA double-strand break repair, ubiquitination, cancer variants, DNA end resection, homologous recombination, 53BP1.