Abstract

Breast cancer is the most frequent malignant disease in the female population worldvide. About 10 % of all cases are of hereditary origin. The inactivation of tumor suppressor gene *BRCA1* is the main genetic predisposing factor in breast cancer in the Czech Republic. Primarily, BRCA1 participates in DNA double strand break repair. Depending on cell cycle phase, the damage is repaired by homologous recombination or non-homologous end joining. Alternative splicing variants of BRCA1 are frequently detected during the genetic screening of high risk patients. The clinical significance of these variants is unknown. Understanding of the nature of breast cancer genetics is the critical factor for early diagnosis. Based on earlier studies from the Institute of Biochemistry and Experimental Oncology 1st Faculty of Medicine Charles University, two alternative splicing variants which were repeatedly detected in patients, were chosen for functional analysis.

The aim of this work is to investigate the impact of alternative splicing variants BRCA1Δ5 and BRCA1Δ10 on DNA double strand breaks repair. Particular variants were over-expressed in the cells of model system. Activity of homologous recombination (HR) and non-homologous end joining (NHEJ) was scored by *in vitro* DNA repair assay. The cellular localization of alternative splicing variants was determined by a fluorescent microscopy. It was found that BRCA1Δ5 statistically decreases the activity of HR but does not have the impact on NHEJ. BRCA1Δ10 did not alter the activity of HR or NHEJ. Despite the fact that BRCA1Δ5 has an impact on HR activity, it is not caused by changes in cell localization. Cell localization of BRCA1Δ5 was predominantly nuclear, same as for wtBRCA1. BRCA1Δ10 was co-localized with wtBRCA1 in nucleus, even though it lacks nuclear localization signals.

The results of this work indicates that defective alternative splicing of BRCA1, which forms aberrant splicing isoforms, can have a negative impact on DNA double strand breaks repair. These defects may lead to genome instability and potentially to malignant transformation.