14.Streszczenie w języku angielskim | Summary

DNA polymerase theta (Polθ) and its inhibitors (Polθi) have gained particular attention in the recent years. Polθ is a DNA polymerase involved in several DNA repair mechanisms, but mainly in theta-mediated end joining (TMEJ) – one of the DNA double-strand breaks (DSBs) repair pathways. The DNA repair destabilization and genetic mutations are the cancer hallmarks, making it possible to use the synthetic lethality approach to selectively kill cancer cells by inhibiting one of the DNA repair proteins. Furthermore, cancer cells with alterations in HR or NHEJ pathways often become dependent on TMEJ.

The main objective of the research was to determine the influence of Polθ inhibition and its combination with PARP or Rad52 inhibition and alkylating agents on glioblastoma and melanoma cells, simultaneously assessing their impact on normal cells. In order to evaluate it, we analyzed cell viability, cell apoptosis, cell proliferation and invasive character, level of DNA damage, cell cycle distribution and gene expression profile.

The results show that inhibition of DNA polymerase θ reduces the viability of glioma and melanoma cells by around 50%, through the induction of apoptosis, accompanied by a reduction in cell proliferation and elevated DNA damage. Combination therapy with θ polymerase inhibitors and PARP1 or RAD52 results in an increased anti-tumor effect against glioma and melanoma, compared to single application of these compounds, most likely by inducing synthetic lethality. The addition of alkylating compounds temozolomide or dacarbazine for dual inhibition of repair proteins can significantly increase treatment efficacy, although it is also associated with increased toxicity to normal cells.

In conclusion, based on the results we presume that inhibition of Polθ with simultaneous inhibition of PARP or Rad52 brings a synthetically lethal effect on glioblastoma and melanoma cells, having a minimal effect on normal cells. Moreover, the addition of alkylating drug strengthens the anticancer effect.