Abstract

Radiation and genotoxic drugs after more than 70 years since their discovery still belong to the cornerstones of cancer treatment. However, these types of therapy often suffer from severe adverse effects and resistance caused by DNA repair mechanisms. The basic feature of cancer cells is genome instability, leading to various mutations and upregulated or otherwise defective DNA repair, making the cancer cells vulnerable to additional interference with the DNA damage response (DDR) mechanisms. This is the fundamental idea behind the DDR targeted therapy, which has been thoroughly studied for almost two decades. The main goals of this therapy is an improvement of the efficacy of DNA damaging treatments leading to lesser doses and adverse effects but also enabling selective targeting of defective cancer cells. The development of this area of research was very slow at the onset, but last few years it finally brought the first compound into therapy and several others into clinical trials.

Among the plethora of signal and effector proteins involved in DDR, three related kinases ATM (ataxia telangiectasia mutated), ATR (ATM and Rad3-related) and DNA-PK (DNA-dependent protein kinase) play the principal roles in initiation and regulation of signaling pathways in response to DNA double and single strand breaks (DSB and SSB). I have focused my research on these three kinases, and during my studies, I have designed and synthesized three sets of compounds, which were then tested as chemo- and radio- sensitizers. Several compounds proved to be very potent in different cancer cell lines and will be submitted to more advanced biological testing.