Abstract

The frequent cause of failure of prostate carcinoma radiotherapy and chemotherapy is the emergence of resistance and a progress into the essentially incurable metastatic form of disease. Although the mechanisms of the radioresistance and chemoresistance are still not well understood, recent studies indicate that transcription factor Snail, a key mediator of the epithelial-mesenchymal transition and subsequent metastasis formation, plays a critical role in the development of the chemoresistance and radioresistance in the tumor cells. As the activation of the optimal DNA damage response pathway is the determining factor for the cell survival after chemotherapy and radiotherapy, we hypothesized the role of Snail in the transcription regulation of these processes. In this study, we first analyzed the relationship between Snail and ATM kinase, as the ATM was recently reported to regulate stability of Snail by its phosphorylation. Although, we observed a modest effect of ATM inhibition on Snail levels after cancer cells exposure to ionizing radiation, we did not fully reproduced the recently published findings. Furthermore, we evaluated the role of Snail in transcription regulation of cyclin-dependent kinase inhibitor $p21^{waf1/cip1}$. Our data point towards the suppressive role of Snail in $p21^{waf1/cip1}$ regulation, independent on the status of tumor suppressor p53. Finally, we attempted to identify the novel Snail transcriptional target genes, specifically those involved in the DNA damage response. Based on presence of putative Snail DNA binding elements (E-boxes) in their promoter regions, we selected two factors known to function in DNA damage response and cell cycle regulation - hSSB1 and CCNB3 - as potential transcription targets of Snail. However, manipulating Snail levels by ectopic overexpression or knock-down by RNA interference had no effect on mRNA levels of these two selected genes.