ABSTRACT

Cancer is a complex of diseases caused by mutational alterations of normal cells and is a leading cause of death worldwide. Transforming events in the context of cancer include deregulated expression or activation of oncogenes and inactivation of tumor suppressors, one of which is ATM. The ATM kinase serves as a guardian of genome stability, playing a key role in the DNA damage response (DDR). Activated by DNA double strand breaks (DSBs), ATM triggers a number of signaling cascades, inducing cell cycle arrest and DNA repair via homologous recombination (HR) or, in cases of excessive damage, apoptosis. ATM-deficiency on the organismal level is characterized by a complex phenotype that involves reduced overall survival, enhanced radiosensitivity, and predisposition to cancer, mainly of hematopoietic origin. ATM-deficient cancer cells strongly rely on non-homologous end joining (NHEJ) and its central player, DNA-PKcs (DNA-dependent protein kinase, catalytic subunit), as a dominant remaining pathway to repair DSBs. Thus, DNA-PKcs is a promising target in ATM-deficient cancers. Though cancer-related ATM inactivation is typically associated with poor prognosis, it is currently unknown whether ATM-deficient cancer cells rely on a consistent absence of ATM. Examples from related tumor suppressors, such as TP53 and BRCA2, show that restoration of the missing tumor suppressor can lead to dramatic tumor regression (TP53), but can also be tolerated by malignant cells (BRCA2).

In this work, we aim to characterize DNA-PKcs as a therapeutic target in ATM-defective cancers and to investigate the role of ATM re-expression in initially ATM-deficient malignancies.

In a set of experiments performed in ATM pro- and deficient settings, we were able to confirm the addiction of ATM-deficient human and murine cells to DNA-PKcs. We could also show the tolerance of ATM-wildtype cells to DNA-PKcs inhibitors, illustrating the advantages of these molecules as potential therapeutics, due to the lack of toxicity in normal tissues. We further revealed the inability of ATM-deficient cells to repair DNA lesions when DNA-PKcs was inhibited. Finally, we demonstrate that DNA-PKcs inhibitors are effective in an Atm-defective murine model of Myc-driven B-cell Non-Hodgkin Lymphoma (B-NHL), and can prolong survival of lymphoma-bearing mice.
In order to investigate the biological effects of ATM re-expression in cancer, we generated a reactivatable Atm allele, which phenocopies Atm-knockout mutants with regard to radiosensitivity, defects in immune cell maturation, and cancer predisposition. We show that Atm reactivation in autochthonous T cell lymphomas and Myc-driven B-NHLs induces lymphoma regression. We further employed transplantation experiments to distinguish between Atm reactivation in cancer cells and non-cancerous tumor stroma, and revealed both cell autonomous and non-cell autonomous effects of ATM re-expression.

Together, our data suggest that DNA-PKcs is a potential drug target for the treatment of ATM-defective malignancies. Furthermore, this data served as a background for initiation of a phase I clinical trial, aiming to assess the safety and tolerability of a dual DNA-PKcs and mammalian target of rapamycin (mTOR) inhibitor for patients with advanced solid tumors and hematologic malignancies. Our results also demonstrate that a continued absence of Atm expression is critical for the in vivo maintenance of an oncogenic state in B- and T cell lymphomas. In addition, our data indicates that impaired immune surveillance contributes to cancer predisposition in Ataxia-telangiectasia (A-T) patients, suggesting transplantation of ATM-proficient immune cells as a possible approach for cancer treatment in this patient group.