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Abstract

Exploiting DNA Repair Defect in Triple Negative Breast Cancer Using CDK Inhibition Strategy †

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Abstract: Triple-negative breast cancer (TNBC), representing 15% of breast carcinomas, is an aggressive breast cancer subtype with a high probability of metastasis and limited treatment options. Noticeably, BRCA-deficiency occurs in 25% of the TNBCs and results in deficient homologous recombination (HR) repair. Interestingly, PARP inhibitors (PARPi) have shown synthetic lethality in a BRCA-deficient context; however, their efficacy is frequently hampered by intrinsic or acquired resistance mechanisms involving restoration of the HR. In that regard, the role of some CDKs proven to regulate key HR actors was of interest to us. In this study, we aimed to understand the rewiring pathways determining resistance to PARPi in BRCA-deficient cancers and to assess the role of transcriptional regulating CDKs such as CDK7, CDK9, or CDK12 in the transcriptional regulation of key HR genes. Our ultimate goal was to determine whether and which CDK inhibitors could be effective approaches to repress HR gene expression and induce pharmacological HR-deficiency. As such, these CDK-inhibitors (CDKi) could be molecules of choice allowing sensitization of tumors that would otherwise respond poorly to DNA damaging treatment. With this purpose, we used in vitro and in vivo (PDX) models of TNBC and studied the attenuation of the HR response in tumor cells and PDX models treated with CDK-inhibitors. Our final aim was to determine the most efficient combination of CDKi and PARPi Our HR read outs were RAD51 and BRCA1 foci formation upon PARPi treatment. We also measured the modification of RNA and protein expression levels induced by CDKi treatment on a series of diagnostic HR genes (BRCA2, PALB2, ATR, FANCD2), as a measure of HR repression. We present data comparing the relative efficiency of three 3 CDKi; dinaciclib, NVP-2, and SR-4835, which have different specificities and inhibit different CDKs with variable efficacy.

Keywords: Triple Negative Breast Cancer; PARP; CDK; DNA damage; homologous recombination; BRCA-deficiency

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