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Ex vivo DNA damage response assays in tumor slices to predict therapy response

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One of the hallmarks of cancer is genomic instability, which has been studied extensively in tumor cell lines. It has been much more difficult to study how DNA damage response (DDR) pathways operate in living tumors. Therefore, we developed several techniques to grow short term tumor cell cultures or tumor slices 'ex vivo' and study the DDR by inducing DNA damage in cultured tumor cells or slices. Several DNA repair proteins accumulate as visible foci on DNA double strand breaks (DSBs). We used this phenomenon to study accumulation of the general markers of DNA breaks (gamma-H2AX and 53BP1) and the homologous recombination repair pathway (RAD51) after DSB induction. BRCA1 or BRCA2 deficiency has been shown before to lead to a defect in RAD51 foci formation. We were able to show that BRCA1 deficient and proficient xenograft tumors could be discriminated well on the basis of this assay. We also screened human tumors and found that a BRCA1 deficient tumor metastasis was RAD51 foci deficient, while most sporadic tumors were proficient. Interestingly, we were also able to identify a sporadic tumor that was RAD51 foci deficient. This tumor slice also showed high sensitivity to PARP inhibitor treatment, another hallmark of BRCA1/2 deficient cells. Therefore, we conclude that we developed a robust assay for identifying BRCAdeficient tumors, which will be important to select patients for PARP inhibitor treatment. Furthermore, other therapeutic interventions can also be tested in this system, which maintains tumor slice integrity and proliferation for at least one week.

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