A pan-cancer analysis of inferred homologous recombination deficiency identifies potential platinum benefit in novel subtypes

Personalized medicine in cancer aims to improve treatment outcome, by exploiting the molecular alterations of the individual tumor to inform therapeutic decisions. Ovarian and triple-negative breast cancers with defects in homologous recombination (HR) DNA repair are highly sensitive to treatment with platinum-based DNA-damaging agents. Reliable biomarkers to identify HR-deficient cancers prior to the initial treatment may be used to stratify patients for platinum chemotherapy. Extensive genome damage caused by deficient HR is readily observed as high frequencies of allelic imbalance and loss of heterozygosity in cancers with loss of either of the tumor suppressor genes BRCA1 or BRCA2, but is also common in ovarian and triple-negative breast cancers with no BRCA1/2 mutations, indicating HR loss due to alternative mechanisms. Recently, three independent methods were published that each quantitate the state of HR deficiency in a given cancer, by summarizing different types of DNA aberrations that are likely to be caused by improper DNA repair. Here we compare the three scores, named NtAI (1), LST (2), and HRD (3), utilizing a panel of 4400 patients representing 13 cancer types from The Cancer Genome Atlas. We found that the three scores are highly correlated with each other, suggesting they measure the effect of similar types of DNA damage. We found a strong association with overall survival only in ovarian cancer, which is consistent with frequent BRCA-related HR deficiency reported for this type of cancer. Next, we compared the distribution of the scores across cancer types, and found that those types ordinarily receiving platinum as standard of care have the highest median scores. Importantly, in most types not generally given platinum chemotherapy we also found small sub-populations of high scoring tumors, which may represent subtypes with a previously overlooked potential to respond to platinum agents. Lastly, we used RNAseq to identify genes whose expression is associated with high DNA aberration scores. We compared the 100 genes most highly correlated with each score and found a shared set of 53 genes; these were enriched for genes involved in cell cycle progression, mitosis and chromosome segregation. This suggests that replication stress, perhaps combined with or induced by HR deficiency, could play a role in the generation of the measured DNA aberrations. Overall, our results demonstrate that the three methods measure correlated aberration patterns possibly generated through replication stress, and that they show prognostic potential in patients who receive platinum chemotherapy. In addition, we identify subsets of patients suffering from cancers not presently receiving platinum chemotherapy, who may benefit from it.

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