Pan-cancer analysis of genomic scar signatures associated with homologous recombination deficiency suggests novel indications for existing cancer drugs - DTU Orbit (30/08/2017)

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Ovarian and triple-negative breast cancers with BRCA1 or BRCA2 loss are highly sensitive to treatment with PARP inhibitors and platinum-based cytotoxic agents and show an accumulation of genomic scars in the form of gross DNA copy number aberrations. Cancers without BRCA1 or BRCA2 loss but with accumulation of similar genomic scars also show increased sensitivity to platinum-based chemotherapy. Therefore, reliable biomarkers to identify DNA repair-deficient cancers prior to treatment may be useful for directing patients to platinum chemotherapy and possibly PARP inhibitors. Recently, three SNP array-based signatures of chromosomal instability were published that each quantitate a distinct type of genomic scar considered likely to be caused by improper DNA repair. They measure telomeric allelic imbalance (named NtAI), large scale transition (named LST), and loss of heterozygosity (named HRD-LOH), and it is suggested that these signatures may act as biomarkers for the state of DNA repair deficiency in a given cancer. We explored the pan-cancer distribution of scores of the three signatures utilizing a panel of 5371 tumors representing 15 cancer types from The Cancer Genome Atlas, and found a good correlation between scores of the three signatures (Spearman's ρ 0.73-0.87). In addition we found that cancer types ordinarily receiving platinum as standard of care have higher median scores of all three signatures. Interestingly, we also found that smaller subpopulations of high-scoring tumors exist in most cancer types, including those for which platinum chemotherapy is not standard therapy. Within several cancer types that are not ordinarily treated with platinum chemotherapy, we identified tumors with high levels of the three genomic biomarkers. These tumors represent identifiable subtypes of patients which may be strong candidates for clinical trials with PARP inhibitors or platinum-based chemotherapeutic regimens.

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