Advancing cancer genomics

The field of cancer genomics is currently in an exciting and fast-paced era. With advances in sequencing technologies, computational approaches and tumor models, understanding of cancer processes is at an all-time high, and the application of new methods to studying cancer holds great promise for developing important breakthroughs in cancer treatment and prevention.

Last month, the American Association for Cancer Research (AACR) hosted its annual meeting (https://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=174), where more than 22,000 participants gathered to report and discuss the latest developments in cancer research. We were particularly excited to hear about impressive innovations in the realm of genetics and genomics, from single-cell analysis to patient-derived organoids to mathematical models of tumor evolution. In this month's issue, we are pleased to feature a trio of studies that have taken interesting approaches to analyzing the genetics of cancer.

New statistical methods are advancing understanding of germline risk variants for cancer. Gusev et al. present a transcriptome-wide association study (TWAS) of high-grade serous epithelial ovarian cancer, identifying putative causal genes associated with susceptibility. The TWAS approach identifies genetic predictors of gene expression levels from samples with both genotype and expression information. These genetic predictors can then be analyzed in larger cohorts that lack such gene expression information. TWAS hits identify differentially modulated genes that can be prioritized as causal for disease risk. In this study, Gusev et al. built gene models from expression quantitative trait loci (eQTL) and alternative-splicing quantitative trait loci data from tissues relevant to ovarian cancer, and integrated these with a large ovarian cancer genome-wide association study (GWAS) dataset. They nominated 25 candidate susceptibility genes and performed in vitro functional experiments to validate some of the candidates. The combination of approaches used makes this insightful analysis a strong model for future cancer TWAS efforts.

Cancer mutation signatures represent the cumulative outcome of DNA damage and repair processes. These genomic readouts can present information about potential responses to specific therapies, even without identifying an underlying genetic mutation. This method is especially relevant for homologous-recombination-deficient cancers, which can respond well to inhibition of poly(ADP–ribose) polymerase (PARP). Gulhan et al. present SigMA, a computational tool that can detect homologous-recombination-deficiency mutation signatures from sequencing data obtained from targeted gene panels. Circumventing the need for genome or exome sequencing data and removing the ambiguity of determining the pathogenicity of gene-specific mutations can greatly expand the clinical utility of mutation signatures as classifiers of therapy response. Indeed, the authors show that patients with ovarian cancer identified as being homologous-recombination deficient have longer overall survival with platinum therapy treatment. Thus, in addition to being informative about the underlying biological mechanisms contributing to tumor formation, mutation signatures have the potential to be a clinically useful tool for better precision medicine.

The need for more accurate models of cancer initiation, evolution and treatment response is critical for translating basic-research discoveries into clinically relevant information. Bolhaqueiro et al. derived tumor organoids from colorectal cancer patients and analyzed chromosome instability over time. The use of organoids specifically enables tracking of aneuploidy and segregation errors, as well as determining the heterogeneity of these processes. In addition to observing chromosome-instability phenotypes through live microscopy, the authors performed single-cell sequencing to assess variations in karyotype. They found higher cell-to-cell heterogeneity in tumor organoids with higher chromosome instability. Because organoid models are amenable to manipulation and analysis, they can be used to study tumor dynamics at unprecedented resolution. Thus, patient-derived organoids provide an experimental platform for analyzing temporal dimensions of cancer in a controlled manner.

Where is cancer genetics heading? Single-cell analysis and spatial transcriptomics are rapidly moving to the forefront as ways of understanding tumor heterogeneity and the tumor microenvironment. Characterizing interactions with the immune system and predicting responses to immune-checkpoint inhibitors will be important for developing more efficient therapies. Understanding is needed regarding how tumor cells evolve, metastasize and respond to treatment, and what factors, genomic and otherwise, contribute to these processes. We are interested in studies of epigenetic dysregulation in cancer and of how non-coding somatic variation affects tumorigenesis. Importantly, framing the emergence of resistance as an inevitable outcome of cancer therapy calls for adjusting the approach to diagnosis and treatment. Better mathematical and experimental models are needed to explore these questions, and we are excited to see progress in these areas.

As we think about the future of cancer genetics, we are delighted to welcome into this exciting arena our new sister journal, *Nature Cancer* (https://www.nature.com/natcancer/), which aims to publish studies relevant to all aspects of cancer research, from basic preclinical studies to translational and clinical work. Having a dedicated cancer journal of broad scope will reinforce and complement our focus on the genetics and genomics of cancer, and bring a fresh, holistic perspective to this challenging disease. We eagerly await the conceptual, methodological and clinical advances that are emerging from all areas of cancer research, a dynamic field that is becoming increasingly comprehensive and cross-disciplinary. ❐

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