Molecular pathology selected abstracts

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Classifying tumors by immune archetype as an approach to immunotherapy

March 2022—Why are immunotherapies effective for some patients but not others—even among those with the same histologic tumor type and similar mutational burdens? To address this important clinical question, members of the Immunoprofiler Initiative (IPI) at the University of California, San Francisco hypothesized that the response of an individual tumor to immunotherapeutic agents is likely dependent not just on the biologic characteristics intrinsic to the tumor cell but also the complex interactions taking place in the nearby immune microenvironment. To characterize the cells and immune processes taking place in the tumor immune microenvironment, the IPI investigators obtained fresh tumor tissue from 364 tumor biopsies across 12 cancer types and categorized the tumors into clustered groups based on the detailed characteristics of each tumor's immune microenvironment. The tumor types studied included melanoma, pancreatic ductal carcinoma, bladder carcinoma, sarcoma, gynecologic tumors, colorectal carcinoma, hepatocellular carcinoma, head/neck tumors, primitive neuro-ectodermal tumor, glioblastoma, lung adenocarcinoma, and renal cell carcinoma. The complex data used for this analysis came from cell imaging, flow cytometric identification of the heterogeneous immune and stromal cell types populating the tumor microenvironment, and comprehensive transcriptomic data obtained from the subcompartments of these tumor and nontumor cells. The tumor microenvironments of these diverse tumor types comprised a wide variety of immune cells, including myeloid cells, macrophages, NK cells, and B cells. The heterogeneity of these immune cells exceeded that of the focused T lymphocytes that are the target of current immunotherapies. The IPI investigators applied an unbiased clustering approach to the heterogeneous data to categorize the tumors into 12 groups that they referred to as immune archetypes. They also showed that the immune archetype of a particular histologic tumor type is not unique and that the same immune archetype is often shared across widely divergent tumor types. Some archetypes were drawn from a few cancer subtypes, while others were drawn from many. For example, some bladder carcinomas have an immune archetype similar to that of some lung tumors, but they may have a different immune archetype than other bladder carcinomas that appear to share the same cell type origin and tumor cell immunophenotype. The implications of this immune archetype heterogeneity for immunotherapeutics may be profound. Immunotherapies used to treat some tumors, for instance, may be targeting immune cells or immunologic processes, or both, that may be absent or downregulated in a particular tumor. This may explain some of the observed heterogeneity of antitumor responses to these agents. Therefore, future clinical trials of novel immunotherapies may use patient-stratification procedures based not only on the intrinsic properties of the tumor cell or its histologic subtype but also the immune archetype of the tumor microenvironment. The responses and nonresponses to these novel immunotherapies may ultimately depend on whether the tumors have the same immune archetype classifications. The data generated through the IPI's research can provide a template for understanding cancer immunity and serve as a framework for directing immunotherapies so they are most beneficial.

Combes AJ, Samad B, Tsui J, et al. Discovering dominant tumor immune archetypes in a pan-cancer census. *Cell*. 2022;185:184–203.

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Use of a screening molecular diagnostic blood test in early pregnancy to predict pre-eclampsia

Pre-eclampsia is a common cause of maternal morbidity, affecting approximately five percent of pregnancies worldwide and leading to such significant adverse outcomes as intra-uterine growth restriction, preterm birth, placental abruption, fetal distress, and fetal death. It also has long-term chronic disease sequela, including maternal hypertension and cardiovascular disease. Pre-eclampsia typically is not diagnosed until late in pregnancy, despite the placental disease-defining pathogenic processes having originated much earlier. The authors created and validated a novel molecular diagnostic maternal blood test to characterize women who are at risk of the disease months before it presents clinically, when intervention may be more effective. They analyzed the longitudinal transcriptional profiles of 1,840 normal pregnancies (2,539 samples) among women of diverse ages, geographies, body mass indices, and races using cell-free RNA (cfRNA) obtained from plasma via a simple blood draw. These analyses initially were used to create a detailed definition of gestational age and normal fetal, placental, and maternal changes in gene expression across the gestational timeline. For comparison purposes, the authors developed a detailed cfRNA transcriptional profile from 524 blood samples of 72 pre-eclamptic women and 452 control cases drawn 14.5 weeks before delivery. They identified seven genes with expression levels specific for pre-eclampsia. The authors then created a mathematical model using the disease and normal cfRNA transcriptional profiles to estimate the probability of future pre-eclampsia. They showed that the cfRNA profile of a single early pregnancy blood sample could predict pre-eclampsia with a sensitivity of 75 percent and a positive predictive value of 32 percent. This represents a sevenfold improvement in positive predictive value over the current gold standard predictive pre-eclampsia methods, which rely on ultrasound testing in patients already considered at risk due to hypertension. Consensus-management guidelines for hypertension during pregnancy include using low-dose aspirin. However, identifying which patients should adhere to such a regimen has been challenging, particularly in first pregnancies. With the ability of this new test to better predict those at future risk of pre-eclampsia at an earlier stage, obstetricians may be able to target treatment to the right patients; begin therapy sooner in the disease course, when it will be more effective; and, perhaps more importantly, test new preventative treatments for this common disease as they become available. The concept of using the cfRNA from blood to define the normal longitudinal profile of gene-expression events during pregnancy should provide promising insights into the biology of many other pathologic processes of pregnancy and may contribute to novel interventions to prevent or treat them.

Rasmussen M, Reddy M, Nolan R, et al. RNA profiles reveal signatures of future health and disease in pregnancy. *Nature*. 2022;601:422–427.

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