Battling cancer, one cell at a time

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New research suggests that the identification and examination of key cell signaling events required for initiation and progression of cancer might be best accomplished at the single cell level. The research, published by Cell Press in the October issue of the journal *Cancer Cell,* provides new insight that may lead to better diagnosis and treatment of some complex cancers.

Recent advances in flow cytometry, a technique that allows detailed examination of individual cells, have enabled simultaneous measurement of cell type and signaling pathways. Lead study authors Dr. Garry P. Nolan from the Stanford University School of Medicine and Dr. Mignon L. Loh from the UCSF Children's Hospital and the Helen Diller Family Comprehensive Cancer Center were interested in determining whether examination of cellular signaling abnormalities caused by genetic mutations associated with cancer could provide a precise correlation between aberrant signaling events and disease physiology.

"We had a strong hunch that we could use 'deranged' cellular signaling to track how cancer cell populations behave at diagnosis through therapy, as well as during remission or return of the cancer," explains Dr. Nolan. "By measuring how signaling proteins respond to certain stimuli at diagnosis and which are modified by resistant cancers, we are essentially monitoring key highways that cancers use to drive their own growth. The advantage of diagnosing a patient's cancer at the single cell level provides us an approach for early detection of cancer and yield insights into how cancer cells are responding or adapting to therapy. A byproduct of the single cell technique, when appropriately extended, is that we should eventually be able to predict those pathways cancer cells might be using to circumvent current therapies and more intelligently direct the patient towards alternative treatments."

The researchers focused on juvenile myelomonocytic leukemia (JMML), an aggressive myeloproliferative disorder of young children. JMML is difficult to diagnose and has a complex molecular profile. Although genetic lesions impacting Ras signaling and alterations downstream of the activated GM-CSF receptor (both linked with inappropriate cell growth and survival) have been linked with JMML, there are very few methods for identifying therapeutic agents and assessing efficacy in JMML patients.

The researchers used flow cytometry to profile signaling at the single cell level, including molecules associated with GM-CSF and Ras signaling, for the presence of primary JMML cells with altered signaling behavior that correlated with disease physiology. Cells samples came from JMML patients, healthy individuals and patients with other myeloproliferative disorders, some who had initially been diagnosed with JMML. An unexpected STAT5 signaling signature was seen in most of the JMML patients, suggesting a critical role for JAK-STAT signaling in the biological mechanism of this cancer and suggesting potential targets for future therapies.

"This work successfully used single-cell profiling to follow patients over time and show that disease status in JMML – at diagnosis, remission, relapse and transformation – was indicated by a subset of cells with an abnormal signaling profile," says Dr. Loh. "Revealing cell subpopulations, even rare cells, that are associated with disease opens additional avenues for measuring minimal residual disease, assessing biochemical effects of targeted therapies at the single cell level and understanding drug actions and mechanisms of diseases of heterogeneous origins and manifestations in diverse patient populations."

Source: Cell Press

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