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Study provides first systematic survey of metabolites across tumor types

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In an advance reminiscent of the earliest maps of genomic mutations in cancer, investigators at Dana-Farber Cancer Institute and Memorial Sloan Kettering Cancer Center have completed the first systematic survey of the products of biochemical reactions within cancer and their relation to the progress of the disease. The products, known as metabolites, arise from the myriad chemical reactions that keep cells alive and functioning.

Published online today by the journal *Cell Systems*, the survey results provide scientists around the world with a curated dataset with which to track metabolic changes in cancer cells and potentially uncover vulnerabilities that can be targeted by novel therapies. A website accompanying the new report enables researchers to study patterns of variation in metabolite levels across multiple types of cancers, explore how these patterns change as cancers progress, and look for connections between metabolites and drug susceptibility.

"Scientists have known for more than 100 years that metabolic changes are important in cancer, but over the last three decades the field has been dominated by discoveries of the genetic and genomic changes that occur in cancer cells," says the study's senior author, Chris Sander, PhD, of Dana-Farber. "In the last five to 10 years, there has been a resurgence of cancer metabolism research - with a focus on the differences in the metabolic functioning of cancer cells vs. normal cells - and in using that knowledge as the basis for new therapies. The drug methotrexate and, more recently, drugs that inhibit enzymes such as glutaminase or

isocitrate dehydrogenase, are excellent examples. We think there is more to come."

The revival has been propelled in part by technological advances that enable scientists to identify large numbers of the metabolites present in normal and cancerous cells - much as advances 20 years ago have made it possible to canvas cells for hundreds or thousands of genomic irregularities.

Metabolism is the catchall term for processes that drive every aspect of cell life - consuming energy, growing, dividing, and performing specific functions within the body. It is as basic to the life of normal cells as to cancer cells, although their metabolisms can differ in a variety of ways. Much of cell metabolism involves chemical reactions sparked by enzymes. The products of these reactions are metabolites, which themselves can interact to form other metabolites. The assortment of metabolites within a cell is referred to as its metabolome.

For the current study, researchers built a broad dataset of cancer cell metabolites by merging data from 11 studies involving more than 900 tumor tissue samples and seven different cancer types. Their analysis of the data showed that the composition of metabolites in normal tissue is often far different from that in corresponding types of tumor tissue. Across many tumor types, however, the investigators found that several metabolites showed consistent increases or decreases in abundance compared to normal tissue.

The researchers also collected data on the stage and grade of each tumor (measures of tumor progression and aggressiveness). By linking this data to the metabolite data, they found that a small number of metabolites were associated with aggressive tumors in many cancer types. One such metabolite, kynurenine, which was elevated in aggressive tumors regardless of where they originated, is known to help cells evade an

attack from the immune system. "Our findings offer the most comprehensive look to date at the differences in metabolic programming between normal and cancer cells, and across various kinds of cancer," says Ed Reznik, PhD, of Memorial Sloan Kettering, the co-lead author of the study with Augustin Luna, PhD, of Dana-Farber. "We expect the metabolomics dataset will be an important tool as the field of cancer metabolism moves forward."

Provided by Dana-Farber Cancer Institute

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