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Using a 'systems biology' approach to look under the hood of an aggressive form of breast cancer

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Using a "systems biology" approach – which focuses on understanding the complex relationships between biological systems – to look under the hood of an aggressive form of breast cancer, researchers for the first time have identified a set of proteins in the blood that change in abundance long before the cancer is clinically detectable. The findings, by co-authors Christopher Kemp, Ph.D., and Samir Hanash, M.D., Ph.D., members of Fred Hutchinson Cancer Research Center's Human Biology and Public Health Sciences divisions, respectively, are published online ahead of the Aug. 1 print issue of *Cancer Research*.

Studying a mouse model of HER2-positive breast cancer (cancer that tests positive for a protein called human epidermal growth factor receptor 2) at various stages of tumor development and remission, the researchers found that even at the very earliest stages the incipient tumor cells communicate to normal tissues of the host by sending out signals and recruiting cells, while the host tissues in turn respond to and amplify the signals.

"It is really a 'systems biology' study of cancer, in that we simultaneously examined many genes and proteins over time – not just in the tumor but in blood and host tissues." Kemp said. "The overall surprising thing we found was the degree to which the host responds to cancer early in the course of disease progression, and the extent of that response. While a mouse – or presumably a human – with early-stage cancer may appear

normal, our study shows that there are many changes occurring long before the disease can be detected clinically. This gives us hope that we should be able to identify those changes and use them as early detection tools with the ultimate goal of more effective intervention."

Traditionally, it has been thought that tumor cells shed telltale proteins into the blood or elicit an immune response that can lead to changes in blood-protein levels. "What is new here is that the predominant protein signals we see in blood originate from complex interactions and crosstalk between the tumor cells and the local host microenvironment," Kemp said.

Until now, such tumor/host interactions have been primarily studied one gene at a time locally, within the tumor; this is the first study to monitor the systemic response to cancer in a preclinical tumor model, tracking the abundance of cancer-related proteins throughout tumor induction, growth, and regression. Of approximately 500 proteins detected, up to a third changed in abundance; the number increased with cancer growth and decreased with tumor regression.

"We found a treasure trove of proteins that are involved in a variety of mechanisms related to cancer development, from the formation of blood vessels that feed tumors to signatures of early cancer spread, or metastasis," Kemp said.

Proteins associated with wound repair were most prevalent during the earliest stages of cancer growth, which could point to a potential target for early cancer detection. "Rather than blindly search for cancer biomarkers, an approach based on comprehensive understanding of the systems biology of the disease process is likely to increase the chances to identify blood-based biomarkers that will work in the clinic," Kemp said.

The next steps will involve selecting the most promising protein

candidates found in mice and determining whether the same circulating proteins are markers of early breast cancer development in humans, with the ultimate goal of designing a blood test for earlier breast cancer detection.

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