

FEBRUARY 08, 2005

Genetic Signature May Predict Breast Cancer Survival

Howard Hughes Medical Institute researchers have discovered that the activation of specific components of the genetic machinery used to close a wound may also be a powerful predictor of which breast cancers are likely to spread and which women are likely to survive the disease.

The researchers said their findings would give clinicians an important tool for planning breast cancer therapies—for example, distinguishing patients who will benefit from chemotherapy from those who may not. The new findings build on earlier studies that demonstrated that activation of genes involved in repairing wounds is also a characteristic shared by epithelial-tissue cancers, such as breast, lung and gastric cancers.

Led by Marc van de Vijver of the Netherlands Cancer Institute and Howard Hughes Medical Institute investigator Patrick O. Brown, the researchers published their findings February 8, 2005, in the early online edition of the *Proceedings of the National Academy of Sciences*. Brown, postdoctoral fellow Howard Chang and colleagues at Stanford University School of Medicine collaborated on the studies with researchers from the Netherlands Cancer Institute, Rosetta Inpharmatics in Seattle and the Norwegian Radium Hospital.

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- Patrick O. Brown

In earlier studies published last year in the open-access journal *PLoS Biology*, Brown, Chang and colleagues discovered that treating skin cells, called fibroblasts, in culture with blood serum—an important initiator of wound healing—switches on a characteristic set of wound-response genes. Such

genes—which trigger cell migration, tissue remodeling, blood vessel growth and other wound-healing processes—were also thought to be activated in cancers. Indeed, the researchers found in the earlier studies that the genetic “wound-response signature” is predictive of poor survival and increased metastasis in breast, lung and gastric cancers.

“Those initial studies pointed to a strong pathogenetic link between the wound response and cancer and they provided an experimental model that we could use to study the underlying mechanisms,” said Brown. “Secondly, they strongly suggested that the molecular signature of the wound-response would be a clinically useful tool for recognizing at an early stage which cancers are at high risk of progression.”

To test the prognostic value of the wound-response signature, Brown and Chang collaborated with van de Vijver and his colleagues to apply their analysis using the signature to a group of 295 breast cancer patients at the Netherlands Cancer Institute. These patients had been genetically profiled as part of an earlier study to determine the prognostic value of 70 genes that had been shown to correlate with cancer progression.

“The data from this group of patients were particularly valuable because this is the largest cohort of patients who have had these gene expression profiles done and for which there is long term follow-up and other extensive clinical information,” said Brown. “This gave us a chance to obtain a strong independent test of the performance of the wound-healing signature. Also, we could compare its performance to classic clinical risk markers and learn how best to integrate information with that from another gene-expression signature.”

Integrating multiple prognostic factors will be important for clinical application, said Brown, because “clinicians don't want to just pick one or another prognostic factor and use it in isolation. Rather, they want to be able to take into account all the available information and make the best treatment decision.”

When the researchers applied the wound-response signature to the genetic data from the patients, they found that it provided useful new prognostic information. Breast cancers with the activated wound-response genetic signature were twice as likely to recur with distant metastases and the patients were three times as likely to die within 10 years as those with a “quiescent” wound signature.

The researchers then incorporated the wound-response signature into an analytical model that included other clinical parameters—including lymph node status, estrogen receptor status, tumor size, and histological grade—characteristics that are traditionally used to predict risk. They then tested that model on a clinical decision-making scenario to see how well the model could assess the value of treating patients with adjuvant chemotherapy

in addition to surgery and radiotherapy. While adjuvant chemotherapy improves outcomes in those with high risk of metastasis, exposure to chemotherapy for patients who do not need it presents an unwarranted risk.

Since the researchers already had the outcomes of such treatment as part of their data on the patients, they could determine how well their integrated model predicted the treatment's value. The researchers could also use the data to analyze how effectively the wound-response signature contributed to the decision to pursue a particular course of treatment.

“What we found was a surprise—that the wound-response signature, of all the factors, provided the most information,” said Brown. “It's non-redundant, providing a lot of independent information over and above what we would have derived from looking at all the classical prognostic markers.”

The researchers also found that when they integrated three diverse gene expression signatures, including the wound-response signature, to evaluate the patients, they all gave consistent predictions of outcomes.

“I believe that we will discover more of these gene expression signatures that reflect specific physiological features of tumors that we can then integrate into better predictive models,” said Brown. “And they will do a lot better at predicting the risk of metastasis and progression for individual patients than clinical prognostic markers now being used. And as we get better at predicting whether a cancer is likely to recur or metastasize, we can do a better job of balancing the risks and benefits of various kinds of treatments such as chemotherapy.”

This work demonstrates an emerging strategy and a way to look more intelligently at microarray data," said James Jacobson, chief of the National Cancer Institute's Diagnostic Biomarkers and Technology Branch. "There are a number of strategies like this going forward. They will need further clinical evaluation, but I think they hold a lot of promise. The data seem to correlate with important clinical parameters, and perhaps more importantly, they may provide us with additional targets for therapy.

Currently, Brown and his colleagues are developing simpler assays to measure the wound-response signature than the more complex DNA microarrays that the researchers used to analyze gene activity in this study. These assays under development—which could be more readily used in clinical laboratories—use antibody-based markers that react with proteins produced by activated wound-response genes to define the wound response signature.

Brown emphasized that the increasing links between an activated wound-response signature and cancer makes the wound-response machinery an even more important target of study to understand such cancers.

“We have a cell culture model in which we can explore the molecular signaling mechanisms involved in regulating this response,” he said. “And if we find that some of these molecular players have a causative role in promoting progression and metastasis, we have a potential route for developing inhibitors of this response.”