One Step Forward Toward Identification of the Genetic Signature of Glioblastomas

Boris Pasche; Richard M. Myers


http://jama.ama-assn.org/cgi/content/full/302/3/325

Contact me if this article is corrected.

Contact me when this article is cited.

Neurology; Neurogenetics; Neurology, Other; Oncology; Brain Cancer; Genetics; Genetic Counseling/ Testing/ Therapy; Genetic Disorders; Genetics, Other

Contact me when new articles are published in these topic areas.
One Step Forward Toward Identification of the Genetic Signature of Glioblastomas

Boris Pasche, MD, PhD
Richard M. Myers, PhD

Cancer is a disease of the genome at the level of gene expression, epigenetic modifications such as DNA methylation, and DNA alterations. For more than 3 decades, many lines of research have shown that acquisition of genetic changes is a major and required step in the development of most cancers. First, ionizing radiation and chemicals that damage DNA and cause mutations also cause cancer.1 Second, genomic alterations such as translocations that result in the production of a specific gene fusion product are associated with some types of cancer. Such is the case for the translocations between chromosomes 9 and 22 in chronic myeloid leukemia and the translocation between chromosomes 15 and 17 in acute promyelocytic leukemia.2 Third, the introduction of genomic DNA from human cancer cells into normal cells can render the normal cells cancerous.3

In the past 2 decades, many genomic alterations have been identified in cancer. Sequencing of the human genome and improved high-throughput DNA sequencing technologies have provided the tools for a comprehensive identification of the most common genetic alterations as well as nongenetic changes in the genome in cancer cells. Identification of these alterations has the potential to unveil the Achilles’ heel of many different forms of cancer. The feasibility of this approach is exemplified by the use of imatinib for the treatment of chronic myeloid leukemia, as the drug effectively blocks the deleterious activity of the single genetic alteration triggering the disease.4

However, most solid tumors, including glioblastoma multiforme (GBM), the deadliest of all brain tumors, exhibit a much more diverse pattern of genetic alterations,5 which until recently had not been comprehensively characterized. Two recent studies of genetic and functional genomic changes throughout the genome in GBM have pointed at key genes and pathways that are altered at the DNA level, at the expression level, or at both. Parsons and colleagues6 sequenced the coding regions of 20661 genes and examined expression of these genes with next-generation DNA sequencing technologies in 22 glioblastomas and identified both known and new key changes in this cancer. In another study, a consortium of scientists in The Cancer Genome Atlas studied genetic, epigenetic, and genomic alterations in 206 GBM tumors compared with controls and identified several known and several new genes that play a role in the development of the disease.7 Two articles in this issue of JAMA take this global genomic approach a step further by identifying and validating networks of altered genes that may play a crucial role in the development and progression of GBM, providing additional potential targets for novel therapies.8,9

While numerous recurrent genetic abnormalities have been discovered in cancer, identifying which ones act as indispensable contributors of disease development and progression and which ones act as mere bystanders is a major challenge that hitherto has not been met. This problem has become particularly acute recently with new next-generation DNA sequencing technologies that sample many more base pairs, even to the level of sequencing of whole genomes, than classic Sanger sequencing.10 This vastly increased capability has allowed investigators to begin identifying a very large number of DNA sequence changes, especially in cancer, so distinguishing which ones are of functional significance and contribute to cancer phenotypes in primary or secondary ways is becoming a critical issue. To begin addressing this problem, Bredel et al10 hypothesized that a combination of distinct chromosomal alterations work together to facilitate gliomagenesis in a cooperative fashion. Their starting material consisted of 45 glioma specimens of varying morphology, which were assessed for the presence of altered gene dosage by using a complementary DNA microarray containing more than 40,000 elements corresponding to more than 27,000 gene clusters, thus providing extensive coverage of known protein-coding genes.

Bredel et al identified 9 networking regions on chromosomes 1, 7, 8, 9, 10, 12, 13, 19, 20, and 22, displaying 37 associations. Then, by analyzing a different set of 219 GBMs that were collected and studied by The Cancer Genome Atlas,7 the same approach revealed a similar association and

See also pp 261 and 276.

©2009 American Medical Association. All rights reserved.

Author Affiliations: Division of Hematology/Oncology, University of Alabama at Birmingham, and UAB Comprehensive Cancer Center, Birmingham (Dr Pasche); and HudsonAlpha Institute for Biotechnology, Huntsville, Alabama (Mr Myers). Dr Pasche is also Contributing Editor, JAMA.

Corresponding Author: Boris Pasche, MD, PhD, Division of Hematology/Oncology, University of Alabama at Birmingham, 1802 Sixth Ave S, NP 2566, Birmingham, AL 35294-3300 (boris.pasche@ccc.uab.edu).
confirmed 21 of the 37 associations. The authors observed that genetic alterations were more likely to reduce rather than to increase gene expression. They also found that the majority of regions involved in tight associations with each other were more likely to have tumor-promoting (83% of genes) and developmental (30%) functions than all gene dosage–driven genes.

To dissect the network of interacting genes, the authors selected genes with the highest level of connectivity and named them “hub” genes. Genes interacting with hub genes and with documented tumor-related biological functions were named “hub-interacting” genes. The interaction among hub genes and hub-interacting genes was integrated based on gene dosage of each gene constituent of a gene pair to identify potential cooperative tumorigenic relationships.

To determine whether the most interactive genes were associated with prognosis, the authors assessed the survival association of gene dosage for 27 highly interactive genes, which had been validated with a separate set of GBMs. They found that 7 of these genes were significantly associated with survival. They further showed that this set of 7 genes was associated with survival across several different groups of patients with GBM.

In the companion paper by Yadav et al., the authors examined the functional relationship between 2 highly interactive genes identified in the first study, annexin A7 (ANXA7) and epidermal growth factor receptor (EGFR), the former underexpressed and the latter overexpressed in a large proportion of GBMs. To mimic the partial loss of ANXA7 observed in GBM, ANXA7 expression was reduced by inhibiting gene expression with a small inhibitory RNA, an effective and specific method to decrease transcript levels. By using this approach, the authors found that GBM cells with decreased ANXA7 have increased tumorigenicity, express significantly higher levels of EGFR, and, importantly, enhance EGFR signaling. To assess whether there is a cooperative effect on gliomagenesis of combined loss of ANXA7 and gain of EGFR, they compared the tumorigenic potential of glioblastoma cells engineered to underexpress ANXA7 and overexpress EGFR. These experiments unveiled a tumorigenic synergism between ANXA7 loss and EGFR amplification.

The potential clinical implications of these findings are significant. First, they highlight a pattern of codependent genetic interactions, which will need to be taken into account when designing novel therapeutic interventions in this otherwise therapy-refractory disease. Second, they provide a novel prognostic tool that may guide future therapeutic interventions.

These findings also underscore the role of haploinsufficiency in brain tumor development and progression and the usefulness of focusing on genes with documented functional relevance. The central role of haploinsufficiency and altered gene dosage in the development of other tumors, such as colorectal cancer, was recently reported for the TGFBR1 gene. Discovery that Tgfbr1 haploinsufficiency acts as a potent modifier of tumor development in a mouse model of colorectal cancer prompted validation in humans and led to the identification of 2 novel haplotypes associated with decreased TGFBR1 allelic expression and markedly increased risk of colorectal cancer. These combined lines of evidence suggest that altered gene dosage may emerge as a genetic hallmark of several forms of cancer.

These articles, particularly the one by Bredel et al., highlight the value of publicly available data sets and clinical information for the study of important diseases like cancer. Similar to the Human Genome Project, very large, comprehensive, genome-wide data sets from projects like The Cancer Genome Atlas and other projects are available to researchers to examine, mine, manipulate, and discover new findings prior to and after publication. No single analysis exhausts the valuable information in such data, and the principle of many minds and laboratories working on the data to supplement and complement new studies is science at its best.

These 2 articles on GBM are just the beginning, and many more reports on other cancers and other diseases are expected to be available in the near future; indeed, the amount of data and comprehensiveness of covering of the whole genome in such studies are expected to rapidly increase as the new DNA sequencing technologies improve even more. Once the new alphabet of these tumors is known, scientists will have the capability to decipher the language, which will usher in a new era in cancer research.

Financial Disclosures: Dr Pasche reports that he has filed patents related to TGFBR1 in colorectal cancer. No other disclosures were reported.

Funding/Support: Supported by National Institutes of Health grants R01 CA108741, R01 CA112520, and P60 AR048998.

Role of the Sponsor: The National Institutes of Health had no role in the preparation, review, or approval of the manuscript.

REFERENCES