understanding of these diseases and enhance drug therapy trials. The main limitation of NIRF is poor penetration (several millimeters through human brain). As the authors point out, targeted antibodies for magnetic resonance and nuclear imaging will soon circumvent this limitation and allow for whole-brain molecular imaging of inflammation. Neurosurgery, as a specialty, is in an optimal position to engage the research questions and the clinical opportunities that will emerge from this exciting field.

BERNARD R. BENDOK, MD
VASCULAR BIOLOGY AND
ENDOVASCULAR RESEARCH

Genomics of Human Glioblastoma Multiforme: A Glimpse of the Future

Despite the improved prognosis for many cancer patients, the survival for those with glioblastoma multiforme (GBM) remains dismal. Even with aggressive intervention, including resection, radiation, and chemotherapy, the overall 2-year survival rate is only 25% in the most optimistic series, and 5-year survival rates are consistently in the low single digits. Therefore, it is evident that novel therapeutic paradigms are necessary to overcome the inherent limitations of conventional treatments. Emerging data offer encouraging evidence that patient-specific therapies tailored to the unique biology of an individual's GBM may improve clinical outcomes. As a result, substantial research effort has focused on the identification of genetic alterations in GBM that might help define subclasses of GBM patients with differing prognoses and/or response to specific therapies.

Although several gene alterations have been reported, including TP53, EGFR, and PTEN, none of these alterations have been sufficiently specific to a particular subclass, for example in primary or secondary GBMs. To this end, Parsons et al. sequenced 20 661 proteins coding genes in 22 human GBM samples (**Science 321:1807–1812, 2008**). They determined the presence of amplifications and deletions using high-density oligonucleotide microarrays and expression profiles using serial analysis of gene expression and next-generation sequencing technologies. This analysis led to the discovery of a variety of genes that were not known to be altered in GBMs. The most frequently mutated of these genes was found in the active site of isocitrate dehydrogenase 1 (IDH1) in 12% of GBM patients. IDH1, on chromosome 2q33, encodes isocitrate dehydrogenase 1, which catalyzes the oxidative carboxylation of isocitrate to α-ketoglutarate, resulting in the production of nicotinamide adenine dinucleotide phosphate (NADPH). The IDH1 protein forms an asymmetric homodimer and is thought to play a substantial role in cellular control of oxidative damage through generation of NADPH. This study showed that mutations in IDH1 preferentially occurred in a large fraction of young patients (mean age, 33 years) and in most patients with secondary GBMs, and they were associated with a significantly improved prognosis, with a median overall survival of 3.8 years in patients with IDH1 mutations as compared with 1.1 years for patients with wild-type IDH1.

Another related breakthrough relates to The Cancer Genome Atlas (TCGA), launched in 2006 as a $100 million pilot collaboration between the National Cancer Institute and the National Human Genome Research Institute with the aim of systematic characterization of genetic and epigenetic alterations in all human cancers. The GBM was chosen as the first type of cancer to be studied in TCGA, and the highly anticipated interim results of its first analysis were recently published (**Nature 455:1061-1068, 2008**). This pioneering report presents the integrated analysis of multiple types of genomic data gathered on 206 GBMs from investigators at 18 centers; the sequencing of 601 genes, methylation status, gene expression data, copy number alterations, and clinical data were available for analysis. The initial findings confirmed the importance of cardinal oncogenic signaling pathways—multiple genetic alterations were detected in the phosphatidylinositol-3-OH kinase (PI 3-kinase), p53, and Rb pathways—and highlighted several novel findings. Among these was conclusive evidence of TP53 mutation in primary GBM, long thought to be relevant only in secondary GBM, and the detection of inactivating mutations or deletions of NF1 in 23% of samples. Mutations in ERBB2, a member of the EGFR family, were found in 11% of patients. Interestingly, 10% of patients harbored mutations in PIK3R1, which encodes a regulatory protein in the PI 3-kinase complex; this mutation may inactivate a regulatory subunit, thereby constitutively activating the catalytic subunit of the PI 3-kinase complex.

An additional novel finding highlights the utility of integrated analysis centers on the relationship of MGMT status and mutations in mismatch-repair (MMR) genes. An analysis of mutation, methylation, and clinical response data revealed that patients with MGMT methylation—known to predict response to temozolomide—also harbor MMR mutations. The authors posited that MGMT methylation combined with alkylator treatment may confer a selective pressure to lose MMR function, resulting in a "hypermutator phenotype" wherein oncogenic mutations are unchecked and recurrence is spurred. This has clear relevance to treatment paradigms.

These genomics studies provide a novel view of GBM molecular biology with promising clinical utility. It is conceivable that genomic alterations can identify a biologically specific subgroup of GBM patients and that new treatments can be designed to take advantage of these alterations. Next on the horizon is just as sizeable an undertaking: deciphering the functional relevance of the incredible amount of information in these powerful datasets, and to start to develop relevant correlations of particular groups to GBM behavior, including responsiveness to specific therapies.

RICARDO J. KOMOTAR, MD
OMAR N. SYED, MD
JEFFREY N. BRUCE, MD
E. SANDER CONNOLLY, JR, MD
TECHNICAL & CLINICAL RESEARCH

IAN F. DUNN, MD
ROBERT M. FRIEDLANDER, MD
BASIC SCIENCE RESEARCH
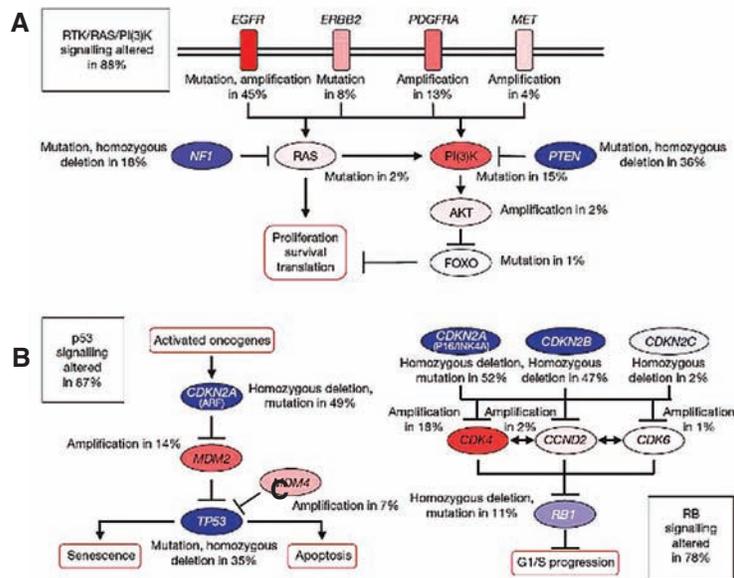
Frequent genetic events in GBM involving (a) PI 3-kinase, (b) p53, and (c) Rb signaling pathways; red indicates activating events; blue represents inactivating events. Depth of shading correlates with frequency of event.