Trial Watch

METABOLIC MUTATIONS IN GLIOMAS

Glioblastomas (World Health Organization (WHO) grade IV gliomas) can occur as primary tumours or be derived from grade II or III gliomas such as astrocytomas or oligodendrogliomas. Primary and secondary glioblastomas cannot be distinguished by histopathology, but research by Yan, Parsons and colleagues has shown a genetic basis for the categorization of these into two clinical subgroups.

The authors previously identified somatic mutations of isocitrate dehydrogenase 1 (*IDH1*) at codon 132 (R132) that were relatively infrequent in primary glioblastomas but common in secondary glioblastomas. In this study, they analysed *IDH1* mutations in a larger cohort of tumour samples (939) comprising 445 central nervous system (CNS) tumours and 494 non-CNS tumours. Somatic mutations at R132 were identified in 161 of the CNS tumours and none of the non-CNS tumours. No other mutations of *IDH1* were found in R132 mutation-negative tumours, but nine mutations of the analogous R172 in the homologue *IDH2* were identified. Interestingly, the *IDH1* and *IDH2* mutations were almost exclusively found in WHO grade II and III astrocytomas and oligodendrogliomas and glioblastomas derived from these lower-grade tumours, at a frequency of more than 70%. Furthermore, analyses of both low- and high-grade tumour samples from seven progressive gliomas revealed that all seven pairs had *IDH1* mutations.

The authors also confirmed and extended previous results indicating improved outcome and differences in age for patients carrying IDH1 R132 or IDH2 R172 mutations. Median overall survival was higher for patients with either glioblastomas (31 months for patients with *IDH1* or *IDH2* mutations versus 15 months for those without, $p = 0.002$) or anaplastic astrocytomas (65 months for patients with *IDH1* or *IDH2* mutations versus 20 months for those without, $p < 0.001$). In addition, patients with glioblastomas or anaplastic astrocytomas with mutated *IDH1* or *IDH2* were significantly younger than those with wild-type *IDH1* or *IDH2*.

IDH1 and IDH2 convert isocitrate to α-ketoglutarate in the citric acid cycle (concommitantly reducing $NADP^+$ to NADPH). IDH1 R132 and IDH2 R172 mutants expressed in an oligodendroglioma cell line had lower enzymatic activity (as shown by NADPH production) than the wild-type proteins. The arginine at 132 or 172 is involved in the regulation of these proteins. Although the authors found reduced enzymatic activity with mutation of this amino acid, it is possible that under physiological conditions they could be gain of function mutations and thus possible therapeutic targets.

These data help to explain the biological differences between primary glioblastomas and glioblastomas that have developed from WHO grade II or III gliomas. Furthermore, the fact that mutations in IDH1 and IDH2 were limited to a single amino acid should facilitate detection of these mutations for diagnostic purposes.

ORIGINAL RESEARCH PAPER Yan, H. *et al.* *IDH1* and *IDH2* mutations in gliomas. *N. Engl. J. Med.* **360**, 765–773 (2009)
FURTHER READING Thompson, C. B. Metabolic enzymes as oncogenes or tumor suppressors. *N. Engl. J. Med.* **360**, 813–815 (2009)