Chapter 14

HUMAN GLIOMA DIAGNOSIS FROM GENE EXPRESSION DATA

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1. Introduction

One goal for gene expression profiling in cancer research is to develop a new paradigm for the molecular classification and objective diagnosis of tumors. Motivation for such a new diagnostic tool is the subjectivity and frequent ambiguity associated with classical histological diagnosis based on morphological features. Current molecular approaches suffer from several drawbacks. For example, molecular classification based on single gene molecular markers is vulnerable to the vicissitudes of non-representative tissue sampling in the face of well known tumor heterogeneity. At the other extreme, current gene expression array platforms typically display hundreds to thousands of genes on a single microarray. Diagnosis using such a large number of genes is not practical and is likely to yield suboptimal results. We suggest, alternatively, that the ideal diagnostic tool for clinical use would be a customized expression array comprised of less than 100 genes, with each of these possessing robust differentiating power with respect to the particular cancer under investigation.

In support of this hypothesis, we have carried out a gene expression pilot study using 25 glioma tissue samples that encompass four different glioma subtypes: oligodendroglioma, anaplastic oligodendroglioma, anaplastic astrocytoma, and glioblastoma. The complete microarray platform employed contains 597 genes. To develop a cDNA microar-
ray suitable for reliable diagnosis of the four glioma subtypes, a robust algorithm is required to select a subset of specific genes that have the requisite diagnostic power.

In this chapter, we provide an introduction and overview of current glioma diagnosis and classification, which is largely based on a classical histopathological approach, followed by a discussion of the possibilities for molecular classification based on a gene expression approach. Finally, we describe a novel method for the selection of subsets of genes required for diagnostic microarrays.

2. Glioma diagnosis: from histology to microarray

2.1 Histopathological glioma classification and diagnosis

The current paradigm for brain tumor diagnosis and classification, as exemplified by the recently revised World Health Organization Classification of Tumours of the Nervous System (Kleihues and Cavenee, 2000), is based primarily on morphologic pattern recognition: the identification of similarities between the phenotypic characteristics expressed by tumor cells compared to those of normal central nervous system constituents as assessed by light microscopic examination of H&E-stained tissue sections, immunohistochemistry, and electron microscopy. Although the morphologic approach has unquestionably been of considerable utility, there are nevertheless a number of shortcomings. Using traditional phenotypic criteria, for example, the identity and classification of some tumor types, such as mixed oligoastrocytomas, is highly subjective and overly dependent upon the individual pathologist’s relative weighting of various morphologic characteristics. Currently prevailing histology-based classification methods also do not permit accurate prediction of clinical behavior or response to specific therapeutic agents and regimens for individual patients within a given histologic rubric, as, for example, is the case for anaplastic astrocytoma, in which individual patient response to treatment and survival varies significantly. Another problem is the failure of morphology-based classifications to accurately predict individual patient sensitivity to the toxic effects of various therapies, such as radiation necrosis.

There is thus a need on many levels for a more precise, effective and objective approach to brain tumor diagnosis, classification, grading, and prognosis. The first significant development in the molecular classification of brain tumors was the recently recognized association between the combined loss of heterozygosity (LOH) for chromosomes 1p and 19q and