

Preface

Although primary neoplasms of the central nervous system collectively account for only 2–3% of all human malignancies, they are nevertheless responsible for up to 7% of lives lost from cancer before the age of 70. Gliomas are the most common primary brain tumors, the majority of which are malignant neoplasms that diffusely infiltrate the surrounding brain tissue, have an inheriting tendency for recurrence, and eventually lead to death by causing increased intracranial pressure followed by central regulatory failure. Glioblastoma multiforme represents the most common types of gliomas in adults and it is one of the most aggressive human cancers. Despite multimodal treatment, including neurosurgical resection, local irradiation, and systemic chemotherapy, glioblastoma patients presently cannot be cured and still face an exceptionally poor prognosis as indicated by a median survival time of less than one year in population-based analyses. Furthermore, both tumor growth and aggressive therapy may harm the brain, which is the organ that defines the personal self and is the source of basic human abilities such as reasoning, remembering, and emotion. Thus, glioma patients often experience profound changes in their neurological and cognitive abilities, which in turn may dramatically reduce their quality of life. The poor prognosis of patients with malignant glioma urgently calls for the development of novel, more effective but less neurotoxic, treatments. At the same time, new molecular markers are needed to facilitate an individualized therapy and help to stratify patients into the best available treatment regimens. To achieve these important goals, a better understanding of the molecular and cellular path mechanisms involved in the initiation and malignant progression of gliomas is an indispensable prerequisite. Fortunately, molecular studies over the past two decades have identified a variety of chromosomal, genetic, epigenetic, and transcriptional aberrations that are specifically associated with the individual types of gliomas. In addition, certain molecular aberrations have been linked to therapy response and patient survival, thereby establishing clinically important predictive and prognostic biomarkers.

The main objective of this book is to provide a state of the art update concerning novel molecular and cellular approaches for the treatment of malignant gliomas, with a particular focus on targeted RNA-based strategies. Internationally distinguished

experts working in the basic sciences, neuropathology, and clinical neurooncology have contributed comprehensive chapters to this book covering the major topics of the current research in the field.

The first chapter of the book is mainly focused on recent progress in molecular neurooncology and the clinical significance of molecular markers in the diagnostic and prognostic assessment of gliomas. *C. Belda-Iniesta et al.* provide an update on the molecular biology of malignant gliomas, including recent results obtained from large-scale gene expression profiling using microarray-based technologies. In addition, the concept of glioma stem cells is discussed, which may have very promising implications for the future for targeted gliomas treatment and overcoming the inherent resistance to therapy.

Novel pathogenesis-based strategies for brain tumor treatment, including anti-angiogenic approaches, vaccination strategies, cellular therapies, and targeted inhibition of growth factor receptor pathways, are all topics covered in detail in the chapters by *M. Hutterer and G. Stockhammer* as well as by *K.K. Jain*.

A critical review on the role of gene and oncolytic viral therapy for malignant glioma and the present scientific challenges in this particular field of research is contributed by *A.M. Sonabend and co-authors*.

R. Yamanaka's chapter also addresses gene therapeutic approaches, focusing on the role of alpha viral vectors for glioma immunotherapy.

The chapter by *A.M. Barciszewska and co-authors* discusses the changes in DNA methylation patterns that are associated with glioma progression and their potential role in the diagnostic assessment of brain tumor malignancy.

M. Eoli et al. report on the current status concerning the clinical significance of molecular markers in gliomas. A particular focus of this chapter is placed on the prognostic role of combined deletion of 1p and 19q in oligodendroglial tumors as well as the *MGMT* promoter methylation status as a predictive marker for sensitivity to alkylating chemotherapy in glioblastomas. Additional molecular markers that are addressed include the *EGFR*, *TP53* and *PTEN* genes, as well as the stem cell-associated antigen CD133/prominin-1.

Widegren et al. using microarray and proteomic analyses identified many genes showing interesting novel potential targets as well as several proteins already being investigated for immunotherapy.

The next part of the book is specifically devoted to the potential roles of RNA-based strategies in glioma treatment. *D. Schulze and A. Aigner* focus on novel developments concerning nonviral, nanoparticle delivery systems, including liposomal-, lipid- and polymer-based strategies for the effective transport of RNAi into the brain and into brain tumors.

In a treatment approach in humans (*Rolle et al.*), tenascin-C (TN-C) was selected which had been shown previously to be upregulated in glioblastoma and has been suggested to be correlated with the grade of malignancy and to shorten patient survival. After surgical resection of the tumor, patients were treated with dsRNA (ATN-RNA) complementary to a part of the sequence of tenascin-C mRNA. A significant improvement in overall survival without losing the quality of life of the patients was observed.

R.J. Boado and W.M. Pardridge discuss the possibilities for facilitating the transport of RNAi across the blood–brain barrier, including sophisticated methods such as the “Trojan Horse Liposome” technology, which is based on immunoliposomes carrying shRNA expression plasmids for RNAi transfer.

The chapters by *A.E. Lovett-Racke* as well as by *S.P. Mathupala et al.* provide more general overviews on the therapeutic potential of RNAi for brain diseases and outline potential strategies for the effective therapeutic application of RNAi-based methods in the clinical setting. Since primary glioblastomas frequently show gene amplification, rearrangement and overexpression of the epidermal growth factor receptor (*EGFR*) gene, the *EGFR* molecule constitutes an interesting target for specific inhibition by antisense RNA and RNAi approaches.

The chapter by *B. Malzkorn et al.* provides a comprehensive overview on the biogenesis and regulation of microRNAs and their involvement in the pathogenesis of primary brain tumors, such as gliomas, medulloblastomas, and pituitary tumors. Aberrations in microRNA expression and function are increasingly being recognized in brain tumors and many other cancers, with first results suggesting a major impact of microRNA profiles in molecular tumor classification. In addition, modulation of microRNA activity may be a promising new approach for targeted cancer therapy.

The following chapters in the book deal with treatment options for malignant gliomas, ranging from the standard combined modality therapy to a variety of experimental preclinical and early clinical treatments. The current standard of care for high-grade glioma patients is summarized by *J. Drappatz et al.*, who illustrate ongoing therapeutic approaches selectively targeting signaling pathways that are known to be aberrant in malignant gliomas.

Targeted therapy of gliomas using oligonucleotides is the topic of the chapters by *P. Jachimczak et al.* and *T. Schneider*. *P. Jachimczak et al.* provide information on antisense oligonucleotide-based strategies that are already in clinical trials. For example, ongoing prospective trials evaluate the tolerability and efficacy of adjuvant treatment directed against transforming growth factor beta in patients with high-grade gliomas. *T. Schneider*’s chapter outlines the general strategy of antisense oligonucleotide-based treatments and discusses promising gene targets that are aberrantly activated in malignant gliomas.

The chapter by *P. Pu et al.* also addresses this issue and in addition discusses the possibility of combining conventional therapy with siRNA-based inhibition of aberrantly activated oncogenes in malignant gliomas.

It is known that noncoding RNAs (ncRNAs) are important components of regulatory networks governing gene expression in all organisms. *M. Szymanski* describes many ncRNAs which regulate key processes associated with the development and maintenance of specific gene expression profiles. In addition it is shown that also in the nervous system many various classes of ncRNAs exist which play a role in neural cells differentiation and activity.

Y. Fellig et al. address the H19 non-coding RNA gene, which is located at 11p15.5 and subjected to genomic imprinting. Their chapter reports on changes of the H19 imprinting status and aberrant expression in brain tumors, as well as on the

relationship of H19 alterations with hypoxia and p53 function. Furthermore, promising new findings concerning H19-mediated cytotoxic gene therapy, as well as RNAi-based strategies to reduce H19 overexpression in cancer cells, are discussed.

In summary, this book will be of great interest not only for researchers working in molecular and translational neurooncology but also for clinicians involved in the treatment of brain tumor patients. The book provides a state of the art review concerning the molecular pathogenesis of gliomas and the translation of these advances into clinical applications, namely the identification of novel diagnostic, prognostic and predictive biomarkers and the development of innovative pathogenesis-based therapeutic strategies. However, despite the tremendous advances in the molecular genetics of gliomas, we are still far from fully understanding the complex mechanisms that underlie tumor initiation and progression in the individual patient. Nevertheless, recent technological advances permit ever more refined and comprehensive analyses of the genomic, epigenetic, transcriptional, and proteomic changes associated with the individual types and malignancy grades of gliomas. First results obtained from systematic genomic and expression profiling studies already provided interesting novel markers and signatures, which most likely will refine glioma diagnostics and help to guide therapy. A better knowledge of glioma pathomechanisms facilitates the rational design of therapies targeting specific cell populations, such as the glioma stem cells, or cellular mechanisms on which the tumors are dependent for their growth and progression. In this respect, RNA-based strategies represent promising tools, which will hopefully help to identify ways of specifically eradicating tumor cells but leaving the surrounding functional cells of the brain intact.

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