CHAPTER 22

NOTCH SIGNALING AND BRAIN TUMORS

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Abstract: Human brain tumors are a heterogeneous group of neoplasms occurring inside the cranium and the central spinal cord. In adults and children, astrocytic glioma and medulloblastoma are the most common subtypes of primary brain tumors. These tumor types are thought to arise from cells in which Notch signaling plays a fundamental role during development. Recent findings have shown that Notch signaling is dysregulated and contributes to the malignant potential of these tumors. Growing evidence point towards an important role for cancer stem cells in the initiation and maintenance of glioma and medulloblastoma. In this chapter we will cover the present findings of Notch signaling in human glioma and medulloblastoma and try to create an overall picture of its relevance in the pathogenesis of these tumors.

INTRODUCTION TO BRAIN TUMORS

Brain tumors are a heterogeneous group of neoplasms and include all tumors located inside the cranium and the central spinal canal. Primary brain tumors (PBT, also referred to as true brain tumors) arise from cells intrinsic to these cavities, while secondary brain tumors are metastases originating from cancers outside the brain.

PBT are primarily of neuroepithelial origin and are, according to the World Health Organization (WHO) classification, distinguished based on their histological appearance and named based on the cell type they most closely resemble. PBT are further graded as low-grade tumors (non-anaplastic, WHO Grades I and II), or high-grade tumors (anaplastic, WHO Grades III and IV) based on five main features: cytological atypia, anaplasia, mitotic activity, microvascular proliferation and necrosis.¹


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Gliomas are the most common PBT in adults (70% of all brain tumors) with a yearly incidence of approximately 6/100,000 in western countries.\(^1,9\) They are categorized as derived from glial tissue and comprise astrocytomas, oligodendrogliomas, mixed oligoastrocytomas and ependymomas. Further distinction is made based on their grade of anaplasia and the astrocytic tumors include pilocytic astrocytomas (WHO Grade I), diffuse astrocytomas (WHO Grade II), anaplastic astrocytomas (WHO Grade III) and glioblastoma multiforme (GBM, WHO Grade IV). GBM accounts for 50-60% of all intracranial gliomas\(^3\) and is recognized as the most aggressive PBT in adults with a median survival around 15 months.\(^4\) GBM is preferentially located in the cerebral hemispheres and is diagnosed based on the presence of vascular proliferation and necrosis, which thus are considered as hallmarks of GBM. Primary GBM, which represents the vast majority of glioblastomas (95%), arises de novo tumors without evidence of pre-existing lesions and affect mainly elderly people (mean age 62 years).\(^2\) Loss of heterozygosity (LOH) of 10q and mutations in the Phosphatase and Tensin homolog (\(PTEN\)) gene are often found in primary GBM.\(^{2,5}\) Likewise are over expression and abnormal activity of the epidermal growth factor receptor (EGFR), as a result of amplification and/or mutation, frequently observed and are associated with a more aggressive disease.\(^{5,2}\) Secondary GBM progresses slowly from Grade II or III astrocytomas and often harbors inactivating mutations of the tumor suppressor gene \(p53\) as does diffuse astrocytomas and anaplastic astrocytomas.\(^2\) Treatment of GBM remains a significant therapeutic challenge, as the majority of gliomas are difficult to operate due to their location and invasive nature. Furthermore are radiation- and chemotherapy often ineffective and relapse is almost certain, why GBM remains thus far incurable.

Astrocytomas are also common in children, accounting for approximately half of the PBT cases, while the remaining 50% includes tumors rarely seen in adults.\(^9\) Of the latter, medulloblastoma (MB, WHO Grade IV) is the most common embryonal PBT with an annual incidence estimated to approximately 0.7/100,000 for children under the age of 15. MB arises in the cerebellum and has an early onset, is fast growing, invasive, predominately displays neuronal differentiation and has a tendency to metastasize through the cerebrospinal fluid. Histologically, MB is characterized by densely packed small round cells with hyperchromatic nuclei surrounded by scanty cytoplasm, typically exhibiting high mitotic activity and anaplasia. Angiogenesis and necrosis are however uncommon.\(^1,9\) The most common cytogenetic alteration in MB is isochromosomy 17, \(i(17)q\), which results in trisomy 17q and monosomy 17p.\(^{10}\) Together with 6q gain and amplification of \(MYC\) and \(MYCN\), additional common genetic modifications, this has been associated with poor survival.\(^9,12\) Furthermore, aberrant activation of the Wnt and Hedgehog pathways has been implicated in the pathogenesis of a subset of MB.\(^13\) WHO has further classified four different MB histological subtypes, which have been shown to be associated to clinical behavior. As such, desmoplastic/nodular MB and MB with extensive nodularity correlate with an average-risk disease, whereas anaplastic MB and large cell MB tends to display a more aggressive clinical course and are characterized as high-risk disease.\(^{12,14,15}\) Current multimodal treatment of MB has led to a five-year disease-free survival of nearly 90% for children with average-risk and a 60-65% survival rate for children with high-risk disease.\(^{15}\) However, survivors have a highly elevated risk for increased morbidity and mortality later on in life, with disease relapse being the single most common cause of death. They moreover have an increased susceptibility for developing long-term complications as a consequence of neurological effects caused by the tumor or treatment.\(^{15,17}\)