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Medulloblastoma – Genetic Alterations

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1. Introduction

Medulloblastoma (MB) is an embryonal brain tumor of the cerebellum. MB accounts for 4-6% of all primary intracranial tumors. It is the most common malignant brain tumor in children, representing 15-30% of all pediatric brain tumors, with 85% of MBs being diagnosed in patients younger than 18 years of age. The peak incidence occurs between the ages 3-9 years, with about 35% metastasis disease (Crawford et al., 2007; Polkinghorn and Tarbell 2007; Rossi et al., 2008).

In contrast, medulloblastoma is rare in adults and accounts for less than 1% of primary intracranial malignancies in this age group (Brandes et al, 2009; Louis 2007; Padovani et al, 2007).

Based on histopathological features, the 2007 WHO classification of CNS tumors (Louis et al., 2007; Gilbertson and Ellison 2008), has separated MB into five recognizable subtypes: the classic tumor which is the most common subtype of MB in general and in children in particular. The other four variants are: 1. desmoplastic/nodular which is the second most common (10-20% of the cases) in very young patients and adults, 2. MB with extensive nodularity is predominantly observed in infants (less than 3 years old), 3. anaplastic MB, 4. large cell MB is rare in infants, both of which account for 5-10% of the cases. The histological classification and clinical staging have proven to be less than ideal methods for stratification. Histological subtypes are often quite heterogeneous and exhibit highly variable clinical behavior, with anaplastic subtype typically associated with the worst prognosis, followed by classic and desmoplastic/nodular MB, which correlate with improved overall survival.

MB with extensive nodularity and desmoplastic/nodular MB in infants have a better outcome than the classic MB tumors, while large cell and anaplastic MB behave aggressively. Thus infants with desmoplastic MB should be stratified into a low risk therapeutic group while the large cell MB is rare but points to a poor prognosis that often presents with metastatic disease (Gilbertson and Ellison 2008).

The increasing recognition of MB as a heterogeneous disease, with histological and molecular variants that have distinct biological behavior, affected the disease classification and treatment.

In spite of current aggressive therapies, approximately one third of the patients eventually succumb to the disease due to metastasis. Furthermore the post-treatment squeal, which
includes neurological, vascular and long-term neurocognitive impairments, can be devastating for survivors of the disease (Ribi et al., 2005). It is imperative to gain a better understanding of the molecular alterations and other biological squeal in medulloblastoma for future targeted therapies that are more effective and less toxic.

A combination of clinicopathological evaluation and assays based on molecular subgroups of the disease allow stratification of patients into risk groups and more tailored approach to therapy which should prevent the significant adverse effects among survivors. Studies in the last 5 years have helped to build a consensus on the value and means of using molecular markers in the therapeutic stratification of childhood medulloblastoma (Gilbertson 2004; Packer and Vezina 2008; Pizer and Clifford 2009). These studies have revealed the genetic heterogeneity within MB including dysregulation of several signaling pathways. The genetic heterogeneity appears to be the basis for differential response to treatment and give a new impact to the traditional histological subtyping and improve to some extend the accuracy of diagnosis and prognosis and as a consequence the stratification to risk groups (Packer and Vezina 2008).

Although, adult MB is considered different from their childhood counterparts in terms of tumor biology and clinical variables, yet, because of the high incidence of MB in childhood and low incidence in adults most of the studies have been done on the MB of childhood. Some studies documented differences between childhood and adults tumors with regards to localization, cell of origin, histopathologic features, tumor cell differentiation, and treatment outcome. The adult's MB found to be also genetically distinct from the pediatric MB (Korshunov et al 2010).

Here we focused on the genetic alteration reported so far in MB and their significance in sub-typing, stratification, and medical care.

2. Heritability of medulloblastoma

Neither familial cases of MB, nor MB's cases affected by defined environmental factors have been described so far. Also, no specific chromosomal aberration has been described in more then about 40% of the MB cases. Unlike Ewing sarcoma, where t(11;21) can be found in about 90% of the cases, in MB no main specific gene alteration can be detected. Yet, there is a wide basis to believe that inheritable factors play a significant role in MB pathogenesis and prevalence. Some of the evidence that support this point of view are:

A. Age of onset- MB is most prevalent in childhood including about 3% in infancy, mainly medulloblastoma with extensive nodularity, while it is rare in adults. MB is mostly a childhood brain tumor with a peak in 3-9 years age. Inheritable markers are most probably expressed phenotypically at the early ages of life. The younger the patient is, the higher chance that the genetic part is more pronounced, and so in the adults, the latter the age of tumor appearance the higher chance for multi-factorial environmental cause. About 85% of the primary intracranial tumors diagnosed as MB in patients younger then 18 years of age while in adults about 1% of the primary intracranial tumors diagnosed as MB. It is well known that infants are the more vulnerable group with 25-60% rate of cure, while the over all 5-year survival rate in childhood is about 80%. Although, the environmental factors could not be totally excluded, yet the younger age of MB appearance with 35% metastatic, points toward a more pronounced genetic background rather then environmental (Rossi et al 2008, Bar and Stearns 2008).
B. **Severity of the disease** - the most prevalent MB sub-type in infancy is the desmoplastic which is considered the most aggressive sub-type especially when it also appear with metastasis, 35% of the childhood MB are metastatic at presentation. Metastatic phenotype considered as a high risk group with the worst prognosis. Cure rates are lower for infants than for older children. This might point either to the more significant-effective role of the inheritance genetics predisposition in infants then in elderly or adults MB. Also most probably radiotherapy can be particularly more adverse in the immature infant brain (Grill et al 2005; Packer and Vezina 2008; Rutkowski et al., 2009). The main consequence of carnospinal irradiation (CSI) is notably cognitive problems children’s IQ can decrease by as much as 30 points in the standard risk group. The high risk group (metastasis, significant post operative residual tumor) remains poor 5-years event free survival (EFS) being 25-40% the worse prognosis is particularly in younger children. Although 5-years overall survival rates have reached 60-80%, survivors often face a variety of long term neurological, neuroendocrine, and social squeal as a result of conventional treatment regimens (surgery, radiotherapy, and chemotherapy) (Pizer and Clifford 2009) (Packer and Vezina 2008; Rossi et al 2008, Bar and Stearns 2008). It is imperative to gain a better understanding of the molecular alterations in MB for future targeted therapies that are more effective and less toxic.

C. **Predisposition** - Predisposition to develop MB due to known genetic alterations - some MB cases are associated with known hereditary syndromes such as Gorlin, Turcot and Li-Fraumeni. (Reviewed by Ellison 2010, Northcott, 2011; Onvani 2010) will be discussed in the gene alteration part. All the above points support the suggestion that genetic factors cause predisposition for MB’s development.

Most studies on MB have focused on genes that are already known to be involved in the pathogenesis of tumors, such as Wnt, SHH, Notch TP53. The specific genetic pathway/s in MB is/are still unknown.

Studying the different MB’s subtypes with the most advanced technologies will significantly contribute to the overall understanding of MB pathogenesis in general and in particular in MB genetic knowledge.

3. **Chromosomal aberration and its correlation to clinicohistopathological classification**

Cytogenetics and molecular genetics are two different levels of genetic studies. Both of them are in use for characterization of tumors in general and MB in particular. Nowadays, these tests in combination with other standard methods such immunohistochemistry, significantly improved the diagnosis, prognosis and consequently the treatment modalities and survival of the patients with malignant diseases. Cytogenetics, molecular cytogenetics (FISH, CGH) and molecular genetics are three methods that supplement each other, and their combination leads to the identification of the genes that are involved in tumorigenesis (tumor suppressor genes and oncogenes) and thus can give complete information for prognostic and diagnostic purposes. Although, impressive progress has been achieved in the nano molecular genetics, next generation sequencing, proteomics and transcriptomics, in the last decade, yet, we can not give up the "macro-tests": the old gold standard methods such as cytogenetics and histology. The nano tests are still new and very expensive to implicate to routine work up, they are in a developing stage and the accumulated experience with their use is still limited. There is still missing information regarding the whole range of polymorphism and how to differentiate it
from significant changes. Also the exact interactions between all the nano tests (molecular
genetics, proteomics and transcriptomics) are only partially understood so far. Moreover the
significance and the importance of the immerging field of epigenetics is still not clear. The field
of epigenetics is dealing with changes that do not affect the molecular genetics itself but rather
the changes in the expression of the gene/s by changing mythlation, acetylation,
phosphorilation and ubiquitination (Bernstein et al. 2007; Kouzarides 2007). Its effects include
the most delicate interactions of all the living levels, starting from biochemical reaction and the
interactions inside the cell compartments, cell to cell, in the organ, in the host and between the
host and the environment.

Chromosome analysis of tumor cells plays an important role in the diagnosis, prognosis and
follow up of many malignancies. It is a standard of care in hemato-oncology. Culturing solid
tumor cells in vitro is essential for cytogenetic analysis. The success in getting specific
chromosomal aberrations in solid tumors after in vitro culturing is limited because of
technical problems such as: an overgrowth of cells from healthy part of the tissue mostly
fibroblasts, limited growth of the abnormal tumor cells and low quality of the tumor cell
metaphases and also the need for special and well trained cytogeneticists. These are
probably the main reasons for the limited and what seems like a non specific chromosomal
aberration in medulloblastoma. Only about 40% of the medulloblastomas demonstrate
chromosomal aberrations. Presently, advanced technologies such as microarray CGH and
next generation sequencing enable us to better evaluate chromosomal aberrations in
medulloblastoma. It will take some time for the accumulation of new data regarding
chromosomal aberrations using the new methods, mainly because reliable results should be
done on a large cohort which include sufficient size group of all MB subtypes.

Copy number abnormalities of chromosome 17 isodicentric, isochromosome of chromosome
17q, loss of 17p, or gain of 17q are the most frequent chromosomal abnormality in
medulloblastomas (Mitelman database 2011, Aldosari et al 2002; McCabe et al 2006) it is
found in 30-50% of the studied cases (Reardon et al 1997). Isochromosome -isodicentric
chromosome 17 is present in approximately one third of the tumors and in some cases is the
only chromosomal aberration (Mitelman database 2011; Pfister et al 2009; Ricket and Paulus
2004). It has been observed in 25-30% of childhood MB. In fact there is a loss of 17p and a
gain of 17q which is the most common isochromosome in cancer in general (Mitelman
database 2011). This might point toward the fact that i(17q) is a general marker of neoplastic
process rather then a specific marker of MB. Its role as an indicator for a poor outcome in
MB stratification is controversial. The controversial evidence based mainly on the findings
of i(17q) also in Wnt pathway subgroup which in consensus considered as a favorable
outcome. The question whether to consider copy number abnormality of chromosome 17 as
a marker for poor prognosis and to exclude those found to be Wnt pathway, is still in
debate (Pan et al 2005; Pfister et al 2009).

Using more sophisticated and advanced techniques such as CGH to profile a panel of 27
primary MB (Reardon et al 1997) revealed frequent loss of 10q, 11, 16q, 17p, and 8p as well
as recurrent gains of chromosomes 7, and 17q. These losses and gains were also confirmed
by other techniques, such as G-banding, SKY and FISH (Aldosari et al 2002; Avet-Loiseau et
(Speicher and Carter 2005) showed gain of 17q, 7, and 1q and loss of 17p, 11p,10q and 8.
There have also been reports, although less frequently of losses on chromosomes 10q, 11,
17p qnd 22 as well as gains on chromosomes 1q, 7 and 7q (Mitelman database 2011; Bayani
et al 2000).
SKY analysis of 19 primary MB revealed structural aberrations involving chromosomes 7, 17, 3, 14, 10 and 22 (Bayani et al. 2009). Monosomy 6 is strongly associated with Wnt profile in MB (Clifford et al. 2006). Chromosomal abnormalities including loss of chromosome X in females and loss of chromosome 8, have been found mainly in non SHH/Wnt subgroups.

4. Genetic alterations and its correlation with clinicohistopathological classification

Tumorigenesis is a process in which one of the pathways leading to normal cell development has lost its control and its normal function. In addition, the neovascularization, cell proliferation, differentiation, motility and apoptosis (death) are also altered. There are two possible categories in tumor specific genetic alteration; one is inheritable or germ cells mutation and the other is acquired alteration. Also there is a difference between general tumorigenesis pathways and tumor specific pathway and general chromosomal aberration and tumor specific chromosomal aberration.

Usually, the tumor specific pathway is a part of the general tumorigenesis pathways but still it is predominant in one specific tumor subgroup, for example RB gene that causes mainly retinoblastoma, WT gene that causes mainly Wilms tumor, both are also causing predisposition to other tumors. Similarly, the acquired gene alteration occurring during the life time, such as BCR/ABL is causing chronic myeloid leukemia and EWSR1-FLI1 is causing Ewing sarcoma. Specific acquired aberration found in addition to the cancer they caused, also in other cancers, there its significance and its prognostic value is different, for instance BCR/ABL points to a favorable prognosis in CML and points to a poor prognosis in acute lymphocytic leukemia (ALL).

Among the life time acquired mutation, one should differentiate between the first event, such as alteration of a gene that causes the disease and has a diagnostic value and those mutations that are considered as the latter (the second or the third) events for example KRAS and TP53 mutation in adenomatose polyposis coli (APC) and MNP1 or FLT1 mutation in acute leukemia. Those gene alterations have mainly prognostic value and may play as a general event seen in other tumors as well. Unfortunately, neither MB specific chromosomal changes nor MB specific gene were found to be a clear evidence for the possible pathogenesis of MB, neither in MB general nor in one of its subtypes. The understanding of MB pathogenesis is still limited, mainly because most of the MB studies are associated with genes that are already known to be involved in other tumors or syndromes, rather then studying the MB specific gene alterations as the first goal. Indeed, MB is associated with other (tumor's) syndromes such as Gorlin's, Turcot and Li Fraumeni, in which several important developmental signal transduction pathways, including sonic hedgehog (SHH), Wingless (Wnt) and Notch signaling cascades. SHH, Wnt, TP53 and Notch signaling cascades are implicated in the cells migration and localization in the cerebrum, and their proliferation and differentiation. The alterations in these pathways by any component of each signaling pathway may lead to tumorigenesis (Marino 2005; Ingham and Placzek 2006). For example, Gorlin's syndrome characterized by a germ line mutation in the patched homologue 1 (PTCH1) located on 9q22 (Frandon et al. 1992) that served as a negative regulator of SHH gene during normal cerebella development. Mutation in PTCH1 gene can cause predisposition to different tumor development including MB with incidence of 5-20% (Friedrich 2007).
Turcot syndrome is characterized by the mutation in the APC, a tumor suppressor gene that is predisposed mainly (about 90% during life time) to colon cancer adenomatous polyposis coli (APC), (Hamilton et al 1995) but also predisposed to a lesser extend to other tumors including MB (Huang et al 2000). The APC gene regulates the Wnt signaling pathway. Recent advances in gene expression profiling techniques have led to the generation of several molecular classification schemes in MB (Thompson et al 2006; Kool et al 2008; Northcott et al 2010 epub).

In general, based on the molecular studies done so far, three main subgroups were defined: SHH, Wnt and non-SHH/Wnt pathways which include another 2 subgroups which are less distinct (Thompson et al 2006; Kool et al 2008; Onvani et al 2010; Ellison 2010; Northcott et al 2011). SHH pathway subgroup accounts for 15-25% cases of MB and have a poor prognosis, Wnt pathway subgroup accounts for 15-20% cases of MB and mostly has favorable prognosis, and non-SHH/Wnt subgroups account for 60% cases of MB.

According to the Thompson's (2006) classification based on molecular and FISH examination 5 distinct subtypes identified (A to E) including subgroup B in which Wnt pathway and monosomy 6 have been found and subgroup D in which SHH pathway has been found. Kool et al (2008) further corroborated Thompson's classification using CGH and defined 5 subgroups: (A)-Wnt signaling subgroup, (B)-SHH signaling pathway, C and D expression of neural differentiation genes, D and E expression of photoreceptor genes. Subgroups C, D and E are genetically closely related and most often associated with metastatic appearance mainly subgroup E.

SHH pathway MB associated with desmoplastic phenotype (Behesti 2009) and also with large cell and anaplastic MB. They are both reported mainly in infancy and childhood. Metastatic disease at presentation characterizes some SHH pathway mostly large cells and anaplastic MB. Less then half of the SHH pathway MB have PTCH1 mutations or show copy number loss at the PTCH1 locus, 9q22, mutations in SMOH and SUFU are rare thus there must be other undiscovered SHH pathway/s (Thompson et al 2006; Kool et al 2008; Northcott et al 2011).

In contrast Wnt pathway is mostly associated with classic MB (Fattet et al 2009) it has a favorable outcome it tends to be present in childhood in the pre-teen years (6-13 years) but almost do not present in infancy. Most of the children with this tumor survived (Thompson et al 2006). Metastatic disease at presentation is rare in Wnt pathway. There is no report on desmoplastic medulloblastoma with Wnt pathway and also large cell and anaplastic MB with Wnt is rare. The APC protein is a regulator of Wnt signaling that function in a complex with other components to regulate several important developmental processes, including proliferation and specification of neural progenitor cells during early cerebellar development (Sillitoe and Joyner 2007). APC function as a tumor suppressor through CTNNB1 (β-catenin) of sporadic cases of MB, a downstream component of the Wnt signaling pathway (Hamilton et al 1995) this account for 15% of the cases. β-catenin by itself also activates transcription of several oncogenes such as MYC and CCND1 resulting in enhanced cell proliferation (Ellison et al 2005).

Only a small part of the Wnt pathway MBs are found to be carrying mutations in CTNNB1 gene-captured by identification of the nuclear activity of β-catenin in the MB. Mutations in APC and AXIN1/2 are rare, thus there are still undiscovered components also in Wnt pathway (Ellison et al 2005; Fattet et al 2009; Norhcott et al 2011).

Most of non SHH/Wnt MBs have a classic pathology and present in infancy and childhood. About half of the large cell and anaplastic MBs are non SHH/Wnt. Metastatic disease at presentation also falls into the non SHH/Wnt subgroup.
Other molecular markers beside the above three identified groups is the amplification of MYC family (MYC and MYCN proto-oncogenes), that account for 4-15% of MBs (Rossi et al 2008; McCabe et al 2006). MYCN is an early transcriptional target of the SHH pathway and activation by SHH promotes the expression of the cell cycle proteins cyclinD1 and CyclinD2 leading to GCP proliferation (Behesti and Marino 2009). A high expression level of MYC is reported to cause progression of MB to an anaplastic phenotype and has been linked to a poor prognosis while even though MYCN shows some association with large cells and anaplastic MB yet it is less established as a marker for an adverse outcome (Aldosari et al 2002; Pfister et al 2009).

Both SHH and Wnt subgroups rarely show copy number abnormalities of chromosome 17, amplification of MYC and MYCN or any other widespread ploidy changes. MB occurred also in 5% of the Li Fraumeni syndrome’s patients carrying mutation in the suppressor gene TP53 (Northcott 2009). Other known pathways are involved in the normal cerebellar development found also to be aberrant in some of the MB. For example a disturbance of the RAS-MAP upregulation through downstream components such a MAP2K1, MAP2K2, and MAPK1/3. It is found to be correlated with metastatic behavior (Gilbertson and Clifford 2003). Also, overexpression of the EGF receptor family member ERBB2 is linked to metastatic behavior. A number of proto-oncogenes in MB such as CDK6, PDGFRA, KIT and MYCL1 have been found to be amplified by array CGH. A single copy numbers gains of MET locus on chromosome 7q in 38.5% of the cases in 13 MBs (MacBabe 2006; Tong et al 2004).

The Notch pathway was found to be implicated in MBs pathogenesis in a number of studies. Notch promote granule cell precursor (GCP) proliferation and prevents their differentiation (Behesti and Marino 2009). Increased copy number of Notch2 has been found in 15% of the studied MBs. Also, mutated Hes1 gene that unregulated the Notch pathway have been found in a small study group, although it has been associated with poor prognosis and outcome, its role and implication should be carefully considered and further examined (Fan et al 2004; Thompson et al 2006; Kool et al 2008; Northcott et al 2009).

Due to technology limitations and the availability research strategies most molecular studies of MBs , we are still missing the MB specific molecular markers. Hopefully, MB subtypes specific markers will be discovered by using the advanced technologies which enables us to study MB at different levels: DNA by next generation sequencing, gene expression by transcriptomic and protienomic, epigenomic and miRs.

An accurate classification and the stratification will implicate the medical care. An optimal classification will differentiate between MB in each age interval (infancy, childhood and adult) and between the subgroups in each age.

There is a general consensus that a better understanding of the disease biology should allow us to develop more effective and less harmful treatments of MB.

Northcott et al (2011) generated a class prediction algorithm, an 8-gene classification model which successfully predicted the survival status for 47 out of the 60 patients profiled. The markers of the cerebellar differentiation (β-NAP, NSC11, TRKl) and component of the extracellular matrix (lysyl hydroxylase[PLOD], collagen TypeVai and elastin) predict favorable prognosis. While genes involved in cell proliferation and metabolism (MYBL2, enolase 1, LDH, HMGl[y], and cytochrome C oxidase) as well as ribosomal protein coding genes predict poor prognosis.
5. MicroRNA (miR) and its correlation with clinicohistopathological classification

The field on miRNA emerged in the last few years, concentrates on small non-coding, single strand RNA molecules that are found to play a regulatory role on gene expression. Differential microRNA (miR) expression analysis has also contributed to our knowledge on MB pathogenesis. The miRs are the short fragments of endogenous noncoding RNA that play an important role in the developmental processes by regulating gene expression. Target mRNAs are either degraded or translated by specific miRNAs. Ferretti et al (2008) performed one of the earliest expression profiles on MB. Northcott et al (2009) identified amplification of miR17/92 polycistron proto-oncogen in 6% of pediatric MBs and showed upregulation of miR17/92 expression in a large percentage of primary cases. Similarly, Pierson et al. (2008) demonstrated decreased expression of miR-124a in primary MB as well as in MB cell line. Onvani et al. (2010) have reported that miR124a as a negative regulator of CDK6 which are found to be overexpressed in MB (Mendrzyk et al 2005). Additional oncogenic targets, such as miR-30b and miR-30d have also been proposed through miRNA profiling (Lu et al 2009).

Northcott et al (2009) have described subgroup classification based on transcription profile, using mRNA and miRNA examination. They identified 4 distinct subgroups including the well known Wnt and SHH and another two independent subgroup C and D. It has been found that mir17/92, cluster of oncogenic miRNAs, was highly expressed in SHH tumors in association with MYCN expression, while group C was found to be correlated with MYC. High-resolution SNP array profiling on a group of >200 MB revealed high-level amplification of miR-17/92 on 13q31 (Northcott et al 2009). It has been found that miR-17/92 and related paralogs (miR-106a/363 and miR-106b/25) were identified as the most highly upregulated miRNAs in MB when compared with normal cerebellum in this analysis. The combination of miR 17/92 amplification and consistent overexpression suggested miR-17/92 as a key player in MB pathogenesis. There is evidence that miR17/92 might cooperate with SHH in MB, as it showed preferential upregulation in SHH subtype.

Recently the role of miRNA in MB has been studied on 14 primary cases using profile of 248 miRNAs showing a general biased downregulation in MB cells as compared to the control cells. A subset of 86 miRNAs which were previously reported to be expressed in neuronal tissues and/or cancer studied in cohort of 34 among them two neuronal candidates miR-9 and miR-125a were chosen for functional analysis. Induction of their expression resulted in the decrease in tumorigenic features: promoted apoptosis, inhibited cell proliferation and impaired anchorage-independent growth. Moreover loss of miR9 and miR125a correlated well with upregulation of truncated trkC which was identified as a target for posttranscriptional repression (Northcott 2009).

In order to discriminate between miRs deregulation in SHH-driven MB from non SHH-cases, 31 MBs studied using a set of 250 miRs. Two groups were defined GLI1-high and GLI1-low. A set of 34 miRs was found with a significant differential expression between the two classes. For functional analysis of the GLI1-high class three candidates (miR-125b, miR-324-5p, and miR-326) exhibiting reduced expression were chosen based on their predicted capacity to target the SHH family members, Smo and Gli1. They were proven to repress Smo mRNA level in the MB cell line (Ferretti et al 2008).

SNPs array profiling of more then 200 MB revealed copy number aberration of multiple unreported regions including high level amplification of miR17/92.
Another miRNAome study of 90 MB revealed that four distinct molecular subgroups can be described. These subtypes include the well characterized Wnt and SHH subgroups and another 2 subgroup designated C and D (Northcott et al 2009).

The miR-17/92 was the most highly expressed in SHH-driven MB but also in tumors exhibiting high MYCN (SHH) and MYC (group C,Wnt) expression. MiR-17/92 transcriptional upregulation by N-Myc and Myc and confirming miR-17/92 aberrancy in a large percentage of the MBs (about 60%). Based on experiments on mice it was suggested by Northcott et al (2009) that miR 17/92 cooperate with SHH signaling to promote and/or enhance CGNP proliferation.

The miRs studies are still in their initial stage and we are still far from understanding their exact role and how they affect processes in MB pathogenesis.

6. Epigenomic and its correletion with clinicohistopatological classification

Until recently the thought was that genetic alteration is the main cause of each tumor development and progress. Researchers invest their efforts in finding a tumor specific pattern of genetic alteration. Over the past few years another aspect has arisen which is the deregulation of epigenetics to malignancy (Jones and Baylin 2002; Bernstein et al 2007; Kouzarides 2007; Kongham et al 2008; Esteller 2008).

Epigenetics involves nongenetic DNA modifications that result in changes in gene expression. These changes include gene promoter methylation on cytosine residues, most frequently of the CpG islands of the promoter, as well as their histone code. These changes are found to be involved in pathogenesis of tumors including MB, through hypermethylation of promoter of tumor suppressor genes and consequently silencing them (Kongham et al 2008).

Fruhwald et al (2001) showed methylation of up to 1% of all CpG island in 17 primary medulloblastoms, it was linked to poor prognosis.

Epigenetics is defined as "mitotically heritable changes in gene expression that are not accompanied by modifications in primary DNA sequence". It is highly correlated with the MB class were ZIC and NSCL1, encoding transcription factors that are specific for cerebellar granule cells point to the MB arising from cerebellar granule cells.

Anderton et al(2008) have identified tumor –specific methylation of COL1A2 in 77% of the studied primary MBs (46 out of 60) and showed an age-dependent methylation pattern for this gene in desmoplastic tumors, which presented COL1A2 as a potential MB subtype biomarker. Kongkham et al. (2008) identified serin protease inhibitor kuntiz-type2 (SPINT2/HAI-2), an HGF/cMET signaling inhibitor, as a novel tumor suppressor gene that is frequently silenced by promoter hypermethylation in MBs (Kongham et al. 2008). Also Waha et al (2007) found promoter hypermethylation-induced reduction of SCG5 expression in primary 16 out of 23 primary cases compared to normal cerebellar controls (Waha 2007), points to its possible role in pathogenesis of MB. Furthermore, promoter hypermethylation-mediated silencing of CASP8, HIC1 and RASSF1A tumor suppressor genes has also been discovered in more than 30% of MBs by various groups (Lindsey et al 2004).

Pfister et al (2007) showed a striking association between samples classified as either "low methylators" or "high methylators" and patient outcome, where the "high methylators" group exhibited reduced overall survival.

Also the GLI C2H2-type zing-finger protein family member ZIC2 was identified as hypermethylated and thus it has been silenced (Pfister et al 2007).

It has been found that EHMTI function as part of a transcriptional repressor complex that mediates gene silencing by promoting dimethylation of H3K9 (Tachibana et al 2005), a
repressive epigenic modification (Bernstein et al 2007; Kouzarides 2007) in the promoter regions of target genes. An obvious correlation between loss of EHMTI leads to H3K9 hypomethylation.

Another study using microarray-based differential methylation hybridization (Waha et al 2007) identified hypermethylation of the SCG5 (secretory granule, neuroendocrine protein 1[7B2 protein] gene) in 16 out of 23 (70%) primary MB. Expression of SCG5 found to be downregulated in the MB in comparison with normal cerebral controls. Another gene that found to be down regulated is SPINT2 that was found in 41 out of 56 primary MB. Stable expression of SPINT2 resulted in attenuation of the malignant phenotype: inhibiting cell proliferation, anchorage-independent growth in soft agar and cell motility, of cell lines (Kongham et al 2008). This study suggested that SPINT2 is a suppressor gene. Treatment of MB cell lines suggesting that SCG5 is a suppressor gene (Fruhwald et al 2001) or increased gene with demethylation agent (5-aza-2'deoxycytidine) reduced colony formation expression (Anderton et al 2008; Kongham et al 2008).

The MB epigenomic studies demonstrate that not only the genetic alteration can cause loss of control in a cell and transformation to a malignant cell but also other mechanism can cause malignancy, implicated epigenetic gene silencing as important mechanism of the tumor suppressor gene inactivation in MB.

7. Summary

The reported genetic alterations of MB, either chromosomal or molecular, are so far not specific. The main distinct subgroups are the Wnt and the SHH both account for 30-40% of MB. These pathways are common in many other tumors, suggesting they are not exclusive to MB. There are some other pathways involved in MB pathogenesis that might be more specific to MB. Similarly, the chromosomal aberration i(17q) which is found in about 40% of MBs, as well as in many other tumors including in chronic myelocytic leukemia (CML) can possibly be a secondary chromosomal aberration. Some of the features found in different subtypes but not in an equal distribution, for instance i(17q) were found in 34%,36%,12% in classic, large cell and desmoplastic MB respectively and are associate with poor prognosis (Gilbertson & Ellison 2008). Another example NOTCH and PDGF, they both have been found in A and B Kool's subtypes and also subtypes C, D and E share increased expression of neural differentiation genes. Another example is the Wnt-β catenin, found in all subtypes defined in Northcott's classification. This overlapping between the different subtypes, points toward the fact that some of the alterations are not, necessarily, a specific prognostic marker. Studies have been done on a mice model and on cell lines in order to learn more about pathogenesis of MB are important; however the data learned from these experimental systems should be first corroborated with the data learned from human primary MBs, before going to conclusions on the pathogenesis of human MB. This is the reason for focusing in this chapter mainly on the studies done on primary human MBs studies. Due to the variable results, the exact and specific chromosomal changes in MB which is a crucial event in pathogenesis, is still unknown.

Gilbertson and Ellison (2008) wrote in their review: "Genomic-seeing the wood and the trees". The literature is full of studies (over 200 papers) on genetic alteration in MB trying to understand the MB pathogenesis, some of them corroborate with each other. Most of the studies have been done from different research points of view and emphasis, using different technologies. Presently, there are at least 5 different suggestions for classification and
stratification of MB: Thompson’s (2006), WHO (2007), Kool’s (2008), Pefister’s (2008) and Northcott’s (2011). It is very difficult to combine them to one clear cut classification (Table 1).

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<th>&quot;THOMPSON’S (2006) CLASSIFICATION (46)</th>
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<td>A</td>
<td>Gain:17q</td>
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<td>B</td>
<td>Loss: 17p</td>
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<tr>
<td>C</td>
<td>SHH PTCH,SUFU mutation</td>
<td></td>
<td></td>
<td>Monosomy 6</td>
<td>≥3 years</td>
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<tr>
<td>D</td>
<td>SHH PTCH,SUFU mutation</td>
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<td>≤3 years</td>
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<td>E</td>
<td>Gain:17q</td>
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</tr>
<tr>
<td>*KOOL’S(2008) CLASSIFICATION (52)</td>
<td>WHO CLASSIFICATION</td>
<td>PROGNOSIS</td>
<td>MOLECULAR ALTERATION</td>
<td>CHROMOSOMAL ABERRATION</td>
<td>AGE OF ONSET</td>
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<td>Wnt-β-catenin mutation NOTCH, PDGF</td>
<td>Monosomy 6</td>
<td>Older children</td>
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<tr>
<td>B</td>
<td>desmoplastic</td>
<td>SHH PTCH1 mutation NOTCH, PDGF</td>
<td>9q loss</td>
<td>Young children years and adults</td>
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<tr>
<td>C</td>
<td>classic metastases</td>
<td>Neural differentiation genes</td>
<td>17 alteration, loss of X chromosome (females)</td>
<td>children</td>
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</tr>
<tr>
<td>D</td>
<td>classic metastases</td>
<td>Neural differentiation genes Photoreceptor genes</td>
<td>17 alteration, loss of X chromosome (females)</td>
<td>children</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>classic metastases</td>
<td>Photoreceptor genes</td>
<td>loss of X chromosome (females)</td>
<td>Young children</td>
<td></td>
</tr>
<tr>
<td>*PFISTER’S(2009) CLASSIFICATION (80/260)</td>
<td>WHO CLASSIFICATION</td>
<td>PROGNOSIS</td>
<td>Frequency</td>
<td>OS</td>
<td></td>
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<tr>
<td>A</td>
<td>Large cell/anaplastic</td>
<td>Poor prognosis metastases</td>
<td>6%/4%/10%</td>
<td>13%</td>
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</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>WHO Classification (103)**</th>
<th>Molecular Alteration</th>
<th>Chromosomal Aberration</th>
<th>Age of Onset</th>
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<tbody>
<tr>
<td><strong>Wnt</strong></td>
<td>MYC↑, Wnt-β catenin</td>
<td>Monosomy 6</td>
<td>Distributed age median 9-10 years, 3:1 F/M</td>
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<tr>
<td>SHH</td>
<td>Desmoplastic- predominant Anaplastic, large cell</td>
<td>MYCN↑, Wnt-β catenin</td>
<td>Infants ≤3 years-most common, adults ≥16 years</td>
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<tr>
<td>C</td>
<td>Metastases(46.5 %)</td>
<td>OTX2↑, FOXG1B↑, MYC(8q24)↑, Wnt-β catenin, Neural development*</td>
<td>Childhood peak 3-10 years</td>
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<tr>
<td>D</td>
<td>Metastases(29.7 %)</td>
<td>OTX2↑, FOXG1B↑, Wnt-β catenin, Neural development*</td>
<td>Distributed age median 9-10 years</td>
</tr>
</tbody>
</table>

**WHO (2007): Classic, desmoplastic, MB with extensive nodularity, anaplastic, Large cell


** See table 2 in Ellison 2010, Table 2 in Huse and Holland 2010, Table 1-Northcott 2010 J. Clin.Oncol.

Parenthesis -Number of samples

There is also early evidences that epigenetics and miRs might play a role in MB pathogenesis and can be used as a prognostic tool. However, the data regarded to epigenetics and miRs in MB is still limited and uncompleted, as part of the studies done on MB cell line which might point to a candidate involved genes with no assurance for there role in the MB tumor. There are few studies on primary MBs, thus any conclusion from this data is still immature. This
emphasized the need for further studying the MB pathogenesis for either specific germ line mutation or other specific level of alteration (transcriptome, proteome, epigenome levels). These should be done as a multi-center study, on a large size of cohort including sufficient number of samples of each MB subtype including adult and childhood MBs. The study should be performed uniformly using different levels of examinations: histologic, cytogenetic, molecular, transcriptome, proteome, epigenetics, and miRs. Hopefully such a study will provide us with more personalized medical care with less adverse side effects.

8. References


identifies five medulloblastoma subtypes with distinct genetic profiles, pathway signatures and clinicopathological features. PLoS One 3:e3088


Molecular Targets of CNS Tumors is a selected review of Central Nervous System (CNS) tumors with particular emphasis on signaling pathway of the most common CNS tumor types. To develop drugs which specifically attack the cancer cells requires an understanding of the distinct characteristics of those cells. Additional detailed information is provided on selected signal pathways in CNS tumors.

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