Mechanism of paediatric medulloblastoma

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Abstract
Paediatric medulloblastoma, while rare, is a cancer that affects hundreds of children each year between the ages 0-14 years. Prognosis is typically poor and dependent on variant signalling pathways underlying pathogenesis of tumours. The following discussion will briefly describe four molecular pathways and tumour histology of paediatric medulloblastoma, as well as the methods to identify and treat each variant.

Introduction
Medulloblastoma is a malignant, stage IV brain tumour which occurs more commonly in children than adults. Medulloblastoma is the most common form of high-grade embryonal neuroepithelial central nervous system (CNS) tumour in children and the leading cause of death in paediatric cancer patients [1,2]. The incidence of medulloblastoma has been estimated as 4.82 per 1,000,000 persons, with a male predominance and mean age of diagnosis at 5.8 years [1]. The 5-year and progression-free survival rates of children diagnosed with medulloblastoma between 1990 and 2009 has been reported as approximately 70% with children over the age of 14 having a greater survival rate [3,4]. Poor prognosis as indicated by a 5-year survival rate of approximately 13% is associated with medulloblastoma recurrence.

Genomic studies have identified 4 types of medulloblastoma, Wnt and Shh (Sonic Hedgehog), group 3 and group 4, each associated with different prognostic factors. Wnt and Shh were named after the signalling pathways underlying pathogenesis of tumours, while less is known of the biology of the generic group 3 and group 4. Metastases is rare in Wnt and Shh while frequent in group 3 and group 4 contributing to poor prognosis [5,6].

Tumour pathology and location
Tumours with different histology arise from the brain matter near the posterior fossa, commonly affecting the cerebellar vermis and hemispheres, and metastasize through the CNS [5]. Five types of tumours found in children with medulloblastoma have been described. Classic type tumours are found in 70% of cases and are characterized by sheets of round cells with excess cytoplasm [5]. Desmoplastic tumours are composed of undifferentiated cells which form a casing of connective tissue around the neoplasm and originate from the cerebellar hemispheres as well as cells from the external granular layer [5]. Such tumours can also be nodular, forming aggregates of differentiated cells that can be either localized or metastatic [5]. Lastly, large cell and anaplastic tumours are frequently found together and have a mix of round cells with expanded nuclei and cells whose nuclei change shape [5].

Molecular subgroups
The subgroups of medulloblastoma arise from faulty cell signalling pathways within neuroectodermal cells responsible for the formation of parts of the skull, brain, and surrounding structures [5,6]. The Wnt signalling pathway is vital for structural development in children as it triggers mitotic stem cell division and differentiation [5,6]. Normally within a cell, a β-catenin degradation complex composed of multiple proteins keeps intracellular β-catenin levels low [5,8]. When a Wnt protein binds to a Fzd receptor, it activates a Disheveled protein that inactivates the degradation complex, allowing β-catenin to enter the nucleus to trigger transcription [5,6-8]. Common mutations involve germline missense mutations of the Apc gene that codes for the protein adenomatous polyposis coli (Apc) which is a part of the β-catenin degradation complex, as well as somatic mutations to the β-catenin levels gene. As a result, β-catenin cannot be broken down and keeps the pathway activated resulting in excess cell proliferation and tumours [5-7].

The Sonic Hedgehog (Shh) pathway also plays a role in the development of stem cells, the central nervous system, and other tissues [5,9]. The Shh protein must bind to a patched protein located on a brain cell to cause a shape change [5]. In response, a Smoothened (Smo) protein also located on the cell membrane is activated which in turn activates a Gli protein [5]. The Gli protein can then move into the nucleus where it triggers gene transcription and results in cell proliferation [5,9]. Additionally, Sufu proteins play a role in inhibiting Gli to turn off the pathway [5]. Somatic cell mutations are common on the Smo gene that encodes the Smo protein, as well as on the Pch1 and Sufu genes that encode the Patched and Sufu proteins which makes them unable to inactivate Gli [5,8,9]. Furthermore, additional abnormalities have been observed which result in the amplification of Gli proteins [5,8]. As a result, the pathway stays activated and causes excess cell division and tumours [5].

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The cause for group 3 and group 4 subgroups are less clear and are thought to arise from interactions between multiple cell signalling pathways [5]. What is known pertains to the OTX2 gene which aids in brain development and is overexpressed in both groups [5]. Additionally, the Myc gene is mutated in group 3 and causes issues with many genes whose functions include promoting stem cell proliferation [11]. When mutated, the gene amplifies these pathways and results in the formation of tumours [5]. One of the few mechanisms identified in group 4 is that one X-chromosome is commonly missing, but the origin of the tumours is unknown [5].

**Identification**

To identify the presence and location of a gene mutation, microarray analysis is commonly used and is showing great potential for finding the genetic basis of certain cancers [12]. The method of microarray analysis requires tissue cells to be extracted from a cancerous tumour and compared to those of a healthy cell [12]. To begin, mRNA is isolated from the cells, stabilized, and fixed with different coloured fluorescent markers to make cDNA. Next, the cDNA is poured over wells that contain complimentary RNA strands that bind to specific gene regions [12]. The wells are then analysed for the level of fluorescence emitted which indicates the presence of specific genes from the cell's genetic material [12].

Applying this to paediatric medulloblastoma, patients who are suspected of possessing the Wnt subgroup can exhibit additional fluorescence from cDNA extracted from the middle of chromosome 3 as it pertains to the overexpression of the Ctnnb1 gene [8,13,14]. Microarray analysis can also be used to detect the frequent single nucleotide change on the APC gene located on chromosome 5 [13,15]. Additionally, elevated cellular β-catenin levels can be measured through immunostaining [6,8,11]. If the Shh subgroup is suspected, then either additional or reduced fluorescence can be observed on the Ptc1, and Sufu genes located on cDNA from chromosome 9 and 10 as both amplifications and deletions are common [5,9,13]. In contrast, additional fluorescence can be observed on chromosome 7 as the Smo gene is frequently amplified [10,13]. Finally, fluorescence will be observed on DNA near the end of chromosome 8 if a patient is suffering from the group 3 subgroup as this is where the Myc gene is located and is commonly amplified [8,13,16]. Microarray analysis cannot be used to identify group 4 medulloblastoma as its basic mechanism is not yet understood [5].

**Prognosis**

Treatment effectiveness of medulloblastoma varies but normally starts with surgery and is followed up with bothradiation and chemotherapy regardless of the subtype [3,5]. Patients with the Wnt subgroup typically exhibit classic type tumours and have the highest 5-year survival of over 90% [5,8]. The Shh subgroup usually manifests as desmoplastic/nodular tumours, is best treated with high-dose chemotherapy, and has survival closely tied with age of the 0-3 age-group has a 90% 5-year survival rate [5,17]. Patients with group 3 and group 4 subgroups commonly display classic type and large cell/anaplastic tumours, with the latter being less frequent [5,17]. Furthermore, patients have a lower 5-year survival at roughly 60% and 33% respectively due to its tendency to metastasize [5,17]. Therefore, the most effective treatments rely on early detection and include additional radiation treatments to prevent subsequent tumours from forming [5,7,17].

Overall, the best outcomes are found in patients who are above the age of 3, with desmoplastic tumours smaller than 1.5cm³, and who do not present metastases or additional lesions [5]. Although the survival rate for medulloblastoma is improving, many patients are succumbing to the side-effects of treatment which has brought forth alternate therapies that include targeting specific molecular mechanisms and proton-beam therapy [5,17,18].

**Future of treatment in Canada**

Proton-beam therapy is a treatment that is gaining popularity where charged particles are fired at the tumour over a small range [18]. The protons do not pass as far as the particles used in radiation therapy, and the focused range of proton emission makes it much more precise so there is less damage to healthy tissue and cognitive damage is avoided [17-19]. Although it is proving to be an effective way to treat paediatric medulloblastoma and other cancers it is not currently available in Canada. As a result, patients can spend up to $150,000 for treatment in the United States [18,19]. In response to this, CDL Laboratories have announced an investment of $70,000,000 to build a clinic in Montreal with the goal of taking patients in the coming years [18].

**Conclusion**

In conclusion, cell signalling pathways are complex and disruptions within them can lead to cancer. Children are most susceptible to medulloblastoma due to their developing brains and the specific subgroup can potentially be deduced through microarray analysis technology. Additionally, knowing which subgroup a child suffers from is important as it influences the success of treatment. Finally, future research can focus on discovering the mechanism of group 4 medulloblastoma and the use of proton-beam therapy in the hopes to reduce its dismal 5-year survival rate.

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