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Expression of *ATOH1* gene and activated signaling pathways for the neurogenesis of cerebellar granule cells: A review

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Abstract: Granule cells in the cerebellum are derived by the proliferation of cells from the rhombic lips of the metencephalon. Atonal homolog 1 (*ATOH1)*, a protein encoding proneural gene, plays an essential role in the neurogenesis of the cerebellar granule cells. It encodes the basic helix loop helix (bHLH) family of transcription factor ATOH1. Expression of the *ATOH1* gene in the rhombic lips of the metencephalon results in specification and proliferation of the granule neuron progenitors. Four major signaling pathways- Sonic hedgehog (Shh), Notch, Wingless related integration site (Wnt) and Bone morphogenetic protein (BMP) play an essential role in the regulation of the *ATOH1* gene. Shh, Notch and Wnt signalings induce expression of the *ATOH1* gene for the proliferation of the granule neuron progenitors whereas BMP signaling is involved in the differentiation of the granule neuron progenitors into the granule cells. Aberrant expression and mutation of the *ATOH1* gene result in cerebellar medulloblastoma, the phenotype of trembling gait, cerebellar ataxia and hearing loss.

Keywords: *ATOH1* gene; cerebellum; granule cell neurogenesis; medulloblastoma; sonic hedgehog;

1.0 INTRODUCTION

Dorsolateral parts of the alar plate of the metencephalon form the rhombic lips. Rhombic lips compress cephalocaudally to form the cerebellar plate. Two germinative zones, the ventricular zone and rhombic lips, are established in the cerebellar primordium. Granule cells and other glutamatergic neurons are derived by the proliferation of cells from the rhombic lips whereas purkinje cells and other gamma aminobutyric acidergic (GABAergic) neurons are derived by the proliferation of cells from the ventricular zone of the metencephalon (Rahimi-Balaei et al., 2018; Tam et al., 2021). Histological studies showed that the external granular layer is the outermost layer of the fetal cerebellum and it is formed by the migration of cells from the rhombic lips (Amore et al., 2021). Then, the inward migration of the cells from the external granular layer forms the internal granular layer. The internal granular layer is named as granular layer after birth (Marzban et al., 2015). The molecular layer is consists of stellate and basket cells and the purkinje layer has purkinje cells

(Leto et al., 2016; Wefers et al., 2018). Among different types of neurons in the cerebellum granule cells are the highest in number and have intricate connections with other neurons for the functional integrity of the cerebellum. It is essential to understand the neurogenesis of the cerebellar granule cells which are playing an essential role in maintaining the fine movement of the body (Tam et al., 2021).

Proneural genes are responsible for the initiation of neurogenesis during the development of the nervous system. These genes trigger the neuronal lineages to promote into the neuronal progenitors. Neuronal progenitors undergo neuronal differentiation by exiting the cell cycle and by activating the cascade of differentiation genes (Bertrand et al., 2002). The rhombencephalon of the developing brain is segmented along the anteroposterior axis to form rhombomeres and these are the sites of gene expression for the further development of the rhombencephalon. Dorsal parts of the rhombencephalon differentiate into rhombic lips and generate different neuronal lineages. The most anterior part of the rhombic lips is known as the upper rhombic lip and it is responsible to produce granule cells (Belzunce et al., 2020). Granule neuron progenitors migrate from the rhombic lips to form the external granular layer in the embryonic life. They first proliferate and then exit the cell cycle to become granule cells. After the formation of the granule cells, they migrate through the molecular layer and form the internal granular layer (Owa et al., 2018). The rest of the parts of the rhombic lips is known as the lower rhombic lip and it is responsible to produce deep brainstem nuclei and precerebellar nuclei (Belzunce et al., 2020).

The expression of the atonal homolog 1 (*ATOH1*) gene is essential for the neurogenesis of the cerebellar granule cells. In humans, the *ATOH1* gene is located in band 4q22.2 of chromosome 4 within 93,828,753 to 93,830,964 base pairs, with a single exon. In mice, it is located on chromosome 6. *ATOH1* is known as mouse atonal homolog 1 (*MATH1)* in mice (NCBI., 2021). It is acted by regulating the signal transduction pathway of the sonic hedgehog (Shh). The protein encoded by this gene is ATOH1. It belongs to a proneural basic helix loop helix (bHLH) transcription factor and is essential for the neurogenesis, survival and maturation of the cerebellar granule cells and it is also required for the neurogenesis of the brainstem neurons, inner ear hair cells, merkel cells and secretory cells of the intestine. ATOH1 transcription factor consists of two α helices connected by a loop. A larger helix contains basic amino acid residues and it is responsible for binding with DNA. Another helix is smaller in size and consists of flexible loops responsible for dimerization by folding and packing against another helix. Precise regulation of *ATOH1* at its transcriptional and protein levels is essential because of its multiple roles in the formation of various cell types (Jones, 2004; Xie et al., 2017).

The cerebellar primordium consists of two germinative regions; these are the rhombic lips and the ventricular zone. Two genes, atonal homolog 1 (*ATOH1)* and pancreas associated transcription factor 1a (*PTF1-A)* play a crucial role in the neurogenesis of the cerebellar neurons (Belzunce et al., 2020). Atonal bHLH transcription factor 1 (ATOH1) is expressed in the rhombic lips and the pancreas associated transcription factor 1a (PTF1-A) is expressed in the ventricular zone (Hoshino et al., 2005). Granule cells, large projection neurons of the deep cerebellar nuclei and unipolar brush cells are the glutamatergic neurons and they are derived from ATOH1 progenitors (Englund et al., 2006; Machold and Fishell 2005; Wang, Rose, and Zoghbi 2005; Wingate 2001; Yamada et al., 2014). Whereas purkinje cells, nucleo-olivary projection neurons of deep cerebellar nuclei and all the inhibitory interneurons- basket, stellate, golgi and lugaro cells are the GABAergic neurons and they are originated from PTF1-A precursors (Hoshino et al., 2005; Seto et al., 2014; Yamada et al., 2014).

Cellular and molecular studies of the cerebellum are advancing day by day with the advent of modern research methodologies. Still, more studies are required to understand the development and functioning of the cerebellum. The objective of this study is to summarize the role of *the ATOH1* gene and signaling pathways activated during the neurogenesis of the cerebellar granule cells.

2.0 MATERIALS AND METHODS

Total 58 research articles were selected for this review after a rigorous search regarding the *ATOH1* gene, its expression and signaling pathways activated for the neurogenesis of the cerebellar granule cells. Research articles were searched in PubMed and Google scholar databases published in the period of 2000 AD to 2021 AD. Some information regarding the *ATOH1* gene was extracted from the NCBI site. Following keywords were used for the search of research papers: "*ATOH1 gene expression*", "Neurogenesis of granule cells", "Cerebellar granule cells", "Signaling pathways", "Shh signaling", "Notch signaling", "BMPs and granule cells", "Wnt signaling and cerebellum", "Development of cerebellum" and "Mutation of *ATOH1* gene". Among

these keywords, some were used independently and some were used by combing more than one keywords using bullions. Nine articles were searched by using secondary references. After a rigorous search, research articles were screened, duplicates were removed and a total of 58 full articles were selected for the review. The selection process of the research papers was based on, whether the research paper provided the required information to meet the objectives of the study or not, and the publication year of the research paper. Research papers that provided the required information about the *ATOH1* gene, its expression, neurogenesis of the cerebellar granule cells, related signaling pathways and the molecules involved during the neurogenesis of the cerebellar granule cells were included in the study irrespective of animal or human, in vivo or in vitro and geographical distribution of the studies. Research papers published before 2000 AD were excluded from the study. Summary of the selected research articles is given in **Table 1** and **Table 2.**

3.0 DISCUSSION

Expression of *ATOH1* gene encodes bHLH family of transcription factor ATOH1. Expression of the *ATOH1* gene in the rhombic lips of the metencephalon regulates specification and proliferation of the granule neuron progenitors. Four major pathways play an essential role in this process (Corrales et al., 2006; Uziel et al., 2005). Sonic hedgehog (Shh) induces activation of zinc finger/glioma associated oncogene (Gli) transcription factors specifically zinc finger 1/glioma associated oncogene 1 (Gli1). This up regulates the expression of Cyclin D1, Cyclin D2 and Mycn protooncogene, bHLH transcription factor (Mycn). These factors along with jagged canonical notch ligand 1 (JAG1) activate notch receptor 2 (Notch2) and wingless related integration site (Wnt) signaling pathways. Wnt signaling further activates the β-catenin pathway. Activation of these signalings together regulates the expression of bHLH transcription factor ATOH1 for the specification, proliferation and synaptogenesis of the cerebellar granule neuron progenitors and granule cells (Fogarty et al., 2007). Whereas BMP signaling is responsible for the differentiation of the cerebellar granule neuron progenitors into granule cells (Machold et al., 2007). Myeloid ectopic viral integration site 1 (Meis1) factor is involved in the degradation of ATOH1 in the external granular layer via BMP signaling. In addition to the *ATOH1* gene, several proneural genes such as *neurogenin 1 (NEUROG1)* and *neurogenin 2 (NEUROG2)* act as fate determining factors of cells of cerebellar rhombic lips and the ventricular zone into different types of cerebellar neurons (Englund et al., 2006; Schuurmans et al., 2004; Wingate, 2005) **(Figure 1)**.

3.1 *ATOH1* gene is expressed during the neurogenesis of the cerebellar granule cells

Proneural gene *ATOH1* is expressed in the rhombic lips of the metencephalon and maintains the specification and formation of the granule neuron progenitors by controlling the maintenance of the primary cilia on these cells. The primary cilium is an antenna like protrusion on the surface of the granule neuron progenitors (Chang et al., 2019). Its center core consists of an axoneme with nine doublets of microtubules within a ciliary membrane, originating from the basal body (mother centriole) within the cell (Castellino & Kenney, 2019; Chang et al., 2019). For this *ATOH1* regulates the expression of the centrosomal protein (Cep131) in the granule neuron progenitors, which is responsible for the clustering of centriolar satellite in the basal body for maintaining the primary cilium (Castellino & Kenney, 2019). The binding of Shh to the receptor patched1 (Ptch1) relieves its suppression of smoothened (Smo) in the ciliary membrane and that is followed by the activation of zinc finger/glioma associated oncogene (Gli) transcription factors at the tip of the primary cilium. This factor translocates to the nucleus and activates proneural genes including *ATOH1* in the granule neuron progenitors for their proliferation (Chang et al., 2019). Another study suggests that expression of Gli transcription factors activates Cyclin D1, which accelerates the cell cycle and helps in the proliferation of granule neuron progenitors but also upregulates the ATOH1 protein that maintains granule neuron progenitors in an immature state for their proliferation (Miyashita et al., 2021).

ATOH1 gene consists of three paralogs- *ATOH1a*, *ATOH1b* and *ATOH1c* (Belzunce et al., 2020). These are expressed within the rhombencephalon and play an important role in the development of the cerebellum. *ATOH1c* is expressed in the upper rhombic lip whereas *ATOH1a* is expressed in the dorsal cells of the lower rhombic lip and *ATOH1b* is expressed lateral to the expression of *ATOH1a*. Expression of *ATOH1a* is required for the neuronal specification of the cells of the lower rhombic lip whereas progenitor cells of the lower rhombic lip differentiate into neurons by the activation of *ATOH1b*. Thus, it can be said that *ATOH1a* is a cell fate selector gene whereas *ATOH1b* is a neuronal differentiation gene. This transition of expression of *ATOH1a* to *ATOH1b* in the cells is regulated by Notch-activity. *ATOH1a* cells disappear

Table 1: Major gene and signaling pathways expressed for the specification, proliferation and differentiation of the cerebellar granule cells.

Genes/Signalling pathways involved	Major findings	Study models	References
***ATOH1* gene**	The ventricular zone and the rhombic lips are two germinative zones in the cerebellar primordium. Glutamatergic neurons are produced from the rhombic lip and GABAergic neurons are produced from the ventricular zone of the cerebellar primordium. Expression of *ATOH1* is required for the production of glutamatergic granule cells whereas *PTF1-A* is required for the production of GABAergic neurons. ATOH1 regulates the formation of primary cilia on the surface of the granule neuron progenitors for their proliferation. Cyclin D1 stabilizes ATOH1. Mutation of the *ATOH1* gene may occur at its phosphorylation site S193 and may result in a phenotype of trembling gait, cerebellar ataxia and hearing loss.	In vivo and in vitro studies in mouse, zebrafish, and human samples	Amore et al., 2021*; Belzunce et al., 2020; Chang et al., 2019; Diaz et al., 2002; Englund et al., 2006; Fink et al., 2006; Hoshino et al., 2005; Klisch et al., 2011; Leto et al., 2016*; Machold & Fishell., 2005; Marzban et al., 2015*; Miyashita et al., 2021; NCBI., 2021; Puelles & Ferran, 2012*; Rahimi-Balaei et al., 2018*; Sheykholeslami et al., 2013 ; Tam et al., 2021*; Wang et al., 2005; Wefers et al., 2018; Wingate, 2005*; Xie et al., 2017; Yamada et al., 2014
Shh signaling	Shh signaling is essential for: the proliferation of the granule neuron progenitors/granule cells, proliferation of the ventricular zone derived progenitors/cells, cerebellar foliation, patterning of the cerebellum and to increase the size of the cerebellum. Primary cilia regulate the Shh signaling in the progenitors. Ptch1, Smo, Bmi1 receptors are required for Shh signaling.	In vivo and in vitro studies in mouse and chick	Blaess et al., 2004; Carballo et al., 2018*; Castellino et al., 2019; Corrales et al., 2004; Corrales et al., 2006; De Luca et al., 2016*; Grausam et al., 2017; Huang et al., 2010; Lewis et al., 2004; Subkhankulova et al., 2010; Wingate, 2001; Zhang et al., 2000
Notch signaling	Expression of the *ATOH1* gene regulates Notch signaling. Notch signaling regulates the proliferation of granule neuron progenitors and prevents their differentiation.	In vivo and in vitro studies in mouse, embryonic cerebellum study in the allen brain atlas	Gazit et al., 2004; Komine et al., 2007; Lake et al., 2014; Nam et al., 2002; Zhang et al., 2021
BMP signaling	BMP signaling antagonizes with Notch signaling to regulate the neurogenesis in the rhombic lips. BMP signaling inhibits the proliferation and regulates the differentiation of the cerebellar granule cells by degrading ATOH1 using Meis1 and by antagonizing Shh through Smad5 signaling. BMPs activity prevents cerebellar medulloblastoma.	In vivo and in vitro studies in mouse and chick	Angley et al., 2003; Grimmer & Weiss., 2008; Machold et al., 2007; Owa et al., 2018; Qin et al., 2006; Rios et al., 2004; Zhao et al., 2008
Wnt signaling	Wnt/β-catenin signaling regulates stem cell proliferation, their fate determination and protection. It is also required for specification, patterning and synaptogenesis during the development of the cerebellum. Its expression rises in cerebellar medulloblastoma.	Review	Komiya & Habas, 2008*; MacDonald et al., 2009*; Rao & Kühl, 2010*; Toledo et al., 2008*; Wang & Liu, 2019*

Asterisk (*) represents the review article.

upon the inhibition of Notch activity and they become *ATOH1b* cells (Belzunce et al., 2020). From these findings, it can be concluded that the *ATOH1* gene is expressed in the rhombic lips of the metencephalon and it is required for the specification and proliferation of the granule neuron progenitors in the rhombic lips of the metencephalon.

3.2 Sonic hedgehog (Shh) signaling regulates the proliferation of granule neuron progenitors

Hedgehog (Hh) signaling is activated during the period of organogenesis for intercellular communication. Among three hedgehog proteins, ventral midline mesoderm and ventral neural tube secrete the diffusible mitogen Shh during the process of neurulation (De Luca et al., 2016; Zhang, Lin, and Yang 2000). In the cerebellar primordium Shh is secreted by purkinje cells (Corrales et al., 2004; Lewis et al., 2004) and choroid plexi and it is used in the proliferation of the granule neuron progenitors acting through a cascade of signaling pathways within the primary cilium. Canonical Shh signaling is activated by ligand dependent interaction and results in the translocation of Gli family proteins to the nucleus that begins transcription of the target genes (Carballo et al., 2018). Ptch1 and Smo are two essential membrane receptors for Shh signaling. The binding of Shh to Ptch1 relieves its suppression of Smo that activates Gli associated transcription factors Gli1 and Gli2 and expression of Gli1, Cyclins D1/D2 and Mycn. These factors regulate the Notch and Wnt/β-catenin signalings for the expression of the *ATOH1* gene and the progression of the cell cycle for the proliferation of granule neuron progenitors (Grausam et al., 2017), **Figure 1**. Whereas noncanonical Shh signaling is activated through Gli independent mechanisms. Additionally, Shh signaling regulates chemotaxis and cell migration through actin rearrangement and also stimulates the production of the cerebellar interneurons (Carballo et al., 2018).

Mitogenic action of Shh on the granule neuron progenitors is an essential factor also for the formation of the cerebellar fissures (Sudarov & Joyner, 2007) and foliation (Corrales et al., 2004, 2006; Huang et al., 2010). Cerebellar foliation is regulated by the level of Shh signaling. Foliation is impaired in the removal of Shh signaling by decreasing the number of granule neuron progenitors (Corrales et al., 2006). This implies that Shh signaling not only controls the proliferation of granule neuron progenitors but also controls the morphology of the cerebellar foliation. On the loss of Shh activity, there will be a reduction in the number of granule cells resulting in small cerebellar size and abnormal foliation (Lewis et al., 2004).

3.3 Notch signaling promotes the proliferation of granule neuron progenitors

Notch is a transmembrane molecule and it influences the fate of progenitor cells in various organs. Four types of Notch molecules have been identified in mammals, among them, Notch1-3 are expressed in the stem and progenitor cells of the central nervous system and influence neurogenesis and gliogenesis (Blaess et al., 2004; Wang and Liu 2019). The Notch2 receptor is expressed by granule neuron progenitors at the external granular layer. Its expression is increased during the peak of the division of granule neuron progenitors in the external granular layer and bergmann glia (Komine et al., 2007; Nam et al., 2002). Notch signaling begins by the interaction of ligands Delta or Jagged with the Notch molecule. This activates the recombination signal binding protein for immunoglobulin kappa J region (RBP-J) dependent as well as independent and Deltex dependent pathways. RBP-J is a major transcriptional effector of Notch signaling. It is associated with chromatin and plays a role during mitotic cell division (Lake et al., 2014). In RBP-J dependent pathways, the intracellular portion of Notch is cleaved upon ligand binding. Then it passes inside the nucleus and forms a complex structure with RBP-J. This finally results in the expression of various transcription factors responsible for mitotic cell division. Whereas, in RBP-J independent signaling a cytoplasmic protein Deltex is required (Komine et al., 2007; Nam et al., 2002).

The fate of the progenitors and their daughter cells is determined by the expression level of the Notch activity. A study showed that daughter cells with the highest levels of Notch activity have the fate to remain as progenitor cells. Daughter cells with intermediate levels of Notch activity become inhibitory neurons. Whereas daughter cells with very low levels of Notch activity become excitatory neurons. Studies also showed that progenitors change their competence over time to give rise to different types of neurons. For maintaining this dual potential in the progenitors there is a requirement of the Notch activity in the cells. Some of the recent studies showed that cell fate can be changed when *ATOH1* and *PTF1-A* are expressed ectopically interchanging their position. Any type of progenitors may exist in the rhombic lip and ventricular zone of the cerebellar primordium to give either glutamatergic or GABAergic neurons (Zhang et al., 2021). From these findings, it can be concluded that Notch signaling promotes the proliferation of the granule neuron progenitors by mitotic cell division.

Table 2: Other molecules involved during the specification, proliferation and differentiation of the cerebellar granule cells.

Signalling molecules/ Genes/Research methods	Major findings	Study models	References
Fibroblast growth factor (FGF)	FGF is an inhibitor of Shh signaling, promotes differentiation of granule neuron progenitors and stops the proliferation of tumor cells. FGF9 plays role in the postnatal migration of the granule cells.	*In vivo* and *in vitro* studies in mouse	Fogarty et al., 2007; Lin et al., 2009
Choroid plexus	Diminishes the differentiation of granule neuron progenitors of rhombic lips.	*In vivo* and *in vitro* studies in mouse	Krizhanovsky & Ben-Arie, 2006
Neurogenin	Involved in specifying neuronal differentiation and for the sequential phases of cortical specification.	*In vivo* study in mouse	Schuurmans et al., 2004
Genetic inducible fate mapping, High resolution cellular analysis, Mutant studies	Multicellular anchoring centers play role in the pattern formation of the cerebellar foliation.	*In vivo* study in mouse	Sudarov et al., 2007
Cyclin dependent kinase inhibitor 2C *(CDKN2C)* and Tumor protein p53 *(TP53)* genes	Coordinate with Patched to suppress medulloblastoma.	*In vivo* study in mouse	Uziel et al., 2005

3.4 Wnt signaling helps in the proliferation and synaptogenesis of the neurons during the development of the cerebellum

Wnt signaling helps in the synaptogenesis between the neurons during the development of the cerebellum (Díaz et al., 2002; Toledo et al., 2008). It also helps in the specification, proliferation (Komiya & Habas, 2008) and patterning during the development of the cerebellum (Wang & Liu, 2019). It is an autocrine-paracrine signal transduction pathway and acts in three different ways (Subkhankulova et al., 2010). The canonical pathway needs protein β-catenin, while a noncanonical pathway works without the involvement of protein β-catenin. Canonical pathway causes an accumulation of β-catenin in the cytoplasm and its translocation into the nucleus. The noncanonical pathway is activated by binding the Wnt molecule to frizzled (Fz) and its co-receptor. It may use co-receptors neurotrophin receptor homolog 1 (NRH1), receptor like tyrosine kinase (Ryk), protein tyrosine kinase 7 (PTK7), or receptor tyrosine kinase like orphan receptor 2 (ROR2). The noncanonical Wnt/calcium pathway helps to regulate calcium release from the endoplasmic reticulum to control intracellular calcium levels (Komiya & Habas, 2008; MacDonald et al., 2009; Rao & Kühl, 2010). *Wnt* genes are expressed in the cerebellar neurons after the multiplication of the neurons during axonal extension and synaptogenesis and it plays a role in the formation of synapses between the neurons (Lin et al., 2009). These findings suggest that Wnt signaling helps in the proliferation of the progenitor cells and synaptogenesis between the neurons during the development of the cerebellum.

3.5 Bone morphogenetic proteins (BMPs) regulate the differentiation of cerebellar granule neuron progenitors into granule cells

BMPs are members of the transforming growth factor (TGF) family with multiple phenotypic effects on their expression. These regulate cell cycle exit, migration and differentiation of the granule neuron progenitors during the neurogenesis of the granule cells in the cerebellum. Distinct BMPs are expressed in the developing cerebellum and interact with ATOH1 to regulate the differentiation of granule cell progenitors in the rhombic lips (Grimmer & Weiss, 2008; Krizhanovsky & Ben-Arie, 2006). BMP2 and BMP4 are

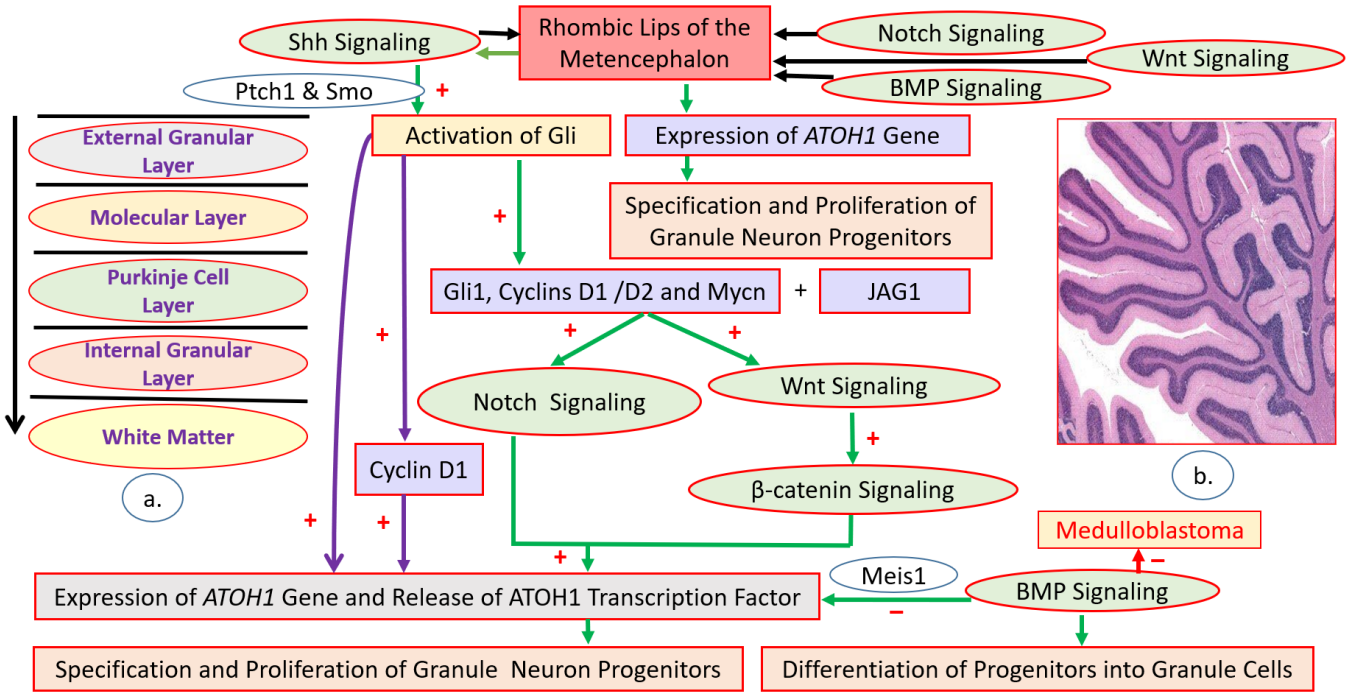

Figure 1. Expression of *ATOH1* gene and activation of signaling pathways for the proliferation of cerebellar granule neuron progenitors and their differentiation into granule cells; a. Layers of fetal cerebellar cortex, b. Adult cerebellum.

expressed in the granule neuron progenitors and the mature granule cells when they are in the external and internal granular layers. They suppress the proliferation of granule neuron progenitors by downregulation of proliferating granule neuron progenitors to exit the cell cycle and regulate the differentiation of the granule neuron progenitors into the granule cells while migrating through the purkinje cell layer (Rios et al., 2004).

BMP7 is secreted from the choroid plexus near the roof plate of the neural tube (Owa et al., 2018). Expression of BMP7 for a longer time antagonizes the differentiation of granule neuron progenitors. Thus downregulation of BMP7 is required for the differentiation of granule neuron progenitors and it is maintained by the expression of neuroblastoma suppressor of tumorigenicity 1 (Nbl1). Nbl1 is expressed under the influence of ATOH1 and relieves the effects of BMP7 and permits the differentiation of granule cell progenitors into the mature granule cells (Krizhanovsky & Ben-Arie, 2006; Qin et al., 2006). Transcription factors, mothers against decapentaplegic homologs (Smads) pass signals from TGF receptors and transfer BMP signals to the nucleus. BMPs bind to the type I or type II serine threonine kinase receptors. Activation of type II receptor transphosphorylates type I receptors. This phosphorylates Smad1, Smad5 and Smad8 proteins. These proteins are involved in BMP signaling to regulate the differentiation of granule neuron progenitors into granule cells (Angley et al., 2003).

3.6 Transcription factor Meis1 coordinates differentiation, maturation and maintenance of the normal morphology of the cerebellar granule cells

There is an expression of transcription factor myeloid ectopic viral integration site 1 (Meis1) in the granule neuron progenitors and granule cells. It is required for the formation of the normal cerebellar structure and the expression of paired box 6 (Pax6) transcription factor in the granule neuron progenitors and granule cells. This forms the Meis1-Pax6 cascade in these cells. Meis1-Pax6 cascade is required for the maintenance of the normal morphology of the granule cells. Meis1 is involved in the degradation of ATOH1 in the external granular layer of the fetal cerebellum via BMP signaling for the cell cycle exit of the granule neuron progenitors and differentiation of them into the granule cells. It is involved in the BMP signaling via induction of Smad family member 1 (Smad1) and Smad family member 5 (Smad5) expressions. It is also involved in the maturation of the granule cells and the formation of their parallel fibers in the molecular layer (Owa et al., 2018). From these findings, it can be concluded that Meis1 coordinates in the differentiation, maturation and maintenance of the normal morphology of the cerebellar granule cells.

3.7 Mutation of *ATOH1* gene and abnormal expression of signaling pathways

ATOH1 gene regulates the specification and proliferation of the cerebellar granule neuron progenitors. These further differentiate into the granule cells. Highly conserved phosphorylation site S193 is located in the bHLH region of the *ATOH1* gene. Mutation of this site from serine to alanine S193A causes partial loss of function of the *ATOH1* gene (Xie et al., 2017). ATOH1 transcription factor interacts directly or indirectly with several molecules such as Shh, Gli1, Cyclins D1/D2, Mycn, Notch, Wnt, BMPs, Meis1. Misexpression of the *ATOH1* gene and any one of these molecules which are involved in the process of neurogenesis of the cerebellar granule cells can result in abnormality of the number, location, morphology and circuits of the cerebellar granule cells. This may manifest as cerebellar related disorders. Point mutation of the *ATOH1* gene results in a phenotype of trembling gait, cerebellar ataxia and hearing loss with the loss of cerebellar granule cells and inner ear hair cells (Fink et al., 2006). Some other studies showed that *ATOH1* gene mutation may result in the absence of an external granular layer in the fetal cerebellum, reduction in the size of the cerebellum and lack of surface foliation (Sheykholeslami et al., 2013; Xie et al., 2017). Ectopic expression of the *ATOH1* gene may result in the unwanted proliferation of the granule neuron progenitors and granule cells leading to the origin of congenital medulloblastoma (Sheykholeslami et al., 2013; Zhao et al., 2008). If there is a null expression of the *ATOH1* gene in the rhombic lips there is improper differentiation of cerebellar granule cells. This may result in trembling gait, cerebellar ataxia and hearing loss (Gazit et al., 2004) **(Figure 2)**. From these findings, it can be said that mutation and abnormal expression of the *ATOH1* gene are related to cerebellar related disorders.

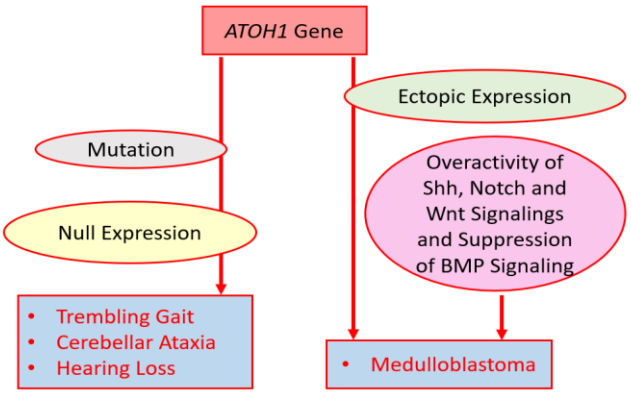

Figure 2. Outcomes of mutation and abnormal expression of *ATOH1* gene and over activity and suppression of the signaling pathways.

4.0 CONCLUSIONS

Expression of the *ATOH1* gene is essential in the rhombic lips of the metencephalon for the specification and proliferation of the cerebellar granule neuron progenitors during the neurogenesis of the cerebellar granule cells. Four major signaling pathways Shh, Notch, Wnt and BMP are involved in the proliferation, synaptogenesis and differentiation of the cerebellar granule cells. Absence of expression of the *ATOH1* gene in the rhombic lips of the metencephalon results in loss of cerebellar granule cells. Mutation and ectopic expression of the *ATOH1* gene change the properties of the cerebellar granule cells and result in the phenotype of trembling gait, hearing loss and cerebellar medulloblastoma. From these findings, it can be concluded that the *ATOH1* gene must be taken as a gene of concern in the diagnosis and treatment of cerebellar related disorders.

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