Review Article

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Dentistry Section

Sonic Hedgehog Signalling Pathway and Ameloblastoma – A Review

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ABSTRACT

Ameloblastoma is a benign but aggressive odontogenic neoplasm arising from odontogenic epithelium. Many theories have been proposed to explain the pathogenesis of ameloblatoma. Numerous signalling pathways have been implicated to be associated in the development and progression of this neoplasm. Studies have found association of various signalling molecules of Sonic Hedgehog Pathway, namely SHH, PTCH1, SMO, Gli 1, Gli 2, Gli 3, with ameloblastoma. Knowledge about this pathway will help us to understand the nature and behaviour of this neoplasm. This will open the door towards new treatment modalities.

Keywords: Apoptosis, Gli, Odontogenic tumor, PTCH1, SMO

INTRODUCTION

Odontogenic epithelium under physiologic conditions forms tooth but can also give rise to many types of tumours in the jaws [1]. These tumours arising from odontogenic apparatus or its remnants can be classified into benign or malignant entities based on their histological presentations. Amongst them ameloblastoma is most frequently encountered which is benign in nature but locally invasive with a high risk of recurrence. There are many histological variants of ameloblastoma but the most common ones are follicular (32.5%), plexiform (28.2%), acanthomatous (12.1%), granular cell (5%), basal cell (2.02%) and desmoplastic (4-13%) type [2,3]. Based on site and type of presentation, the ameloblastomas can be classified as solid/multicystic type, extraosseous/peripheral type and unicystic type [4]. The most common and aggressive type is the solid/multicystic type where as the less common lesions with less aggression are the unicystic and peripheral ameloblastomas [5].

Numerous studies have been found to explain the molecular pathogenesis of ameloblastoma. Cellular changes like proliferation, differentiation, senescence, tumourigenesis etc. occur through the activation or inactivation of related molecular signalling pathways. The important signalling molecules are either over expressed or under expressed during the tumourigenesis of ameloblastomas [6]. The aetiology of ameloblastoma is not yet clear. Clonality, cell cycle proliferation, apoptosis, tumour suppressor genes, osteoclastic mechanisms and matrix metalloproteinases and various signalling pathways are the postulates used to explain the pathogenesis of ameloblastoma [7].

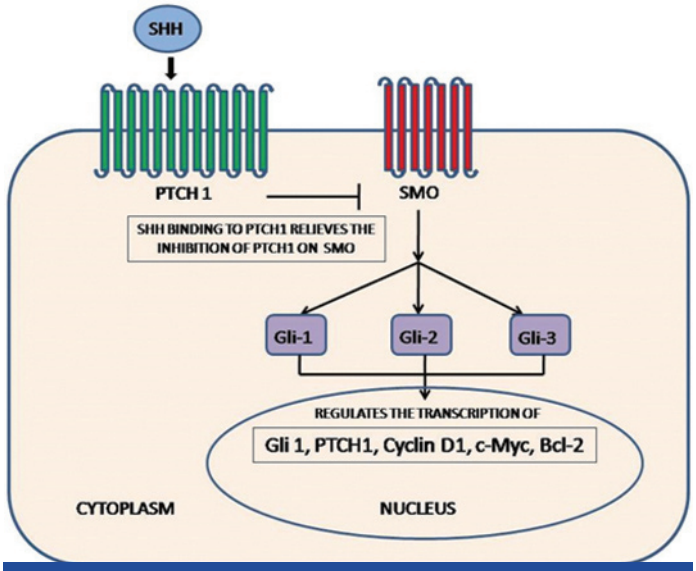
Sonic Hedgehog (SHH) is a mammalian homologue of Drosophila segment polarity gene Hedgehog (Hh), and encodes a secreted protein that activates a membrane receptor complex formed by Patched 1 (PTCH1) and Smoothened (SMO). In absence of SHH protein, the PTCH1 inhibits the SMO [8]. When SHH binds with PTCH1, the inhibition of SMO is suspended and activates the GLI (Glioma) proteins which mediate the SHH signal from cytoplasm to nucleus [9,10]. SHH signal transduction plays a central role in patterning of the limb, axial skeleton, central nervous system, lungs, digestive tract & dermal appendages [8]. The SHH signalling pathway plays a critical role in tooth development [11]. SHH signalling pathway genes were expressed during tooth development from bud stage to the bell stage [12]. These genes are believed to decide the tooth identity, epithelial proliferation during tooth bud formation, and transition from bud to cap stage [13]. Inherited or sporadic alterations in the SHH signalling pathway genes might cause a number of developmental defects and aberrant activation during adult life and has been shown to be related to tumour formation [11]. Various studies are present in literature which have demonstrated the association of SHH pathway and ameloblastoma [8,11,14]. The present review will try to explore the SHH signalling pathway and its role in the pathogenesis of ameloblastoma and whether its various components can be targeted to treat ameloblastoma with minimal or no surgery.

Sonic Hedgehog Signalling Pathway

Hedgehog proteins (Hh) are "signalling proteins" which were first discovered in Drosophila along with many other components of their signalling pathway. These are highly hydrophobic proteins which have a prominent role in proper development of the embryo. In the context of embryonic development, the cells that synthesize Hh ligands are distinct from the responsive cells. The responsive cells are either juxtaposed to the producing cells, or are situated at a significant distance [15]. Hedgehog signalling is initiated by binding of one of the 3 soluble and lipid modified hedgehog ligands namely Sonic, Indian, or Desert Hedgehog, found in the vertebrates, to the receptor PTCH1 [16]. All the three ligands namely Sonic Hedgehog (SHH), Indian Hedgehog (IHH), and Desert Hedgehog (DHH) are identified in humans [15]. PTCH1 is a membrane bound protein with 12 transmembrane domains [8,16]. It forms a heterodimeric receptor complex with SMO, a 7 transmembrane protein [9,17]. In the absence of SHH protein, PTCH1 acts catalytically to suppress the activity of SMO by preventing its localization to the cell surface. Binding of SHH ligand to PTCH1 relieves the inhibition on SMO protein facilitating its surface localization [9,15]. This initiates a signalling cascade, leading to the activation of the glioma-associated (Gli) family of zinc finger transcription factors. In vertebrates there are three Gli proteins namely Gli 1, Gli 2, Gli 3 [9,18]. Gli 1 induces and Gli 3 represses the SHH target genes that include Gli1, PTCH1, Cyclin D1, c-Myc and Bcl-2 and hence regulates cell cycle [Table/Fig-1]. Depending on post transcriptional and post translational processing events, Gli 2 can act in either a positive or negative manner [16].

Sonic Hedgehog Pathway in Cancer

Aberrant activation of the Hedgehog pathway in cancers is caused either by mutation in the pathway (ligand independent) or through



[Table/Fig-1]: Sonic Hedgehog Pathway

Hedgehog protein over expression (ligand dependent) [9]. The relationship between SHH pathway and cancer was established by a mere Observation of Association Between PTCH 1 gene and Nevoid Basal Cell Carcinoma Syndrome (NBCCS) [19]. NBCCS, also known as Gorlin's Syndrome is a rare autosomal dominant disorder characterized primarily by multiple basal cell carcinomas, odontogenic keratocysts of the jaws, and developmental defects, such as bifid ribs, intracranial calcification, and polydactyly [20]. A variety of tumours like ovarian fibroma, medulloblastoma, rhabdomyosarcomas, meningiomas, multiform glioblastoma, and cardiac fibromas are also seen in NBCCS [21]. Many PTCH1 germline mutations have been reported in the literature which was found to be associated with NBCCS [19]. Numerous sporadically occurring basal cell carcinomas are involved with hyper activated SHH signalling pathway. It is seen that 10% of all basal cell carcinomas are associated with inactivating mutations in PTCH1 and activating mutations in SMO [15]. Many cases of medulloblastoma have shown mutations in PTCH1 and SMO [9,15]. Hedgehog overexpression, sometimes accompanied by increased expression of Hh target genes is detected in numerous human tumours like small cell lung cancer, gastric and upper gastrointestinal tract cancer, pancreatic cancer, and prostate cancer [9]. Neuroblastoma is a malignant tumour of the sympathetic nervous system seen in childhood and most common extra cranial solid tumour. It arises from the deregulation in the development of neural crest stem cells which differentiate into the sympathetic nervous system. Most cell lines of the neuroblastoma expressed SMO, PTCH1, Gli1, whereas few cell line expressed Gli 3, supporting SHH activation [22].

Development of tooth and Sonic Hedgehog Pathway

Cells from the oral ectoderm and mesenchyme interact with each other to produce a highly mineralized structure called tooth [13]. The dental lamina which later on gives rise to tooth buds expresses SHH protein [13]. Hardcastle et al., found positive expression of PTCH1, SMO, Gli1, Gli2, Gli3 in the epithelium as well as mesenchyme [12]. But SHH was only detected in epithelium. During tooth development the genes of various components of SHH signalling pathway are expressed suggesting its active and direct role in the early stages of odontogenesis. During tooth development the epithelium expresses SHH but the early odontogenic mesenchymal cells acts as a target for SHH signalling and express PTCH1 and Gli1. This implies that SHH activity directly affects epithelial cell proliferation and produces a tooth bud. This role for the SHH signalling pathway was confirmed by the result of ectopic epithelial invaginations produced when recombinant SHH was placed in oral (not dental) epithelium. But the mesenchymal cells express PTCH1 and Gli1 which leads to various mesenchymal activities during tooth development. The expression of SHH in the enamel knot and PTCH1 and Gli genes in surrounding tooth germ cells confirm the role of enamel knot as a signalling center. Although SHH is expressed in the enamel knot the signalling pathway genes are all absent from the structure implying that the action of SHH is outside the enamel knot [12].

The SHH protein is restricted to localized thickening of oral epithelium and thus marks the first morphological evidence of tooth development. It is known to play a crucial role during the initiation of odontogenesis. To facilitate tooth formation in its correct location there will be controlled SHH expression along the developing oral axis of the mandibular process. There will also be non transcriptional antagonism of this signalling pathway to ensure correct temporo-spatial control of tooth germ initiation. During the early stages of tooth development the SHH signalling is closely controlled along the oral axis of the first branchial arch. Hence SHH pathway plays a key role in deciding the site where a tooth needs to be developed and where it does not [23].

Dassule et al., removed SHH activity from the developing tooth germ at early bud stage to address the role of SHH signalling in growth morphogenesis and differentiation of the mammalian tooth [24]. There was a reduction in tooth size indicating that SHH was important for growth. SHH also patterns the developing cusp. But cytodifferentiation is not altered by SHH.

Sonic Hedgehog Pathway and Ameloblastoma

Expression of SHH signalling pathway has been documented in various odontogenic cysts and tumours [8,11,19]. Heikinheimo et al., reported underexpression of SHH gene in ameloblastoma by using cDNA microarray technique [25]. Barreto et al., also reported PTCH1 protein expression in ameloblstoma suggesting the involvement of SHH signalling pathway [14]. Kummamoto et al., detected the expression of SHH, PTCH1, SMO, and Gli1 mRNA in epithelial and mesenchymal components of ameloblastoma [8]. They also detected the immunohistochemical reactivity for SHH, PTCH1, SMO, and Gli1 in the cytoplasm of cellular components of ameloblastoma. The benign and metastasizing types of ameloblastoma showed stronger PTCH1 expression in neoplastic cells than in stromal cells and reactivity for Gli1 is more evident in neoplastic cells than stromal cells. They suggested that SHH signalling molecules may play a role in epithelial-mesenchymal interaction and cell proliferation in ameloblastoma. Zhang et al., found out that ameloblastoma showed stronger distribution of SHH, PTCH1, SMO and Gli1in the peripheral columnar or cuboidal cells than in the central polyhedral cell [11]. They suggested that SHH signalling pathway might regulate epithelial cells proliferation in ameloblastoma. DeVilliers et al., tried to identify genes or gene products that may have diagnostic, prognostic, or therapeutic potential [26]. They found out that genes that were highly expressed compared with the control RNA included a variety of growth factors and transcription factors. In their study, members of the sonic hedgehog (SHH) pathway also showed variable expression compared with reference RNA. They identified the overexpression of Gli1 and PTCH1 in all the ameloblastomas and confirmed it by immunohistochemistry.

Gurgel et al., in their study examined the expression of genes in the SHH pathway to characterize their roles in the pathogenesis of ameloblastomas [27]. They quantified the expression of SHH, SMO, PTCH1, and Gli 1, genes by qualitative real-time polymerase chain reaction (qPCR). They observed overexpression of SMO, PTCH1, and Gli1 genes in ameloblastoma. However, they did not detect expression of the SHH gene in ameloblastoma. They concluded that the overexpression of upstream and downstream genes in the SHH pathway leads to the constitutive activation of this pathway in ameloblastoma and may suggest a mechanism for the development of this type of tumour.

SHH Pathway and its interaction with Apoptosis in Ameloblastoma

The physiological process called apoptosis, also known as programmed cell death [28] has a very complex role in the pathogenesis of ameloblastoma. Many authors have explored this avenue by evaluating the various molecules associated with apoptosis. Kumamoto studied the expression of Bcl-2 protein expression in ameloblastoma and found positive expression in the tumour cells neighbouring the basement membrane suggesting a cellular proliferative activity [29]. Similar kinds of results were reported by Mitsuyasu et al., [30]. Gurgel et al., also found increased expression of Bcl-2 gene in ameloblastoma during quantification by qPCR [27]. Another study reported positive expression of Bcl-2 as well as Bcl-x in peripheral cells neighbouring the basement membranes [31]. Bcl-2 is an antiapoptotic protein. Various proapoptotic factors like APAF-1, Caspase-9, AIF are also expressed in ameloblastoma but are believed to be suppressed by various antiapoptotic proteins in neoplastic cells near the basement membrane [32]. Luo et al., reported that the expression of proapoptotic proteins such as Fas, FasL, and Caspase-3 were mainly detected in the foci of squamous and granular cells in the center of tumour islands [33]. But the antiapoptotic protein Bcl-2 and proliferating cell marker Ki67 were principally expressed in the peripheral basal cells. Similar findings were reported previously by Sandra et al., [34]. This suggested that ameloblastoma had 2 relatively distinct patterns, an antiapoptotic proliferating site in the peripheral layer and a proapoptotic site in the central layer of the tumour islands [33,34].

Vered et al., investigated the immunohistochemical expression of SHH induced Bcl-2 oncoprotein in odontogenic keratocyst and solid ameloblastoma and found out increased expression of SHH induced Bcl-2 protein in solid ameloblastoma as well as odontogenic keratocyst [35]. Kanda et al., reported positive immune reactivity for SHH, PTCH1, Gli1, Gli2, and Gli3 in almost all tumour cells but not in the stromal cells of ameloblastoma [36]. SHH was expressed in the cytoplasm, PTCH1 in the cytoplasm and cell membrane and Gli proteins only in the nucleus. The reactivity was stronger in the peripheral cuboidal and columnar cells than in the central polyhedral cells of the tumour nests. They obtained ameloblastoma cell line, AM1 from human ameloblastoma tissue which is immortalized by transfection of HPV-16 DNA. They found out that SHH neutralizing antibody induced apoptosis of AM1 cells and demonstrated decreased Bcl-2 and increased BAX expression. In a previous study they demonstrated expression of Bcl-2 in the outer layer of ameloblastoma cells, where as inner cells (stellate reticulum like cells and squamoid cells) did not express the protein [30]. This expression pattern of Bcl-2 was similar to that of SHH in ameloblastoma. Taken together it seems that SHH plays an anti-apoptotic role in the proliferation of ameloblastoma cells.

Agents targeting the SHH Pathway which can be used for non surgical treatment of Ameloblastoma –

The treatment of choice for ameloblastoma is surgery. But other nonsurgical therapeutic modalities are seldom explored. Sauk et al., in their review have proposed many SHH inhibitors which can be proven effective in nonsurgical treatment of ameloblastoma [10]. They include Cyclopamine, Robotnikinin, KAAD-cyclopamine, Jervine, IPI926, GDC-0449, biarylcarboxamide, CUR61414, SANT1, SANT2, SANT3, SANT4, JK184, and GANT61.

Several therapeutic compounds have proven effect as antagonists of the SHH pathway. Cyclopamine, a plant-derived SHH pathway antagonist, acts at the level of SHH signaling and is effective in reducing the viability of cancer cells by blocking activation of the SHH response pathway and abnormal cell growth [26]. DeVilliers et al., quoted several cyclopamine studies which have shown successful responses in breast, pancreatic, and gastric cancer cells, medulloblastoma, and oral squamous cell carcinoma cells. They suggested that the SHH pathway members could play an important role in the tumourigenesis of ameloblastomas and provide a potential therapeutic opportunity. Studies are under way to investigate the effect of cyclopamine on ameloblastoma cells [26].

KAAD-cyclopamine is a chemically-modified derivate of naturally occurring cyclopamine that displays higher potency and reduced levels of cytotoxicity. KAAD-cyclopamine act downstream of PTCH1 and inhibit Gli activity. Robotnikinin is a synthetic small-molecule inhibitor of SHH signalling that acts upstream of SMO. Jervine inhibits transcription of Gli1, Gli2, PTCH1, and other SHH-target genes. SANT 1,2,3,4 targets SMO and represses Gli-mediated transcription in a variety of cell types. IPI-926 represses Gli-mediated transcription in a variety of cell types. Clinical trials on IPI-926 for BCC and pancreatic adenocarcinoma are ongoing. Similarly GDC-0449, Cur-61414, GANT61 represses Gli-mediated transcription in a variety of cell types [37].

Research is needed to see the effect of these agents in the non surgical treatment of ameloblastoma and the day is not far off when application of these agents will definitely reduce the surgical morbidity resulting in a better prognosis.

CONCLUSION

Pathogenesis of ameloblastoma is multifactorial and involves numerous cellular pathways. SHH pathway, which plays a decisive role in the development and patterning of various organs, is integral in odontogenesis and also plays a crucial role in the pathogenesis of ameloblastoma. The pathway appears to be responsible for the proliferation of neoplastic cells. While doing so it also integrates apoptosis in the pathogenesis of ameloblastoma by regulating the expression of Bcl-2 and BAX in the peripheral layer. This opens up a new horizon in tumour therapy by targeting the various components of SHH pathway. Numerous compounds targeting the SHH pathway are being researched presently to be used as chemotherapeutic agents in the treatment of ameloblastoma. Further studies in this direction will definitely change the treatment modality and prognosis of ameloblastoma.

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