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Bone Morphogenic protein-2 in the osteogenic/ odontogenic differentiation of stem cells from apical papilla: A systematic review

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Abstract
The interaction between stem cells and growth factors plays a major role in the regeneration of the pulp-dentin complex. Studies have reported the potential role of Bone Morphogenic Proteins (BMPs) in the growth and differentiation of cells. The purpose of the present systematic review was to analyze the role of Bone Morphogenic Protein-2 (BMP-2) in the osteogenic/odontogenic differentiation of Stem cells from apical papilla (SCAP). The search was conducted across PubMed, Science Direct, Cochrane Library, and Google Scholar. In-vivo and in-vitro studies published between 2000 and 2022 were evaluated for the outcome. The quality assessment of the studies was done using the QUIN assessment tool. After applying the keywords, and filters along with inclusion & exclusion criteria, a total of six articles were selected for the present systematic review, all of which were in-vitro studies. The studies reported that BMP-2 significantly enhanced the osteogenic/odontogenic potential of SCAP cells. Moreover, BMP-2 could act synergistically with various other factors to bring about the desired effect. Being a potential growth factor in the regeneration of the pulp-dentin complex, the application of BMP-2 can be extended to the clinical scenario for various cell-free and cell-based regenerative approaches.

Keywords: BMP-2, Osteogenic differentiation, SCAP, Stem cells from apical papilla

Introduction
Regeneration of the pulp-dentin complex depends upon highly coordinated interaction between three key factors, that often constitute the regenerative endodontic triad, which includes (a) Dental Stem cells (b) Growth factors, and (c) Scaffold [1]. Dental stem cells are undifferentiated, pluripotent progenitor cells capable of differentiating into specific cell types upon appropriate stimulation due to their multiple lineage differentiation capacities and self-renewability [2-4].

Growth factors are bioactive polypeptides or signalling molecules that interact with specific receptors on the cell surface to bring about differentiation, proliferation, migration, and growth of the cell [5]. These include factors like cytokines, chemokines, and various trophic factors which actively stimulate the intracellular biological cascades to bring about the response [6]. Scaffolds provide a three-dimensional network, providing a localized and favourable environment for the interaction between the cellular component and the supplemented growth factors [7].

Bone Morphogenic Proteins are the morphogens or growth factors related to the Transforming Growth Factor beta (TGFb) superfamily that play a central role in the development and maintenance of osseous, cartilaginous, neural, and cardiac tissues [8]. They are distributed widely, both in the mineralized and non-mineralized tissues and are expressed sequentially throughout the period of embryogenesis [9, 10]. These proteins have been shown to regulate the differentiation of stem cells into osteogenic, chondrogenic, and adipogenic lineages [11]. Presently more than 20 subtypes of BMPs have been identified, and BMP-2 particularly serves as a crucial factor in the development of bone and cartilaginous tissue [8, 12, 13].

Stem Cells from Apical Papilla (SCAP) are the group of cells that are concentrated at the tips of the developing tooth root.

They play a central role in the development of the root, and due to their plasticity, they can differentiate into various cell lineages as mentioned before [14]. SCAP cells have been characterized to be superior compared to other stem cells in terms of potency, plasticity, and versatility [15].

The aim of the present systematic review is to provide insight into the role of Bone Morphogenic Protein-2 in the differentiation of SCAP cells into osteogenic/odontogenic lineages.

Materials and Methods

Protocol: The systematic review was carried out according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [16]. The articles were systematically searched in four electronic databases, PubMed, Science Direct, Google Scholar, and Cochrane databases. Figure 1 depicts the PRISMA flow diagram for the systematic review. A comprehensive search of peer-reviewed literature published between 2000 and 2022 was evaluated for the outcome. Two reviewers independently extracted relevant data from the included studies using a pre-designed data collection form, and the discrepancies were resolved through discussion between the reviewers. The main contents of the data collection form included: basic information of studies (title, authors, year) reporting quality; interventions specific information of comparison, outcomes, results, and conclusion. Population, Intervention, Comparison, and outcome strategy for Assessment of scientific literature (PICO):

Population: Stem cells of Apical Papilla cultured in the laboratory or, SCAP cells obtained from non-inflamed or non-infected root apices.

Intervention: Bone Morphogenetic Protein-2.

Comparison: Any comparison.

Outcome: Osteogenic/odontogenic differentiation.

Search strategy: (Table 1).

Selection criteria

Inclusion criteria

Clinical and animal studies, randomized controlled trials, case reports, case series, In vitro studies

Exclusion criteria

SCAP cells obtained from inflamed or traumatic apices, SCAP cells obtained from necrosed teeth or teeth with apical pathosis, SCAP cells obtained from primary teeth, Reviews, and Systematic reviews pertaining to the present study, Intervention of bone Morphogenic proteins other than BMP-2

Quality assessment

All papers selected for inclusion in the systematic review were subjected to rigorous appraisal by two critical appraisers. QUIN tool has been employed for quality assessment which consists of a checklist with 12 criteria [17]. Each criterion was then given a score as (i) adequately specified (2 points); (ii) inadequately specified (1 point); (iii) not specified (0 points); and (iv) not applicable (exclusion from the calculation). The scores were added to get a total score for each included study. The score obtained was used to assess the risk of bias in each study as (> 70% = low, 50%-70% = medium, and < 50% = high), (Table 2).

Results

In total, 2408 studies were identified through PubMed, Google Scholar, Science Direct, and Cochrane databases. All the databases were verified for any other existing systematic review on the proposed review topic. After the removal of the duplicates, 836 articles were reviewed for titles and abstracts by two independent reviewers, out of which 14 articles were selected for full-text screening. Eight studies were excluded as they were not relevant to the present study design. A total of six articles were included in the present systematic review all of which were in-vitro studies (Table 3).

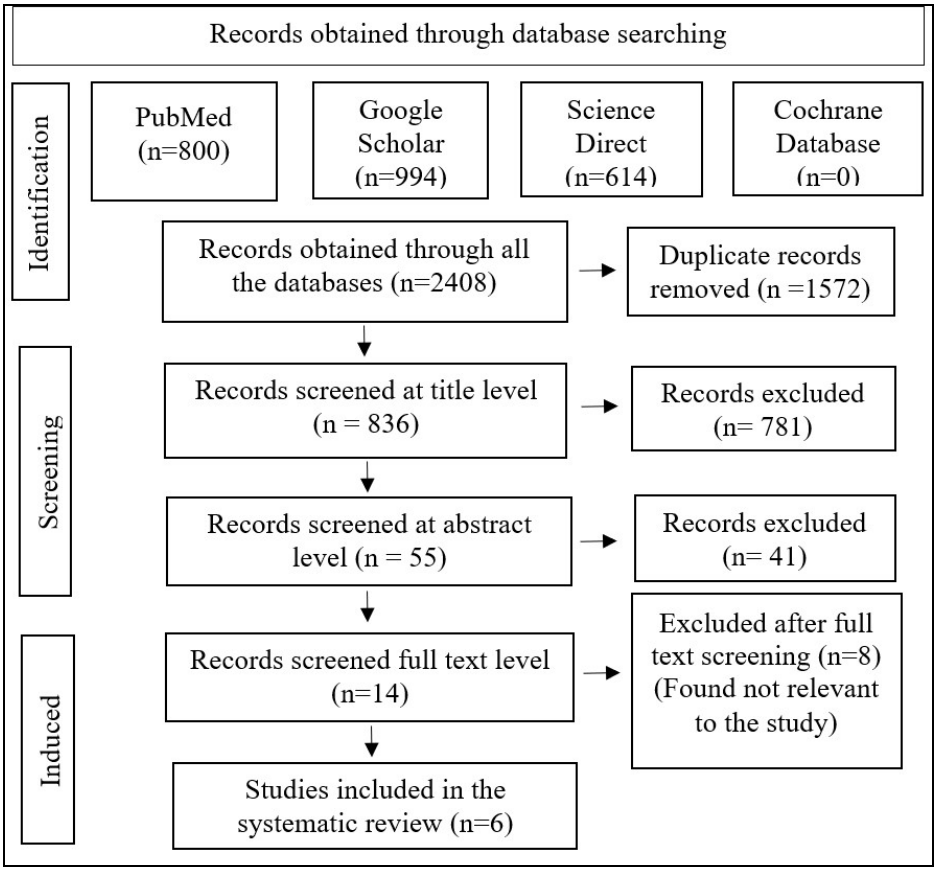

Fig 1: PRISMA flow diagram for the systematic review

Table 1: Databases searched along with the search terms

Database	Search Strategy	Results
PubMed	(BMP2 OR Bone Morphogenetic Protein 2) AND (osteogenic differentiation OR odontogenic differentiation OR bone like OR dentin like) AND (SCAP cells OR Stem cells from apical papilla OR apical papilla cells)	800
Google Scholar	(BMP2 OR Bone Morphogenetic Protein 2) AND (osteogenic differentiation OR odontogenic differentiation OR bone like OR dentin like) AND (SCAP cells OR Stem cells from apical papilla OR apical papilla cells)	994
Science Direct	(BMP2 OR Bone Morphogenetic Protein 2) AND (osteogenic differentiation OR odontogenic differentiation OR bone like OR dentin like) AND (SCAP cells OR Stem cells from apical papilla OR apical papilla cells)	614
Cochrane Library	(BMP2 OR Bone Morphogenetic Protein 2) AND (osteogenic differentiation OR odontogenic differentiation OR bone like OR dentin like) AND (SCAP cells OR Stem cells from apical papilla OR apical papilla cells)	0

Table 2: QUIN tool for quality assessment

Study ID	Min Xiao *et al.* [19]	Min Xiao *et al.* [20]	Wen Zhang *et al.* [21]	Wei Wang *et al.* [22]	Wen Zhang *et al.* [23]	Wen Zhang *et al.* [24]
Clearly stated aim	2	2	2	2	2	2
Detailed explanation of sample size	2	2	2	2	2	2
Detailed explanation of sampling technique	2	2	2	2	2	2
Details of comparison group	2	2	2	2	2	2
Detailed explanation of methodology	2	2	2	2	2	2
Operator details	2	2	2	2	2	2
Randomization	0	0	2	2	0	0
Method of measurement of outcomes	2	2	2	2	2	2
Outcome assessor details	2	2	2	2	2	2
Blinding	0	0	2	2	0	0
Statistical analyses	2	2	2	2	2	2
Presentation of results	2	2	2	2	2	2

Table 3: List of included studies and their main characteristics

Author	Cell type and origin	Isolation and Characterization	Intervention	Activity analysis	Outcome
Min xiao *et al.* [19]	Disease-free impacted third molars at the stage of root development (12 to 18 years)	Clone-like growth. Fibroblast-like monoclonal cells Flow cytometry: Positive for STRO-1, CD105, CD146 Negative for CD34 and CD45	SDF-1α treatment and siRNA transfection to limit the expression of CXCR4	(i)Cell Proliferation CCK-8 assay By measuring the Optical Density at 450 nm (ii) Alizarin red (AR) staining (iii)ALP activity (iv)Relative mRNA expression Runx2, DMP1 and DSPP	No significant difference between SDF-1α treated groups and the control group. Co Treatment of SDF-1α with BMP-2 significantly increased mineralized nodules at 14 days. Si CXCR4 treatment reduced mineralization Co treatment of SDF-1α with BMP-2 significantly increased ALP activity at 14 days. Si CXCR4 treatment reduced ALP activity. SiCXCR4 significantly reduced BMP-2 induced Runx2, DMP1 and DSPP expression
Min Xiao *et al.* [20]	SCAP cells from Impacted third molars at the stage of root development (16 to 18 years)	Clone-like growth. Cells ranged from narrow and spindle-shaped to large and polygonal. Flow cytometry of SCAP: Positive for STRO-1, CD105 and CD146	SDF-1α and BMP-2 cotreatment on cells cultured on Vitrogel 3D system.	(i) Gene expression ALP, Runx-2, BSP, DMP-1, DSPP, OCN (by RT-PCR) ALP and Runx-2 DMP-1 and DSPP (ii) ALP activity In BMP-2 treated group Cotreatment of BMP-2 + SDF-1α (iii)Immunohistochemical analysis CD 31 for blood vessel formation	Increased at 3,7 and 14 days Increased on day 7 Increased on day 14 Evaluated on days 3,7,11 and 14 Increased on days 11 and 14 Increased on day 14 After 8 weeks of implantation
Wen Zhang *et al.* [21]	Human-impacted wisdom teeth with immature roots	Spindle appearance with extending cytoplasmic processes Flow cytometry: Positive for STRO-1, CD24, CD146 Negative for CD45	Lentiviral mediated BMP-2 gene transfection of SCAP cells	(i)Cell Proliferation CCK-8 assay By measuring the Optical Density (ii)Gene expression ALP, OCN, DSPP, DMP1, and BMP-2 GAPDH as housekeeping	On 1, 2, 4 and 8 days after transfection Peak expression of OCN and DMP1 on day 16, and DSPP on day 8. Peaked on day 16 ALP peak on 1st,8th and 16th day

				gene (iii)ALP and AZ staining (iv)Western Blot For BMP-2 gene expression	Peaked 4 days after transfection
Wei Wang *et al.* [22]	Normal impacted third molars at the stage of root development	Fibroblast-like and spindle-shaped Flow cytometry: Positive for STRO-1, CD24, CD146	Injectable PLGA nanofibrous microspheres in which BMP-2 (50micrograms/ml) was present	(i)Cell Proliferation MTS assay SCAP treated with BMP-2 (100 ng/ml) for 7 days. By measuring the Optical density value at 490 nm. (ii) RT-qPCR Gene expression of Col I, BSP, OCN, DSPP (iii)ALP activity (iv)Calcium content quantification	BMP-2 treated groups showed slightly slower proliferation at 1,3 and 5 days Significantly elevated at 2 and 4 weeks Significantly higher at 7 and 14 days Significantly higher when evaluated at 2 and 4 week
Wen Zhang *et al.* [23]	SCAP cells sound mandibular third molars (18 to 20 years)	Spindle-like in shape after eight days of culture Immunofluorescence staining of SCAP: The third passage of cells Positive for STRO-1, CD24, CD146 Negative for CD45	Lentiviral Plasmid Transfection of BMP-2 and Foxc2 genes to SCAP cells	(i)Cell Proliferation CCK-8 assay (ii) RT-qPCR. mRNA expression of Foxc2, BMP2, ALP, OCN, DSPP, and DMP1. GAPDH set as control. (iii)ALP activity and mineralized nodules deposition	On 1,2,4 and 8 days after transfection Peak expression of DMP1 on day 8 and peak expression of other factors on day 16 Cotreatment of Foxc2 with BMP-2 showed significantly higher ALP activity and mineralized nodules
Wen Zhang *et al.* [24]	SCAP cells from immature mandibular third molars	Spindle-like in shape after eight days of culture Immunofluorescence staining of SCAP: The third passage of cells Positive for STRO-1, CD24, CD146	Lentiviral Plasmid Transfection of BMP-2 and VEGF gene primers to SCAP cells	(i)Cell Proliferation CCK-8 assay (ii) RT-qPCR mRNA expression of ALP, OCN, DSPP, and DMP1. GAPDH set as reference gene (iii)ALP activity and mineralized nodules deposition	On 1,2,4 and 8 days after transfection Cotreatment of Foxc2 with BMP-2 showed significantly higher ALP, OCN, DSPP, and DMP1 on day 16 Cotreatment of Foxc2 with BMP-2 showed significantly higher ALP activity and mineralized nodules

ALP, Alkaline phosphatase; AR, Alizarin red; BSP, Bone sialoprotein; BMP-2, Bone Morphogenic protein 2; CCK8, Cell counting kit 8; CXCR4, C-X-C motif chemokine receptor 4; DMP, dentin matrix protein 1; DSPP, Dentin Sialophosphoprotein; Foxc2, Forkhead box protein C2; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; OCN, osteocalcin; SDF-1α, stromal derived factor-1α; siCXCR4, small interfering CXCR4; VEGF, vascular endothelial growth factor

Discussion

Characterization of SCAP cells

Comparative studies reveal that SCAP cells display higher proliferation rates and improved migration compared to other stem cells [18]. The cell culture when incubated for 3 to 7 days ranged from narrow spindle-shaped to large polygonal cells. In the studies included the characterization of the cells was done through multiple lineage differentiation tests, immunofluorescence staining, and flow cytometry. Alizarin red staining for osteogenic/odontogenic differentiation and Oil red O staining for adipogenic differentiation was done to confirm their multiple lineage differentiation. On immunofluorescence staining and flow cytometry, the SCAP cells positively expressed mesenchymal stem cell markers such as STRO-1, CD146, CD24, CD105, and to a lesser extent CD-29 and CD-90 [19-24]. Owing to the perivascular location of SCAP cells the expression of mesenchymal stem cell markers such as STRO-1 and CD146 are seen during the initial stages of differentiation and the expression of these markers diminishes as the cells pass through various stages of differentiation [25]. The expression of CD34 and CD45, a hematopoietic stem cell character, is negative for SCAP cells [19]. CD24 is a specific marker for SCAP cells and is not detectable in other stem cells. The presence of CD24 has been associated with increased stemness as its expression reduces as the cell differentiates and enters the osteoblastic lineage [26].

Osteogenic/Odontogenic differentiation of SCAP cells

There are two basic steps through which the action of BMP-2 on cells could be modulated. First, at the genetic level, DNA that encodes for this growth factor can be delivered either with a plasmid or a viral particle or can be integrated into the cell genome for it to be expressed naturally. Second, either the exogenous or expressed growth factor itself can be introduced at the desired site [27]. Three of the studies involved the integration of the BMP-2 gene into SCAP cells through lentivirus-mediated BMP-2 gene transfection [21, 23, 24]. In addition, the synergistic effects of Foxc2 and VEGF (Vascular Endothelial Growth Factor) along with BMP-2 were also assessed [23, 24]. The transfection efficiency was assessed through Western blot assay by determining the relative mRNA content of the expressed genes. Two other studies determined the efficiency of odontogenic differentiation of human SCAP cells with BMP-2 by seeding them within artificial scaffolds such as VitroGel 3D system, a polysaccharide hydrogel, and PLLA (Polylactic acid) Nano fibrous microspheres which mimics the architecture of collagen fibrils at the cellular level. The SCAP cells grown on the artificial scaffolds showed favourable viability and proliferation although there was no significant difference in the proliferation rate when grown with or without the scaffold

[20, 22]. Collagen-based insoluble matrices have been widely used as natural scaffolds, however, their major drawback is being susceptible to degradation by the host's immune system [27]. Moreover, sustained, and controlled release of exogenous BMP-2 using suitable scaffolds has been shown to increase the potency of endogenous BMPs [28]. The outcome, i.e., osteogenic, or odontogenic differentiation majorly depends on the growth factor itself while the other parameters such as choice of cells and scaffolds act only to tune up the process [27].

RT-PCR (Real Time Polymerase Chain Reaction) and Western blot were the methods employed to determine the total mRNA content of the expressed genes. When treated under optimal conditions with the osteogenic differentiation medium, BMP-2 significantly enhanced the expression of osteogenic differentiation genes such as ALP (Alkaline Phosphatase), OCN (osteocalcin), DSP (Dentin Sialo Protein), DSPP (Dentin Sialo Phosphoprotein), BSP (Bone sialoprotein), DMP1 (Dentin matrix acidic phosphoprotein 1) and Runx-2 [19-24]. ALP is an early marker for odontogenic/osteogenic differentiation while OCN is seen in the later stages of differentiation. DMP-1 has been considered a specific marker for odontoblasts and is involved in bone and dentin mineralization [21]. Specifically, most of these genes exhibited a steady rise as time progressed [23]. Moreover, transfection with VEGF, Foxc2, or co-treatment with SDF-1 alpha (Stromal derived factor-1 alpha) synergistically acted along with BMP-2 to enhance the differentiation of SCAP cells in vitro and in vivo. Foxc2 (Forkhead c2) is a winged spiral protein that is involved in promoting proliferation of the cells, angiogenesis, and osteogenesis [29]. Being a component of neural crest cells Foxc2 also governs the interaction between the epithelium and the mesenchyme during craniofacial development [30]. VEGF has been shown to have a positive effect in inducing osteogenic and odontogenic differentiation of stem cells [24]. SDF-1 alpha is a chemokine that plays an important role in the migration, proliferation, and differentiation of hematopoietic and mesenchymal stem cells [20]. Moreover, SDF-1 alpha along with its receptor CXCR4 acts as an important pathway for the BMP-2-induced osteogenic differentiation of the SCAP cells. Blocking the SDF-1 alpha/CXCR4 pathway inhibited osteogenic differentiation and significantly reduced the expression of osteogenesis-related genes such as DMP-1, Runx-2, and DSPP [19]. The synergistic interaction of these factors along with BMP-2 have shown better outcome when compared to either of these factors used alone.

Mineralization of the hard tissue was determined by Alizarin red staining and BMP-2 positively influenced the mineralization of formed osteoid-like hard tissue. Cotreatment with the above-mentioned factors significantly enhanced the mineralization when compared to those factors used alone [19-24]. The amount of mineralization seen with Foxc2 and BMP-2 together was about twenty times more than when SCAP cells were cultured alone [23]. Cotreatment of SCAP cells with BMP-2 and VEGF could further facilitate bone formation through cell homing [31]. Though the hard tissue formed was more osteoid-like, the formation of dentin-like tissue has been questioned due to the absence of a typical tubular structure. This has been attributed to the absence of a suitable environment that is necessary for odontogenesis in the in vitro models. The microenvironment for odontogenesis requires a critical interaction between the epithelium and the mesenchyme along with numerous signalling molecules to form an organized tubular structure which could not be maintained in the above-mentioned studies [20].

The in vivo odontogenic differentiation of the SCAP cells was determined by subcutaneously implanting the cultured cells into nude mice. BMP-2 showed positive results in relation to mineralization and hard tissue formation. After 4 to 8 weeks of implantation, the BMP-2 treated specimens showed encapsulated vascularized fibrous connective tissue. H&E staining showed osteoid-like and dentin-like deposits along with the formation of collagen matrix and vasculature [20, 22].

Conclusion

Within the limitations of the present systematic review, it can be concluded that BMP-2 has shown positive outcomes regarding the differentiation of SCAP cells into odontogenic and osteogenic lineages both in vitro and in vivo. Moreover, it can act synergistically with other factors to enhance differentiation and proliferation in vitro. Most of the studies included are in vitro studies, and the nature of the interaction of BMP-2 in a root canal model or in vivo scenario needs further evaluation.

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