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The Role of SIBLING Proteins in Dental, Periodontal, and Craniofacial Development

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The majority of dental, periodontal, and craniofacial tissues are derived from the neural crest cells and ectoderm. Neural crest stem cells are pluripotent, capable of differentiating into a variety of cells. These cells can include osteoblasts, odontoblasts, cementoblasts, chondroblasts, and fibroblasts, which are responsible for forming some of the tissues of the oral and craniofacial complex. The hard tissue forming cells deposit a matrix composed of collagen and non-collagenous proteins (NCPs) that later undergoes mineralization. The NCPs play a role in the mineralization of collagen. One such category of NCPs is the small integrin-binding ligand, the N-linked glycoprotein (SIBLING) family of proteins. This family is composed of dentin sialophosphoprotein (DSPP), osteopontin (OPN), dentin matrix protein 1 (DMP1), bone sialoprotein (BSP), and matrix extracellular phosphoglycoprotein (MEPE). The SIBLING family is known to have regulatory effects in the mineralization process of collagen fibers and the maturation of hydroxyapatite crystals. It is well established that SIBLING proteins have critical roles in tooth development. Recent literature has described the expression and role of SIBLING proteins in other areas of the oral and craniofacial complex as well. The objective of the present literature review is to summarize and discuss the different roles the SIBLING proteins play in the development of dental, periodontal, and craniofacial tissues.

Keywords: SIBLING proteins, periodontal, craniofacial, dentin, PDL

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INTRODUCTION

Hard Tissues and NCPs

Most of the hard tissues of the dental–periodontal complex and craniofacial structure develop from neural crest cells and ectoderm (1). Teeth are composed of enamel, dentin, and pulp. Teeth are supported by the periodontium, which is formed by alveolar bone, cementum, periodontal ligament (PDL), and gingiva (2). The dental-periodontal structure contains all forms of hard tissues found in the body: bone, cementum, dentin, and enamel. Such hard tissues are composed of organic and inorganic matter. The inorganic being mostly hydroxyapatite (HA) crystals, and the organic being composed of collagenous and non-collagenous proteins (NCPs), which are essential in making the framework for the inorganic matter to mineralize (3, 4).

NCPs found in the organic matter of hard tissues are known to be regulators of the mineralization of collagen fibers and of crystal growth. NCPs play an important role in the mineralization process of enamel, dentin, cementum, and bone during development. The SIBLING (small integrin-binding ligand N-glycosylated) family is one category of NCPs with notable expression in these tissues (5, 6).

SIBLING Proteins

The SIBLING family includes dentin matrix protein 1 (DMP1), osteopontin (OPN), bone sialoprotein (BSP), dentin sialophosphoprotein (DSPP), and matrix extracellular phosphoglycoprotein (MEPE) (6). These proteins are all located on chromosome 4 in humans and the family is known to have a regulatory function in mineralization and interactions with HA (5). Another common feature ofthe SIBLING family members is post-translational modifications (PTM), a process in which enzymatic modifications of the proteins occur following synthesis (5, 7). All SIBLINGs also contain an Arg-Gly-Asp (RGD) integrin-binding motif in their structure which promotes cell attachment, differentiation, and migration, as well as intracellular signaling by binding to cell surface receptors (8). It is currently accepted that the SIBLINGs pathway of action includes activation of matrix metalloproteinases (MMPs) that mediate extracellular matrix (ECM) processes (9).

DSPP is the most abundant NCP in the dentin ECM. DSPP is inactive in its full form, it undergoes PTM to cleave into two proteins: dentin phosphoprotein (DPP) (10) and dentin sialoprotein (DSP) (11). DSPP products are known to be essential during the development of dentin, and recent studies have described their role in different craniofacial tissues (12–18).

DMP1 is a product of chondrocytes and osteocytes. It is not usually found in its intact form but rather in one of its cleaved products: an N-terminal peptide, a C-terminal peptide, and a glycosylated N-terminal protein. The intact protein and its glycosylated forms appear to inhibit mineralization. However, the phosphorylated cleaved fragments can promote mineralization (19). Studies have described the expression and role of DMP1 in oral and craniofacial tissues (20–22).

OPN is the most abundant and widely distributed SIBLING protein. It acts as an inhibitor of mineralization, and when it is highly phosphorylated, it can promote HA formation. OPN is also involved in the recruitment of osteoclasts and in regulating the immune response (23). OPN plays an important role in regulating the mineralization of the hard tissues of the craniofacial complex (24, 25).

BSP is a HA nucleator, facilitating osteoblast differentiation and maturation, therefore, stimulating mineralization (26). BSP is mostly expressed in bone-forming cells, with lower expression levels in other mineralized tissues such as dentin (27, 28). BSP promotes cellular adhesion and interactions between cells and matrixes, acting in bone formation and remodeling (29).

MEPE expression has been identified in the dental pulp and in predentin, and it is considered to be involved in the mineralization process (30, 31). MEPE is expressed at a very early stage and only expressed during embryonic development and postnatally on days 5–9 in predentin and day 2 in osteoblasts (32, 33). Much remains unclear regarding MEPE pathways of action.

Extensive research has been published regarding the expression and roles of SIBLING proteins in the oral and craniofacial complex. However, much knowledge about their mechanisms of action is still to be discovered. The objective of the present review is to summarize the current knowledge of SIBLING protein's role in oral and craniofacial development.

SIBLING ROLES IN DENTAL, PERIODONTAL, AND CRANIOFACIAL DEVELOPMENT

Most of the periodontium develops from the dental follicle that is derived from the neural crest cells. During tooth development, odontoblasts and dental pulp are originated from the dental papilla. Meanwhile, the periodontium components, cementum, periodontal ligament, and alveolar bone, are formed from the dental follicle. The development potential of the dental follicle has been investigated in studies that transplanted the tooth bud to sites known to be incapable of forming mineralized tissue. For example, after tooth bud transplantation to the anterior chamber of the eye, root formation with cementum and alveolar bone formation were observed (34, 35). Even though the dental follicle proper has all precursors needed for cementum, bone, and periodontal ligament formation, fibroblasts from the perifollicular mesenchyme proliferate during root development and contribute to the PDL fibroblast pool. Perifollicular mesenchyme and perivascular cells may also contribute to originating osteoblasts of the alveolar bone (36).

Tooth

There are four stages of tooth development: dental lamina, bud stage, cap stage, and bell stage (37, 38). Dental hard tissue formation starts at the early bell stage, and the most prominent cells that govern this process are odontoblasts and ameloblasts (37, 38). Odontoblasts are responsible for dentin production and

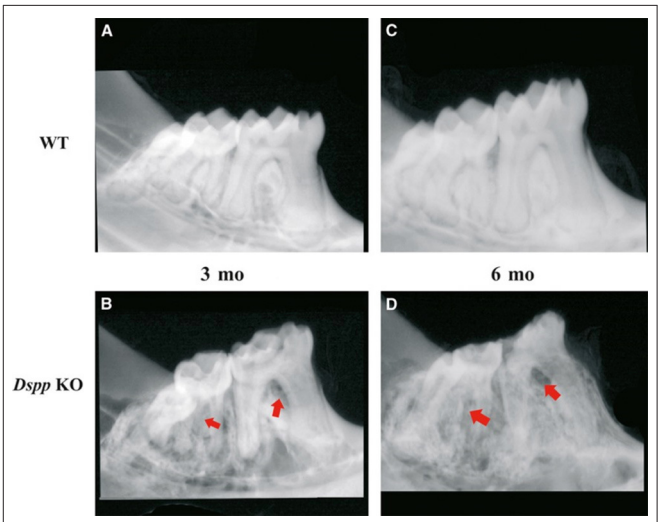

FIGURE 1 | X-ray images of mice mandibles from 3- and 6-month old WT **(A,C)** and *Dspp* KO **(B,D)**. **Figures 3B,D** show reduced dentin layer thickness, with enlargement of the pulp and destruction of the periodontium (red arrows) and crown. Figure from Gibson et al. (58).

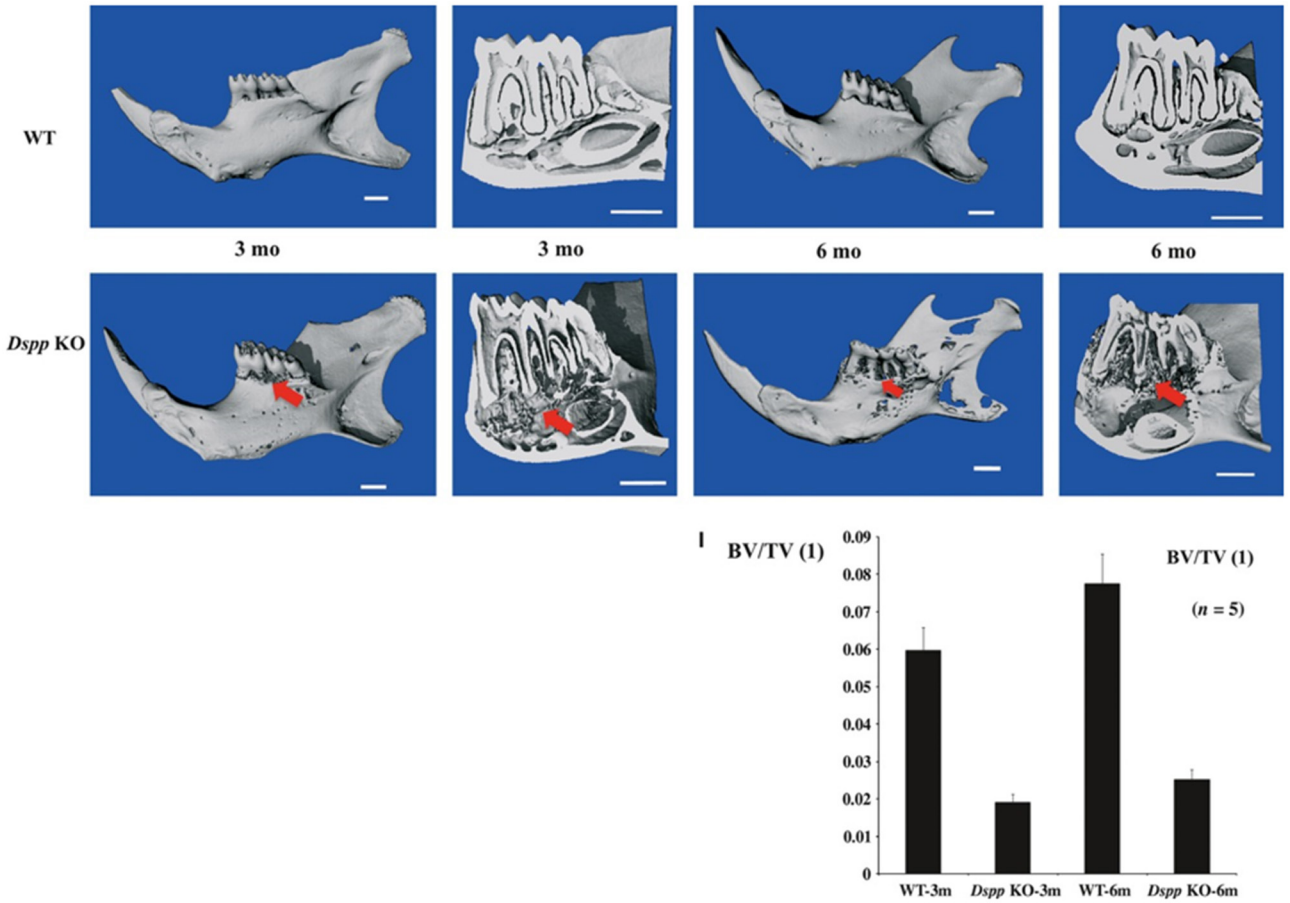

FIGURE 2 | Micro-CT images of mice mandibles from 3- and 6-month-old WT, *Dspp* KO. *Dspp* KO images show destruction of the alveolar bone (red arrows). Bone volume fraction (BV/TV) quantitative analysis shows the impact of the loss of function of DSPP in the alveolar bone. Figure from Gibson et al. (58).

are originated from ectomesenchymal cells adjacent to the dental epithelium. Ameloblasts are responsible for enamel production and are originated from inner enamel epithelium cells (39).

Predentin and osteoid are precursors of their corresponding mineralized tissues, dentin, and bone. In their unmineralized phase they lie between the mineralizing front and their depositing cells and are transformed in their mineralized phase as HA crystals are deposited. The biomineralization process involves multiple interactions between different molecules, among those, are type I collagen and NCPs (40, 41). Some of the roles of SIBLING proteins in dental tissues are discussed next.

DSP and DPP were initially thought to be dentin specific, "but recently their expression has also been shown to be present in bone and cementum" (15, 16). Human studies "have shown" that DSPP gene mutations are related to dentinogenesis imperfecta (DGI) and dentin dysplasia (DD); dentin development disorders that result in dentin hypomineralization and consequently, early tooth loss (12, 13). Mice studies also confirmed that *Dspp* knockout (KO) mice have hypomineralized dentin "that resembles" human DGI. The knockout phenotype presents teeth that are weaker than normal and more susceptible to rapid wear and breakage, with enlarged pulp chambers and widened predentin zone (42, 43). At 1 month of age, a "shell tooth" appearance of the teeth can be noticed, with enlarged pulp chambers. At 3 and 6 months of age extensive destruction of the tooth crown can be noticed, mostly due to the fragility of the dentin (42, 43). Examples of this tooth phenotype are illustrated in **Figures 1** and **2**.

DMP1 was also initially identified in teeth and later in bone (44, 45). DMP1 is present mostly in the peritubular region of dentin and the pulp, and it plays a role in dentin mineralization and the differentiation of odontoblasts (46). Previous *in vivo* studies have shown that *Dmp1* KO animals express hypomineralization of the dentin with widened predentin and reduced dentin layer, caused by an impairment of the conversion of predentin to dentin. Also, the dentin tubules in *Dmp1* KO models lack organization and number of branches compared to control models of the same age (47, 48). A previous study also suggested that DMP1 can regulate crystal size and organize crystal alignment in the dentin (20).

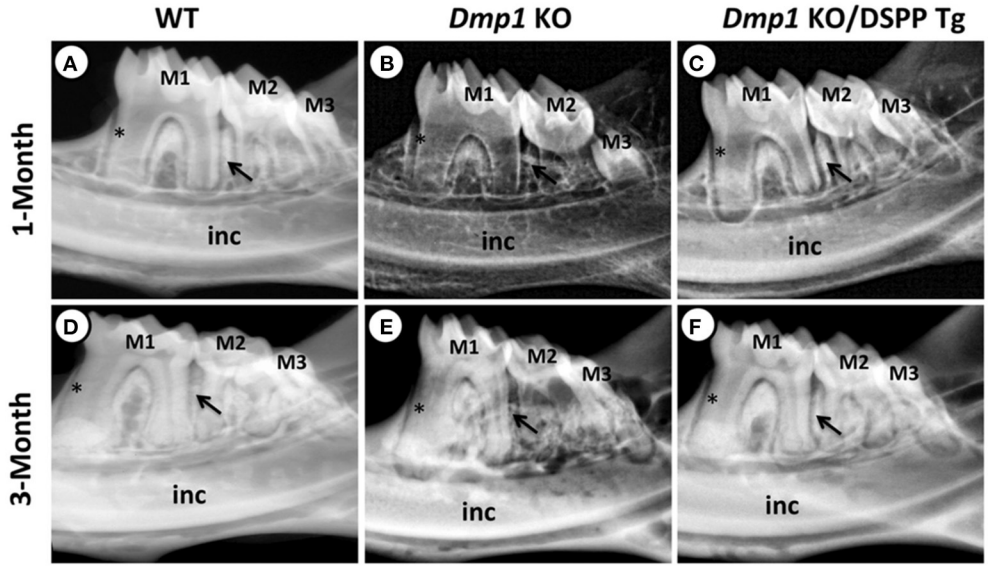

FIGURE 3 | (A–F) X-ray images of mandibles from 1- and 3-month old WT **(A,D)**, *Dmp1* KO **(B,E)**, and *Dmp1* KO mice with transgenic expression of DSPP (*Dmp1* KO/DSPP Tg) **(C,F)**. **(A,D)** Normal dentin layer thickness and alveolar bone opacity. **(B,E)** Increased radiolucency of the molars and alveolar bone, with highest impact in 1 month of age. **(B)** "Shell tooth" appearance of the M1. **(E)** Evidence of periodontal destruction (black arrow). **(C,F)** Show similar morphology compared to **(A,B)**. Overall, WT and *Dmp1* KO/DSPP Tg express a thicker dentin layer compared to *Dmp1* KO (*). M1, First molar; M2, Second molar; M3, Third molar; Inc, Incisors. Figure from Gibson et al. (91).

Examples of *Dmp1* KO tooth phenotypes are illustrated in **Figures 3**–**5**.

OPN is a phosphorylated sialoprotein. It is expressed in predentin, mantle dentin, dentin-cementum junction, and tertiary dentin (25). It is an element of the ECM of teeth. It functions as an inhibitor of mineralization and mediator of interfacial adhesion (31, 49–51). Proper OPN function is closely related to the expression of the *Alpl* gene, which is responsible for the function of tissue-non-specific alkaline phosphatase (TNAP). TNAP dephosphorylates OPN, therefore the loss of function of TNAP leads to increased OPN concentration in the ECM. Molars and incisors of *Alpn* KO mice showed hypomineralization of root dentin, with delayed conversion of predentin into dentin, as mentioned previously. The same models also expressed lack of organization of the odontoblast layer of the pulp (49).

BSP is present in reactionary dentin and in the mineralization front (52). BSP is reportedly specific to mineralizing tissues, such as bone, dentin, cementum, and ameloblasts (52, 53). BSP expression is highest in zones where bone is being formed or remodeled (54). However, it has been found that BSP absence did not cause observational defects in dentin mineralization, development, or cellular organization, and therefore, BSP has no critical impact in dentinogenesis, and its absence could possibly be compensated by other SIBLINGs (55). Recent discoveries by Vijaykumar et al. showed that BSP-GFPtpz^{+} cells are present in *in vitro* mineralization of pulp cells and in reparative dentin formation (56).

MEPE has been suggested to possibly play roles in dentinogenesis, osteogenesis, and pulpal homeostasis (57). In dentin, MEPE might be able to delay mineralization through negative regulation of odontoblasts during their immature stage, and during the formation of dentinal tubules. It also has been suggested that MEPE might inhibit the growth of HA crystals in the matrix of dentin (57). Another study by Gullard et al. showed that. *Mepe*$^{-/-}$ mice molars had thicker predentin, dentin, and enamel and lower expression of SIBLING transcripts compared to WT, and also suggested that MEPE might play a role in the maintenance of non-mineralized matrix (58).

Gingiva

Gingiva is composed of gingival epithelium and the gingival connective tissue, both of different tissue origins. The gingival epithelium originates from the thickened reduced enamel epithelium which is formed as an erupting tooth approaches the oral epithelium. As tooth eruption proceeds, the reduced enamel epithelium fuses with the oral epithelium and forms the junctional epithelial cells (36).

Fibroblasts from the gingival connective tissue are developed from the perifollicular mesenchyme, which is a derivative of the stomodeal mesoderm. Unlike periodontal ligament fibroblasts, gingival fibroblasts do not meet the tooth surface. New gingival fibroblasts are originated from the proliferation of undifferentiated perivascular cells (36).

OPN is not normally detected in healthy mucosa (59). However, it is upregulated in the presence of malignant lesions such as oral squamous cell carcinoma, or premalignant lesions, such as leukoplakia (60). DSPP absence has also been related to detachment of junctional epithelium in mice, leading to periodontal disease. However, this is accompanied by bone destruction and the gingival impacts might be secondary to that

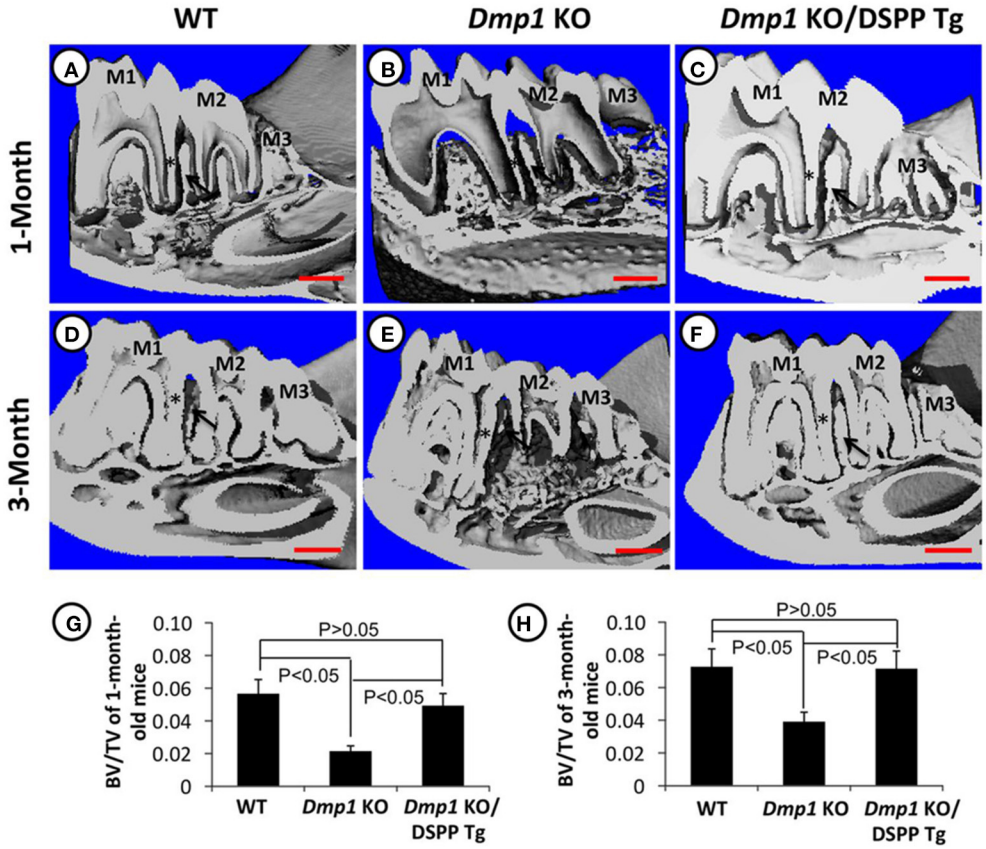

FIGURE 4 | (A–H) Micro-CT images of mandibles from 1- and 3-month old WT **(A,D)**, *Dmp1* KO **(B,E)**, and *Dmp1* KO mice with transgenic expression of DSPP (*Dmp1* KO/DSPP Tg) **(C,F)**. Destruction of the periodontium and enlargement of the pulp can be noticed in **(B,E)** (black arrows) BV/TV analyses show the impact of *Dmp1* KO, as well as the rescue potential of DSPP in *Dmp1* KO background **(G,H)**. As seen in X-rays, WT and *Dmp1* KO/DSPP Tg express a thicker dentin layer compared to *Dmp1* KO (*). M1, First molar; M2, Second molar; M3, Third molar. Figure from Gibson et al. (91).

(61). To the best of the authors' knowledge, limited research is available regarding the role of SIBLING proteins in gingival tissues. Future research would be needed to further understand impacts of their absence in these tissues.

PDL

The development of the PDL is related to tooth root formation. Mesenchymal cells of the perifollicular mesenchyme initialize the synthesis and deposit of collagen fibers and glycoproteins in the developing PDL (62–64). A unique feature of the PDL is that both developing and mature PDL contain undifferentiated stem cells (65–67). OPN, BSP, and DMP1 play a major role in PDL development.

OPN is responsible for preventing ectopic calcification in soft tissues (68–72). In accordance with that, *Ibsp*$^{-/-}$ mice showed increased density in the PDL compared to control. In the absence of OPN, a five-fold increase in inorganic pyrophosphate (PPi) was reported, possibly working to repress cementum growth, compensating the absence of OPN (73).

The periodontal ligament contains periodontal ligament stem cells (PDLSCs) that are responsible for maintaining tissue homeostasis (74). George et al. investigated the mechanisms by which PDLSCs differentiate into osteoblasts. This study demonstrated that DMP1 is transported to the nucleus of PDLSCs where it promotes osteogenic differentiation (75). Another study also pointed out that the PDL of *Dmp1* KO mice "expresses fewer" and irregularly shaped fibroblasts compared to WT (76).

The loss of BSP function has been shown to impact the PDL attachment, affecting Sharpey's fiber attachment and causing disarray of the PDL collagen fibers (55). However, this study pointed out that the integrity of the fibers in knockout models was similar to wild type (WT) at 14 days post-natal (dpn), and disorganization of the fibers could be noticed at 26 dpn, when bone and cementum destruction caused by the absence of BSP had already taken place. Therefore, it must be noted that the PDL impacts might be secondary to destruction of the PDL attachment interfaces.

A study by Gibson et al. showed how the loss of DSPP leads to periodontal disease in mice, including bacterial infiltration in the PDL, which is related to detachment of the PDL. However, it was noted the PDL impacts could be secondary to cementum and alveolar bone loss (61). The histology of this PDL phenotype is illustrated in **Figure 6**.

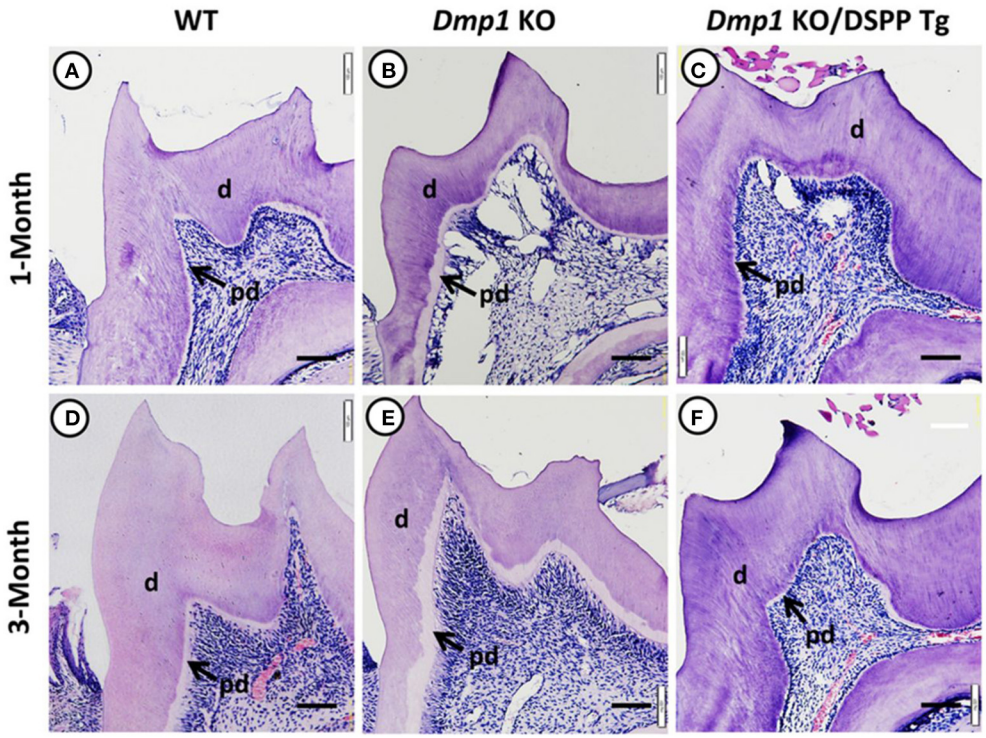

FIGURE 5 | Hematoxylin and eosin staining images of molars from 1- and 3-month old WT **(A,D)**, *Dmp1* KO **(B,E)**, and *Dmp1* KO mice with transgenic expression of DSPP (*Dmp1* KO/DSPP Tg) **(C,F)**. **(B,E)** Widened predentin (pd) zones and enlarged pulp chambers with reduced dentin (d) layer thickness. Figure from Gibson et al. (91).

Alveolar Bone

At the late bell stage of tooth development, bony septa, and bony bridge start to form and separate tooth germs from one another, initiating a socket for each tooth (77). As the root develops, the alveolar process follows the increase in height. While cells in the dental follicle start differentiating into fibroblasts and cementoblasts, some cells from the dental follicle differentiate into osteoblasts that form the alveolar bone proper (77–80). Therefore, the morphology of each individual root determines the structure of the alveolar bone proper. The spongy bone and cortical walls of the alveolar process compose the periosteal bone (77).

Successful tooth eruption requires remodeling of the alveolar bone process, where the gubernacular canal must be opened by osteoclastic activity to allow the developing tooth to erupt (81, 82). The dental follicle has been found to be essential for bone resorption through the eruption pathway as well as new bone formation apically to the erupting tooth (83, 84).

OPN is known to be expressed in the periodontium during tooth development (23). In a study, at 14 days post-natal, the *Spp1* gene was observed in osteoblasts of the alveolar bone and new cementoblasts near the apical root. "It was concluded that lack of OPN in mice promotes more rapid formation of cellular cementum with higher mineral density compared to the control." Observations in the mandibular bone showed that osteoblasts appear normal in number and location, suggesting that OPN acts directly in bone matrix mineralization. OPN also functions as an osteoclast recruiter for bone remodeling during unloading conditions in the tail suspension mouse model (85–87). $Spp1^{-/-}$ osteoclasts present defects such as hypomobility and decreased resorption (88, 89). In the alveolar bone, OPN was shown to be important in force-induced bone resorption, such as orthodontic movement (90).

A previous study has observed alveolar bone loss in $Dspp^{-/-}$ mice, with a significant decrease in bone volume/ trabecular volume (BV/TV), compared to control (91). DSPP absence has also been associated with severe alveolar bone loss and bone porosities in mice, as well as infiltration of inflammatory cells in the alveolar bone (61). The histology of this alveolar bone phenotype is illustrated in **Figure 6**.

The alveolar bone forms by intramembranous ossification, a previous study has described that BSP absence in mice is related to high osteoid concentration resulting in delayed mineralization in the mandible and alveolar bone when compared to WT (55). It has also been reported that $Ibsp^{-/-}$ mice models presented twice the number of osteoclasts in their alveolar bone compared to WT models at 26 dpn, and 8-fold the amount by 60 dpn (55). This study suggested that BSP impacts the osteoid mineralization phase directly during intramembranous ossification, and therefore has a direct role during HA crystal development and maturation.

Literature has already described that DMP1 is important for the conversion of osteoblasts into mature osteocytes

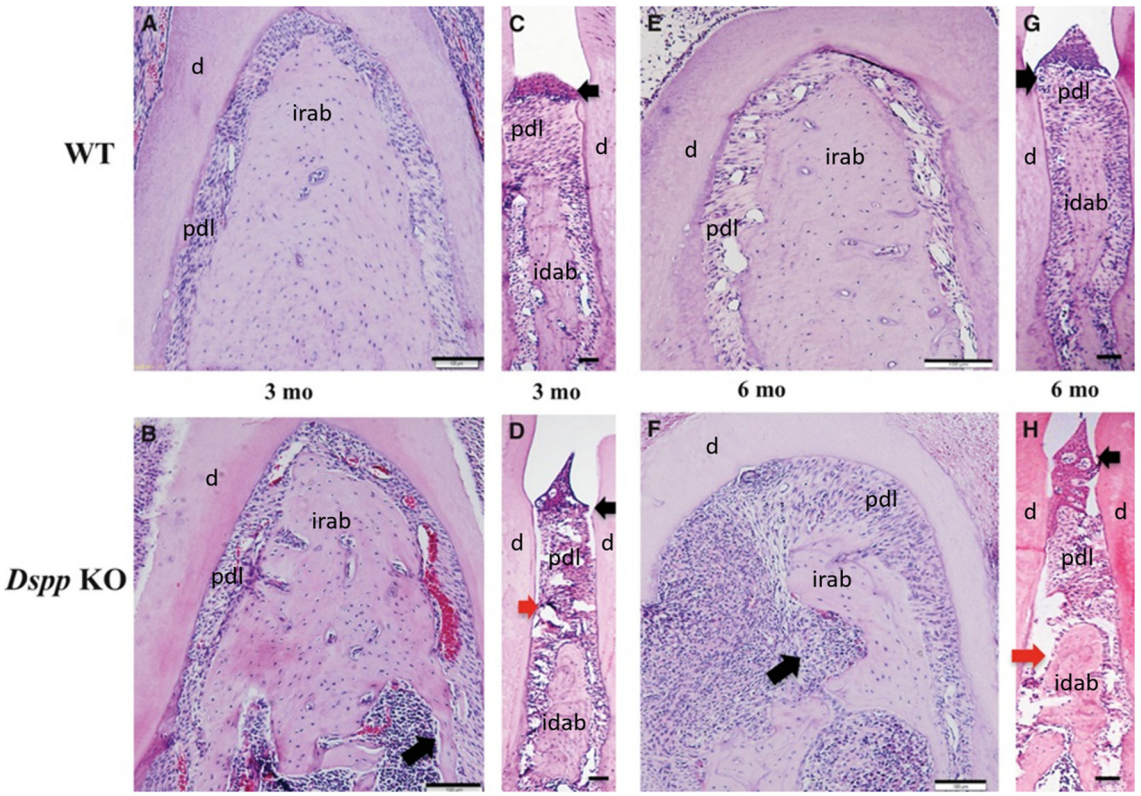

FIGURE 6 | Hematoxylin and eosin staining images of alveolar bone from 3- and 6-month old WT **(A,C,E,G)**, *Dspp* KO **(B,D,F,H)**. **(B,D,F,H)** Destruction of the alveolar bone, with apical migration of the junctional epithelium (black arrows) and destruction of the PDL (red arrows) in **(D,H)**, and inflammatory process in the alveolar bone (long black arrows) in **(F)**. Idab, Interdental alveolar bone; irab, inter-radicular alveolar bone; d, dentin; pdl, periodontal ligament. Figure adapted from Gibson et al. (58).

(92, 93). DMP1 absence was also found to severely impact the formation of alveolar bone, forming porosities in the bone and disorganization of osteocyte lacunae and reduced canaliculi. A previous study investigated the pathway of action of DMP1 in the bone by investigating its impact on odontoblast differentiation markers, COL1A1 and BSP, and found that *Dmp1* KO mice had reduced expression of "these markers and led" to periodontal defects in mice. It is also worth noting that this study found that transgenic DSPP expression was capable of rescuing the osteoblast and odontoblast differentiation impairments in *Dmp1* KO mice, as illustrated in **Figures 3–5** (94). *Dmp1* KO also results in increased FGF23 expression, which is associated with hypophosphatemia in mice and autosomal recessive hypophosphatemic rickets in humans (OMIM 241520) (95, 96).

MEPE expression has also been identified in osteocytes and osteoblasts (30, 31). Previous studies showed that the knockout of *Mepe* gene in mice was related to increased bone formation and bone mass, as well as higher mineralization and increased osteoblastic markers. MEPE's exact role in mineralization is still unclear, studies have suggested that different terminals of *Mepe* gene have different functions. A fragment from the COOH- terminal has been linked to inhibition of mineralization *in vitro*, while, a fragment from the N-terminal has been associated with accelerated mineralization (30, 31).

Cementum

Cementum composition is similar to bone, being 50% inorganic, mostly HA crystals, and the remaining is composed of collagen and NCPs (74). Cementum can be divided into two main forms. Acellular cementum, which serves as an attachment base for the tooth, and cellular cementum, which serves as an active responder to tooth movement and damage. The complete pathway of cementum development is still currently being researched (74). BSP, DMP1, DSP, and OPN are known to be present in cementum.

As mentioned before, acellular cementum is essential for anchoring the PDL fibers to the tooth root surface. The first developmental disease known to affect cementum was hypophosphatasia (HPP; OMIM 241500, 241510, 146300), which causes loss of function of the *ALPL* gene, which encodes tissue-nonspecific alkaline phosphatase (TNAP) (97, 98). This results in increased concentrations of PPi, which is a potent inhibitor of mineralization. This leads to skeletal defects and loss of acellular cementum formation and function, and

therefore further leads to PDL detachment and tooth loss (99–105).

The ECM of cementum is rich in BSP and OPN. Developmental studies of *Ibsp*$^{-/-}$ mice "have shown that this mutation causes a reduction in the formation" and function of acellular cementum, resulting in dysfunctional PDL attachment (55, 106, 107). Similarity in defective cementum phenotypes between *Ibsp*$^{-/-}$ and *Alpl*$^{-/-}$ was investigated. It was concluded that *Ibsp* KO mice feature a 2-fold increase in circulating PPi, elevated OPN expression, and altered mRNA expression of PPi regulators ALPL, SPP1, and ANK in the periodontium. *In vitro* studies also showed that *Ibsp* KO cementoblasts exhibit significantly decreased mineralization capacity and increased PPi (108). The loss of BSP function has also been related to absence of acellular cementum in mice (55).

DSPP has been found to have an active role in cementogenesis. DSPP absence has been related to severe cementum loss in first molars and incisors of 3 month-old mice. This study also suggested that the cementum malformation might be related to postnatal function loss of cementoblasts (61). Similar to DSPP, DMP1 absence has also been found to be related to defective cementum formation of 3 month-old mouse models. This study described the acellular cementum of *Dmp1* KO mice to be thinner and with less cementoblasts, which were irregularly shaped. The cementocyte lacuna was rough, and the cementum formation rate was irregular in KO models, which suggested impaired calcospherite maturation (76).

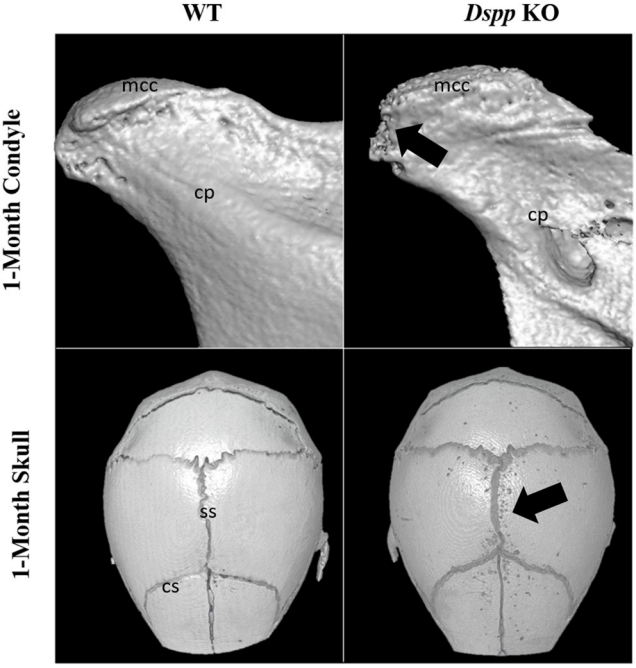

FIGURE 7 | Micro-CT images of mandibular condyles and skulls of 1-month old WT and *Dspp* KO mice. The KO mice show porosities on the MCC surface, as well as around cranial sutures (black arrows). Mcc, mandibular condylar cartilage; cp, condylar process; ss, sagittal suture; cs, coronal suture.

Craniofacial Skeleton

Most of the cranium is formed *via* intramembranous ossification. In this type of ossification, bone development occurs directly from mesenchymal connective tissue (109). Similar to the alveolar bone, osteoid is transformed into bone through the action of NCPs, especially SIBLING proteins.

A previous study found that osteoblasts derived from the skull of mice missing the DSPP protein deposited less mineral content compared to osteoblasts from WT mice, a phenotype of *Dspp* KO skull is illustrated in **Figure 7** (90).

BSP potentially plays a role in maintaining tissue homeostasis by remodeling *via* osteoclastogenic activity (110). BSP has also been suggested to play a critical role during the intramembranous ossification of the calvaria, with delayed mineralization represented by wider sutures in *Ibsp*-/- mice compared to WT during development (55).

A recent study found that the absence of the proteoglycan form of DMP1 (DMP1-PG) could potentially cause premature, narrow, and irregular fusion of cranial sutures. The study suggested that in the absence of DMP1-PG, the differentiation of bone mesenchymal stem cells into preosteoblasts was accelerated, leading to premature mineral deposition (111).

It has been previously shown that the loss of OPN results in impaired osteoclast activity, which leads to impaired bone resorption (88). A more recent publication has outlined that mechanical stress in the sagittal cranial suture of neonatal mice leads to modified expression of OPN, suggesting that OPN is active in the osteoblast differentiation process in cranial sutures (112). Another study has suggested that BSP and OPN have a functional overlap, as they have the potential to compensate for each other's absence in response to a hormonal challenge (113).

Mandibular Condyle

Literature has described the expression of SIBLING proteins in the mandibular condylar cartilage (MCC) and suggested they are active during chondrogenesis (6). IHC results showed DSPP, DMP1, BSP, and OPN expression in different layers of the MCC during development. DSPP absence has been shown to impact the development of the condyle at early ages (6).

DMP1 cleavage has been shown to be essential during chondrogenesis of the MCC. A study has shown that the absence of DMP1-PG could be related to accelerated osteoarthritis in the TMJ cartilage (22). Similarly, a recent study has shown that the post translation modification of DSPP is also essential for the development of the MCC. The same study found that *Dspp*$^{-/-}$ mice showed a reduced volume of subchondral bone in the condyle compared to WT, an example of this phenotype is illustrated in **Figure 7** (114).

CONCLUSION

Some SIBLING proteins were first discovered in isolated tissues, for example, DSPP and DMP1 in dentin. However, recent studies have brought to light a much wider distribution

of the expression of SIBLING proteins in the body. Such distributed expression "suggests that there may be" be many undiscovered roles and pathways of SIBLING protein action. The present review focused on summarizing the expression and roles of SIBLING proteins in oral and craniofacial tissues. Studies included in this review mostly discussed the regulatory function that SIBLING proteins have in mineralization and the impacts of their absences. DMP1, DSPP, and BSP as positive regulators of mineralization, and OPN and MEPE as negative regulators. Some studies have also suggested that SIBLING proteins might be able to partially compensate for the absence of one another.

Further research on the role of SIBLING proteins during periodontal and craniofacial development, as well as which proteins are able to compensate for others absences, could expand our knowledge of the pathways of mineralization and provide potential insight into pathways of rescuing craniofacial defects.

AUTHOR CONTRIBUTIONS

CF, NA, and MG: study conception and design and draft manuscript. CF: data collection. All authors reviewed the results and approved the final version of the manuscript.

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