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Dentin sialophosphoprotein and dentin matrix protein-1: Two highly phosphorylated proteins in mineralized tissues

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ABSTRACT

Dentin sialophosphoprotein (DSPP) and dentin matrix protein-1 (DMP-1) are highly phosphorylated proteins that belong to the family of small integrin-binding ligand *N*-linked glycoproteins (SIBLINGs), and are essential for proper development of hard tissues such as teeth and bones. In order to understand how they contribute to tissue organization, DSPP and DMP-1 have been analyzed for over a decade using both *in vivo* and *in vitro* techniques. Among the five SIBLINGs, the *DSPP* and *DMP-1* genes are located next to each other and their gene and protein structures are most similar. In this review we examine the phenotypes of the genetically engineered mouse models of DSPP and DMP-1 and also introduce complementary *in vitro* studies into the molecular mechanisms underlying these phenotypes. DSPP affects the mineralization of dentin more profoundly than DMP-1. In contrast, DMP-1 significantly affects bone mineralization and importantly controls serum phosphate levels by regulating serum FGF-23 levels, whereas DSPP does not show any systemic effects. DMP-1 activates integrin signalling and is endocytosed into the cytoplasm whereupon it is translocated to the nucleus. In contrast, DSPP only activates integrin-dependent signalling. Thus it is now clear that both DSPP and DMP-1 contribute to hard tissue mineralization and the tissues affected by each are different presumably as a result of their different expression levels. In fact, in comparison with DMP-1, the functional analysis of cell signalling by DSPP remains relatively unexplored.

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Abbreviations: DSPP, dentin sialophosphoprotein; DSP, dentin sialoprotein; DPP, dentin phosphoprotein (alternative names: Dentin phosphophoryn or phosphophoryn); DMP-1, dentin matrix protein-1; SIBLINGs, small integrin-binding ligand *N*-linked glycoproteins; FGF-23, fibroblast growth factor-23; BSP, bone sialoprotein; MEPE, matrix extracellular glycophosphoprotein; OPN, osteopontin; RGD, arginine–glycine–aspartic acid; ASARM, acidic serine–aspartate-rich MEPE-associated; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; DGI, dentinogenesis imperfect; DD, dentin dysplasia; ECM, extracellular matrix; DGP, dentin glycoprotein; DPPcKO, DPP conditional knockout mouse; SLRP, small leucine rich repeat (SLRP); rER, rough endoplasmic reticulum; MAPK, mitogen-activated protein kinase; BMP, bone morphogenetic protein; GRP78, glucose-regulated protein; HSP70, heat shock protein 70; IP3, inositol 1,4,5-triphosphate; ARHP, autosomal recessive form of hypophosphatemia; TLD, tolloid; MEP1B, meprin Aβ; GAG, glycosaminoglycans.

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1. Introduction

Dentin sialophosphoprotein (DSPP) and dentin matrix protein-1 (DMP-1) share many similarities in both their gene and protein structures, and it is now believed that DSPP arose from DMP-1 by a gene duplication event.[1] Evolutionary analysis of DSPP genomic sequence indicated that the creation of ancestor DSPP by DMP-1 duplication event may be indispensable to toothed animals.[2] DSPP and DMP-1 are both cleaved into two protein chains; the N-terminal regions are proteoglycans that contain chondroitin sulfate chains, and the C-terminal regions are highly phosphorylated (Fig. 1).[3–9]

It is now obviously accepted that DSPP and DMP-1 play important roles in hard tissue development. DSPP and DMP1 are positive regulators of hard tissue mineralization with DSPP acting on dentin and DMP1 acting on both bone and dentin. Their essential roles for hard tissue development and mineralization *in vivo* have been analyzed utilizing many knockout and transgenic mouse models (summarized in Tables 1 and 2).

Despite the similarities between DSPP and DMP-1, a recent *in vitro* study suggested that phosphorylated forms of both DSPP and DMP-1 would be able to act as nucleators of apatite crystal formation in the presence of collagen, with DSPP inducing highly organized intrafibrillar collagen mineralization and DMP-1 inducing the deposition of mineral particles along the collagen fibril axis.[10] These discrete roles indicate the biochemical differences between DSPP and DMP-1.

2. The features of the SIBLING family and the properties of DSPP and DMP-1

The SIBLING family consists of five extracellular matrix proteins: DSPP, DMP-1, bone sialoprotein (BSP), matrix extracellular glycophosphoprotein (MEPE), and osteopontin (OPN). Human chromosome 4 (mouse chromosome 5) contains a SIBLING family gene cluster (4q21) located immediately proximal to a cluster of enamel matrix protein genes (4q13) (Fig. 1). The SIBLING family was defined on the basis of their common structural, biochemical and genetic features.[11] These include multiple phosphorylation sites, a highly acidic nature, the presence of an arginine–glycine–aspartic acid (RGD) integrin binding site, and a proteolytic-resistant acidic serine–aspartate-rich MEPE-associated (ASARM) motif.[12,13] Three SIBLINGs, DMP1, BSP, and OPN, can specifically bind to pro-matrix metalloproteinase-9 (proMMP-9), proMMP-2, and proMMP-3, respectively. This specific binding facilitates either a conformational changes or the release of tissue inhibitor of metalloproteinase (TIMP) from the MMP–TIMP complex thereby making the MMP proteolytic active site accessible.[14] The activation of MMPs by binding of the SIBLINGs results in induction of specific

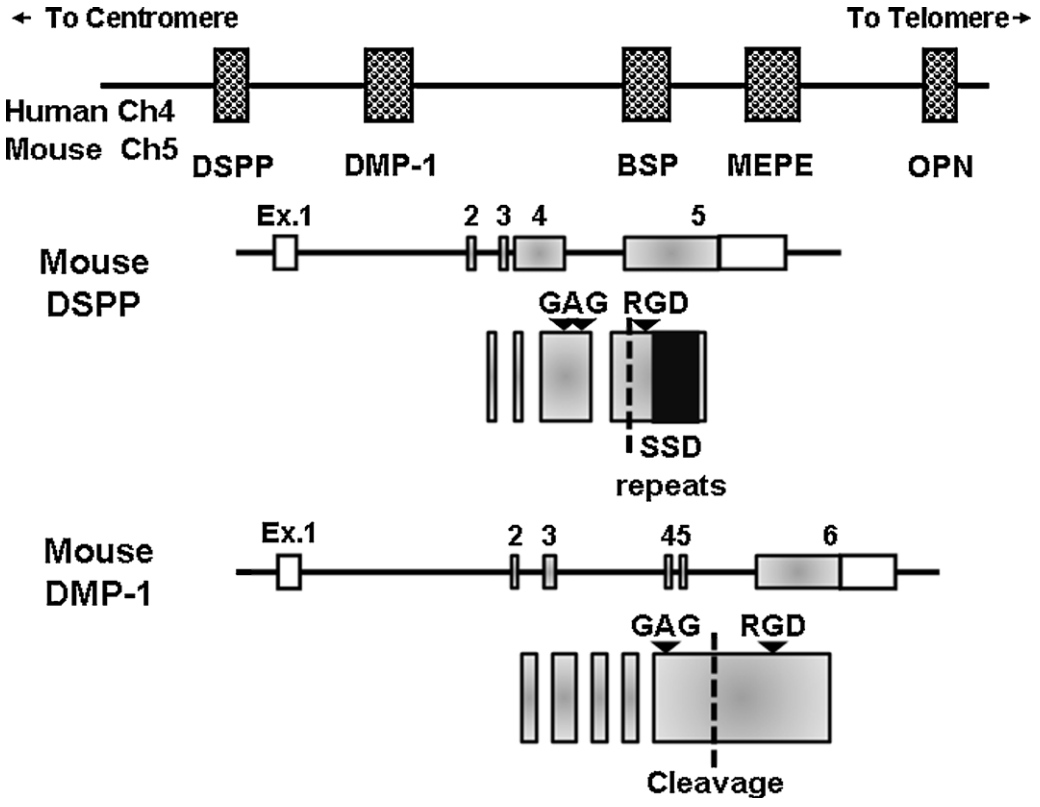

Fig. 1 – The genomic location and exon–intron structure of mouse DSPP and DMP-1. SIBLING proteins are located next to each other on human chromosome 4 and mouse chromosome 5. Two glycosaminoglycans (GAG) sites have been reported in mouse DSPP (serine242 and serine254) and one GAG site in DMP1 (serine 89).[8,9] The amino acids are numbered after signal peptide removal. SSD repeats: serine–serine–aspartic acid repeats sequence.