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Dynamic Expression Profiles of the Extracellular Proteoglycans are Implicated in Epithelial –Mesenchymal Crosstalk at the Time of Early Odontogenesis

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Mammalian tooth generation utilization has been done in numerous studies for evaluation of the molecular mode in the form of an illustrative model which is believed to simulate organogenesis. The reciprocal crosstalk subsequent to induction amongst dental epithelium along with neural crest obtained mesenchyme illustrate the usually the frequent design for the generation of ectodermal placodes used in various kinds of epithelial organogenesis like salivary glands, lungs, Kidneys, mammary glands, hair follicles, limb buds. Preserved signalling pathways like wingless -related integration site (WNT), Bone morphogenetic protein (BMP), sonic hedgehog (SHH), Fibroblast growth factor (FGF) are considerably implicated in modulating signalling connection, at the time of tooth generation [1]. Different signalling molecules, morphogens along with cytokines crosstalk with extracellular constituents, like proteoglycans to shift as well as escalated signal transduction pathways in cells [2]. An intricate balance amongst these signal transduction pathways is key regarding modulating the biological events of tooth generation inclusive of epithelial invagination in addition to mesenchymal condensation [3]. Collecting validation illustrates that proteoglycans are frequent in the formation of mammalian tee that variable stages and are key signalling controllers at the time of organogenesis [4]. Nevertheless, their part regarding modulating odontogenesis, specifically the interaction amongst the dental epithelium as well as mesenchymal partitions, still have to be worked out [5].

Proteoglycans mirror a family of polysaccharides macromolecules constituted of a core protein in addition to covalently associated glycosaminoglycan side chains (GAG). They have broad expression on cell surfaces apart from within the extracellular matrix (ECM) of eukaryotic cells [6]. Their expression motif is precisely controlled in various spatiotemporal aspects for modulating different biological along with pathological events like organogenesis, tissue generation apart from starting of cancer as well as its propagation (see fig 1 &2) [7].

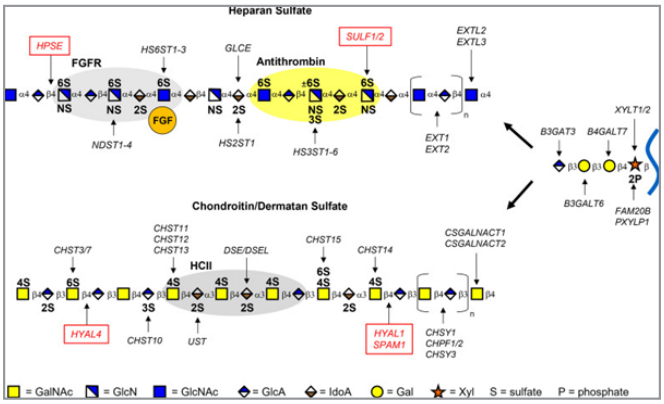

Figure 1: Courtesy ref no-7-Heparan and chondroitin/dermatan sulfate biosynthesis. Assembly of the chains is performed by a large

group of biosynthetic enzymes located in the Golgi. Heparan sulfate (HS) and chondroitin sulfate (CS)/dermatan sulfate (DS) share a common tetrasaccharide linker (Xyl-Gal-Gal-GlcA) that is attached to a serine residue of the core protein. HS and CS/DS assembly is initiated by EXTL3 (HS) or CSGALNACT1/2 (CS/DS), respectively, followed by polymerization and sulfation at specific sites. The gray and yellow ovals signify binding sites for ligands/proteins. FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; HCII, heparin cofactor 2; GalNAc, N-acetylgalactosamine; GlcN, glucosamine; Gal, galactose; GlcA, glucuronic acid; GlcNAc, N-acetylglucosamine; IdoA, iduronic acid; Xyl, xylose.

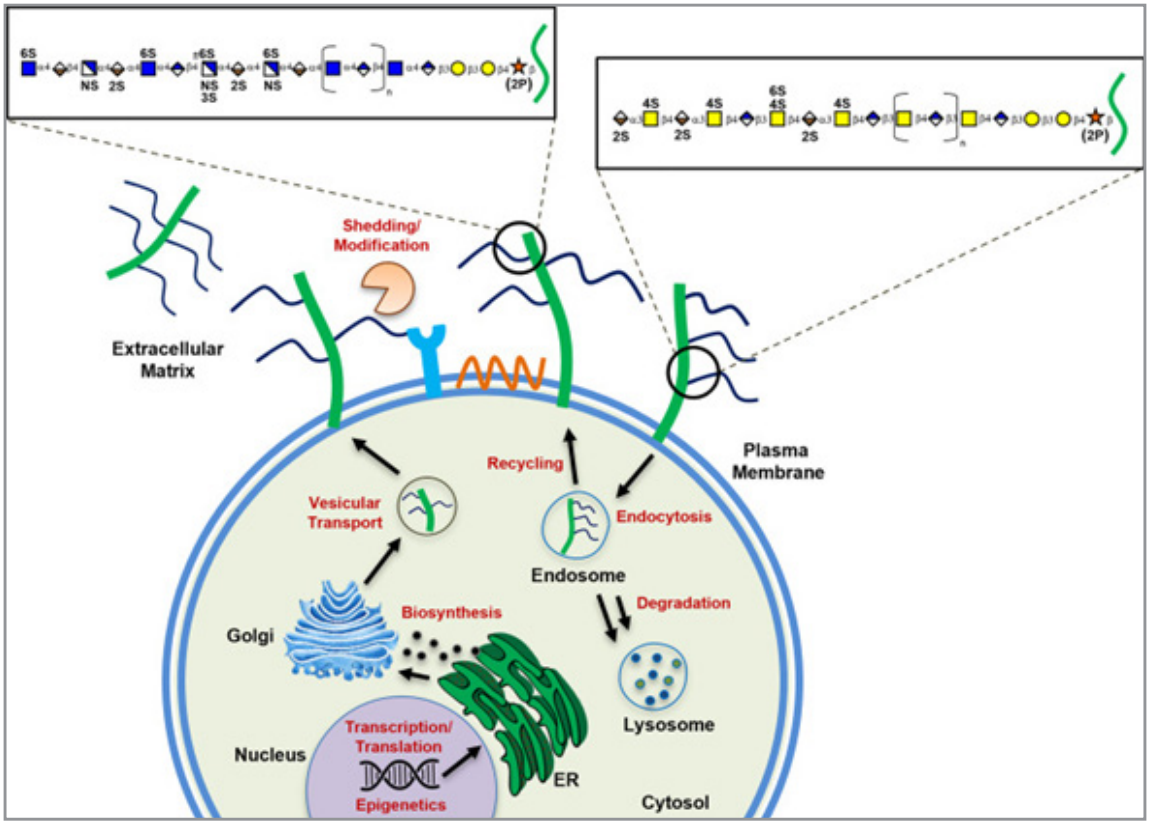

Figure 2: Courtesy ref no-7-Regulation of glycosaminoglycan (GAG) biosynthesis. Illustration depicting regulatory pathways controlling heparan sulfate (HS) and chondroitin sulfate (CS)/dermatan sulfate (DS) biosynthesis in the cell. Red lettering indicates potential steps of regulation before presentation of GAG chains in the extracellular space.

GAG 's portrays linear polysaccharides that are constituted of recurrent disaccharide units. Dependent on these disaccharide units GAG 's gets classified into 5 primary kinds; i) hyaluronic acid (HA) ii) Chondroitin sulfate (CS) iii) dermatan sulfate (DS) iv) heparan sulfate (HS) v) Keratan sulfate (KS).

Bio generation of GAG 's is an event where no template is implicated, numerous enzymes participate which modulate the recurrent disaccharide units along with develop different sulfation motifs. With such extensive structural variations GAG 's possesses the capacity of; i) broad variety of bind in regions for various signalling molecules to aid in their diffusion, ii) hamper their binding to receptors, iii) control the signalling bidirectionally, iv) or bind apart from confer protection to signalling molecules from protease breakdown [8].

Unique spatiotemporal proteoglycans expression has been found in recent studies at the time of tooth morphogenesis along with mineralization [9]. Furthermore, the prior studies of Wu, et al., observed that GAG 's modulate a fine balance regarding dental epithelial stem cells homeostasis by controlling FGF10/FGFR2b signalling to restrict the numbers of teeth in early stage of murine odontogenesis [10]. This observation pointed that proteoglycans in addition to GAG 's are necessary controllers of signalling networks in the early stage of tooth generation to drive dental stem cells fate guarantee as well as epithelial –mesenchymal crosstalk. Nevertheless, their part in the early odontogenesis, in particular continue to have inadequate work. The probable part of unique proteoglycans along with their sulfation motifs in odontogenesis continue to be uncertain as well. Thus Chen et al., aimed to evaluate the gene profile of extracellular proteoglycans as well as their GAG chains which are probably implicated in dental epithelial – mesenchymal crosstalk with the utilization of high – throughput sequencing to yield greater insight regarding early odontogenesis [11]. They carried out whole transcriptome profiles of mouse dental epithelium along with evaluated mesenchyme by RNA sequencing (RNA seq). 1281 along with 1582totalgenes that had differential expression pattern were isolated amongst the dental epithelium along with mesenchyme at E11.5 as well as E13.5 respectively. Enrichment evaluation illustrated that extracellular areas along with ECM receptors crosstalk were significantly abundant at E11.5 as well as E13.5 both. Polymerase Chain reaction (PCR) evaluation validated that the extracellular proteoglycans family illustrat-

ed unique alterations at the time of epithelial –mesenchymal crosstalk. Maximum proteoglycans illustrated greater transcript quantities in the dental mesenchyme, while just occasional were upregulated in the epithelium at both stages. Moreover, 9 proteoglycans illustrated dynamics expression alterations amongst these 2 tissue chambers. Gpc, 4, Sdc2, Spock2, Dcn, along with Lum got expressed in greater quantities in the dental epithelium at E11.5, while their expression was significantly greater in the dental mesenchyme at E13.5, that corresponded with the odontogenic probable transfer. Furthermore, the glycosaminoglycan bio generational enzymes Ext1, Hs3st1/5, Hs6st2/3 along with Sulf1 further illustrated early upregulation in the epithelium, however illustrated greater expression in the mesenchyme subsequent to odontogenic probable transfer.

Hence this study documented the dynamics expression profiles of the extracellular proteoglycans along with their bio generational enzymes at the time of epithelial –mesenchymal cross talk. Thus, greater understanding provided by this study regarding part of extracellular proteoglycans along with their unique sulfation motifs in early odontogenesis [11] (see Fig3-6).

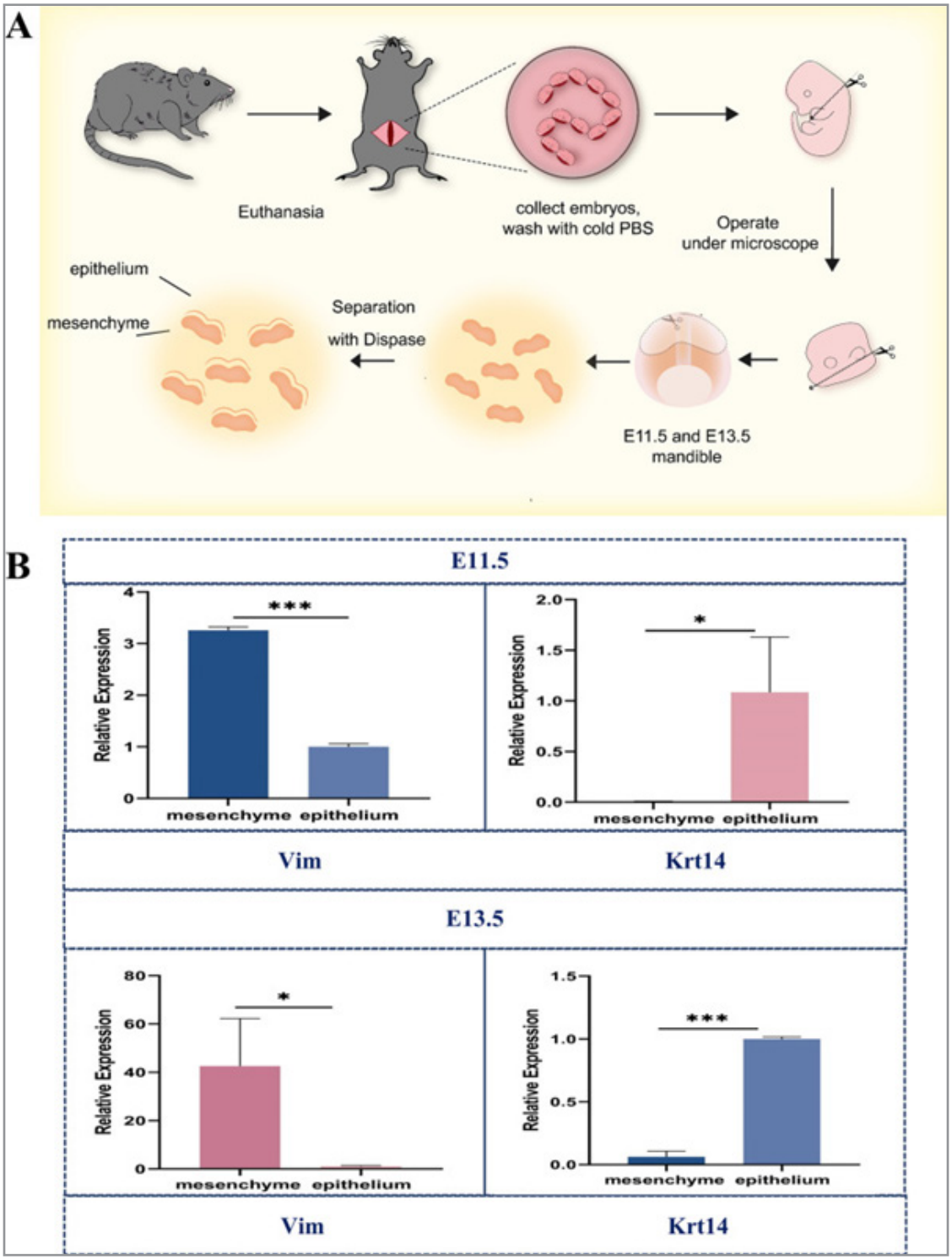

Figure 3: Courtesy ref no-11-Workflow for sample preparation and validation. A Workflow for sample preparation; B Expression levels of markers of mesenchymal and epithelial tissue samples from E11.5 and E13.5. (*, $p<0.05$; ***, $p<0.001$)

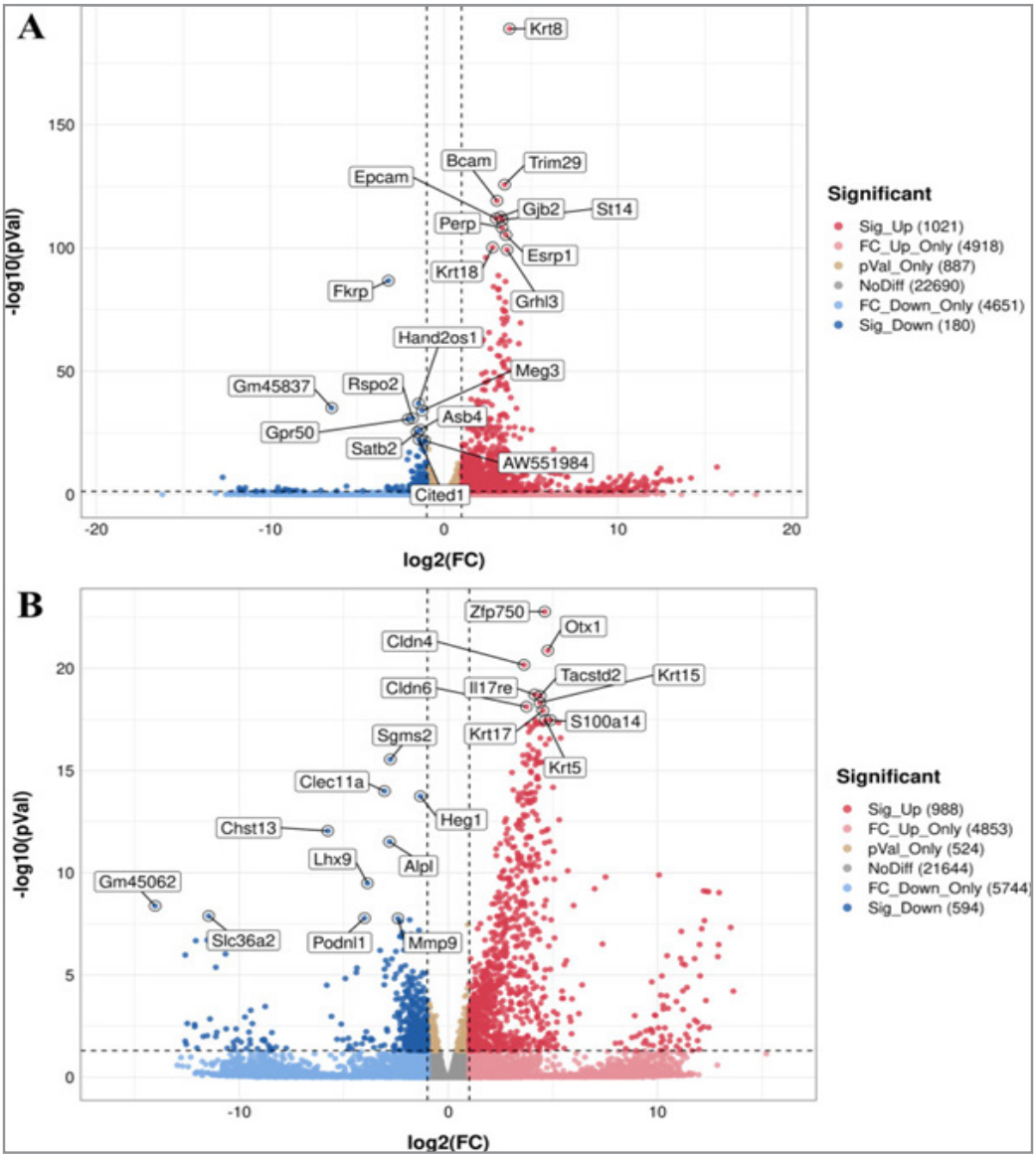

Figure 4: Courtesy ref no-11-Differentially expressed genes in different groups. A Volcano plot for DEGs between the E11 epithelium group and the E11 mesenchymal group. B Volcano plot for DEGs between the E13 epithelium group and the E13 mesenchymal group. (DEGs, differentially expressed genes)

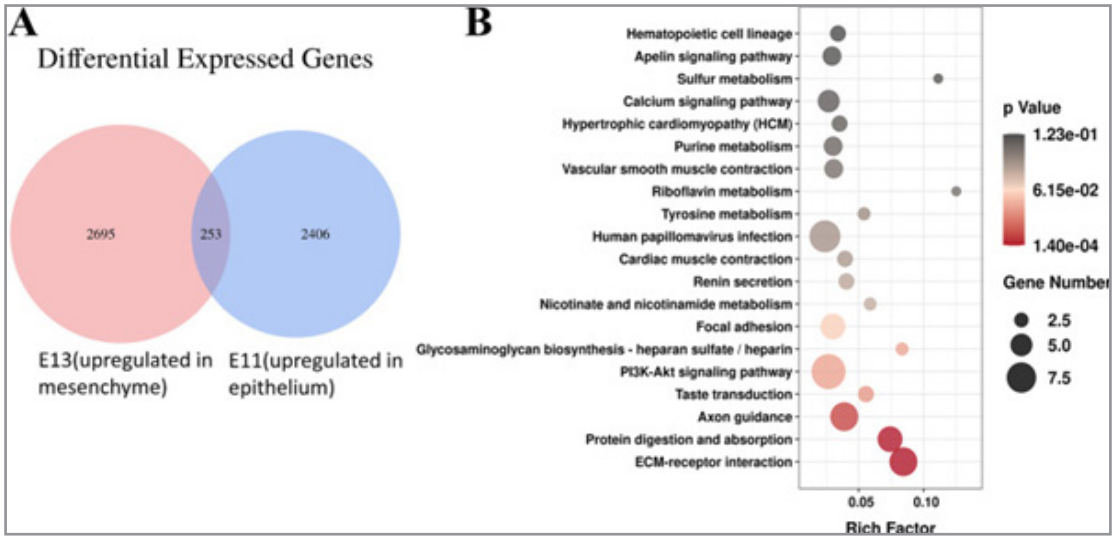

Figure 5: Courtesy ref no-11-Venn graph, and KEGG enrichment analysis of DEGs with dynamic upregulation in the dental epithelium at E11.5 and in the mesenchyme at E13.5. A Venn diagram for intersecting DEGs; B KEGG pathway analysis for intersected DEGs.

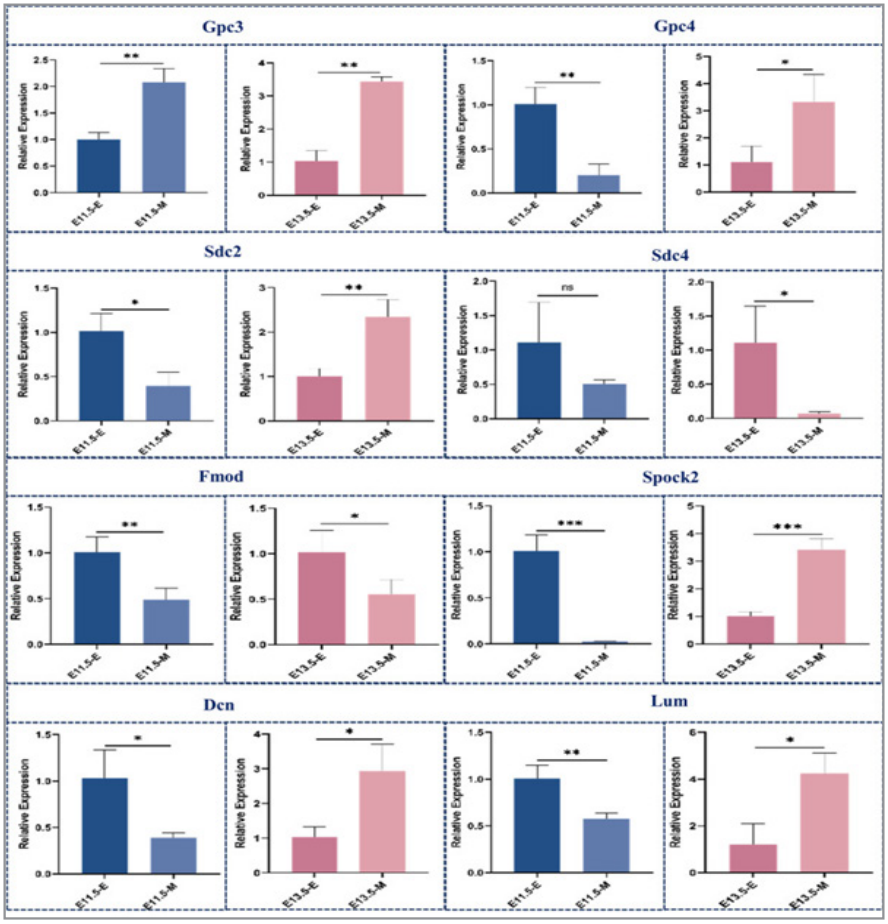

Figure 6: Courtesy ref no-11-qRT–PCR analysis of proteoglycans in the dental epithelium and mesenchyme at E11.5 and E13.5. (E, Epithelium; M, Mesenchyme) (*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$)

Conclusions

Their observations pointed that proteoglycans illustrated spatiotemporal diverse expression unique at the time of tooth generation. The proteoglycans isolated in this study can aid in acquiring insight regarding the molecular modes behind the epithelium-mesenchyme crosstalk at the time of odontogenesis. Alterations in proteoglycans might possess a key part in the control of multiple signal transduction pathways that precisely drive tooth development. Detailed experiments inclusive of gain-of-function and loss-of-function studies with utilization of the candidate shift genes isolated identified in this study are required to be conducted for further illustration of the part of proteoglycans at the time of tooth generation.

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