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Perspective Article

The mineralized extracellular "Matrix" reloaded: A tissue engineering perspective

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The tissue microenvironment consists of soluble and immobilized growth factors, ECM proteins and cells that orchestrate tissue-specific cell growth, differentiation and survival[1-4]. The SIBLING protein family consists of ECM proteins such as BSP, osteopontin (OPN), Dentin Matrix Protein 1 (DMP-1) and Dentin Sialophosphoprotein (DSPP)[5]. Proteins of the SIBLING family have been known to elicit signals that cause changes in cell function and fate.

Phosphophoryn (PP) is a cleavage product of DSPP[6], and has been implicated as a regulator of mineral crystal formation[6-9]. PP is the most abundant non-collagenous protein (NCP) in dentin ECM comprising ~50% of dentin ECM proteins[6] and also present in bone[10]. The majority of the protein sequence consists of $(DSS)_n$ repeats where n could be as high as 24 and approximately 85-90% of the serine residues are phosphorylated[7,11,12]. Typical of other NCPs, the physiochemical properties of PP dictate high affinity for Ca^{2+} and implicate a role in nucleation or modulation of hydroxyapatite (HA) crystal formation[13-15]. An RGD domain is present at the N-terminal end of PP[7,13], suggesting an auxiliary function in ECM-cell communication and initiation of intracellular signaling pathways. PP could have an important regulatory role in intracellular signaling for osteogenesis and growth factor-like activity.

The non-collagenous protein, phosphophoryn (PP) hypothesized to play a role in dentin biomineralization due to its highly acidic and anionic character appears to have a signaling function as we previously demonstrated. PP, a member of the SIBLING family of proteins, communicates with the cell via RGD/integrin interactions; however, recent data suggest integrin-independent functions. PP initiates changes in gene expression and cell phenotype in progenitor cells and could play a role in cell differentiation and maintenance of the phenotype in mineralizing cells via the MAP Kinase pathway. We have recently shown that in addition to the involvement of the MAPK pathway, PP also activates the Smad Pathway. We have further identified a crosstalk between the MAPK and Smad intracellular signaling pathways during PP stimulation. The Smad pathway seems to be important for perpetuation of the MAPK signal. PP appears to directly activate Smad1 independently from BMP2 although PP can up-regulate the gene expression of BMP2 at a much later time of Smad1 activation by PP. Activation of these signaling pathways resulted in transcriptional activity and regulation of target genes important for dentinogenesis/osteogenesis. Thus, PP may have a critical role in cell fate determination. The crosstalk between pathways suggests that PP's effect could be interpreted through a complex network of molecules.

In addition to the signaling role, we have investigated the role of post-translational modification, phosphorylation in particular, in regards PP's role in biomineralization. We have established tissue culture systems to address simultaneously the signaling and mineral nucleation role.

The dual roles of PP lead to many interesting questions in regards to the function of specialized extracellular matrix proteins of mineralized tissues that could affect the biomineralization process as well as cell signaling and gene expression. These aspects of PP's role will be discussed in light of our current results and how these functions could be used for tissue engineering purposes.

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