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Commentary

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Building a Solid Foundation: CCS in Developing Skeleton and the CCN Family Role

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The inauguration of Cell Communication & Signaling includes the introduction of a Commentary section which will identify concepts and current research of interest to the readership. In this first Commentary I have highlighted the complex processes of cartilage and bone formation and the potential role of the CCN family of proteins, in particular CCN2 (CTGF). We invite authors of papers cited and other investigators interested in the subject areas to submit further insights via the Commentary section and indeed in this manner to help develop a lively forum for discussion and interaction.

In its simplest organizational perspective, a committed mesenchyme initiates formation of cartilage where differentiating chondroblasts progress to become chondrocytes and in doing so lay down a highly specialized extracellular matrix. Hypertrophy of one zone of chondrocytes and death through apoptosis set the framework for ensuing stages in osteogenesis, beginning with a scaffold for growing bone, and then vascularization of the territory which then brings in osteoblasts and osteoclasts to initiate formation of trabecular bone further remodeling and therein the development of a second prominent and unique extracellular matrix. The list of morphogenetic factors, growth factors, steroids and key transcription factors that orchestrate this complex process is already extensive and continues to grow, almost mimicking the process itself [1,2]. Outside to inside and vice versa signaling events are critical to the process of cartilage and bone formation since the different cell populations involved must coordinate their activities in order to realize the ultimate anatomical structure. Thus it is not surprising that disruptions in these intricate communications and loss of factors would lead to development of mild to severe abnormalities. Add to this the importance of precise timing of signaling events and attention to physiologically effective concentrations of factors that dictate growth, differentiation and apoptosis, it is evident that specific molecules are needed to assist in 'pacing' the developmental steps. In this first Commentary we highlight a number of reviews and studies that address the complex biology of cartilage and bone formation, a prime example of cell-cell interaction, communication through diffusible factors, and critical signaling pathways of cell behavior that are inimical to the development of the skeleton. While these processes require a variety of growth factors and hormones we bring attention to one member of the CCN family of genes [3], CCN2(CTGF), that plays a key role in building cartilage and bone tissues.

The work stemming from the laboratory of Dr. Takigawa and colleagues [4–6] focuses on the role that CCN2 plays in bone formation and particularly in the vascularization events. CCN2 has multiple effects on a number of cell types promoting chemotaxis, migration, adhesion, proliferation, differentiation and /or extracellular matrix formation. CCN2 is maximally expressed in hypertrophic chondrocytes prior to the initiation of osteogenesis and angiogenesis. CCN2 shares homology with other members of the CCN family noted for their molecular organization into basically four structural domains: an IGFBP module, a von Willebrand type C repeat, a thrombospondin type 1 repeat and a C-terminal module; these modules are involved in protein-protein interactions and associations with components of the extracellular matrix. The definitive functions of these modules has still to be

worked out, but their homology to the larger parent molecules suggest possibilities for multiple protein partners and intricate modulatory functions. CCN family proteins, and their isoforms, are distributed intracellularly as well as extracellularly [3]. In other words, nature appears to have imbued CCN2 and likely the other CCN proteins with structural features that could integrate them into intracellular as well as extracellular molecular machines. The challenge will be to understand the full complexity of their activities, biological functions, and clinical relevance [3].

More recent studies by Safadi et al [7], Ivkovic et al [8], and Friedrichsen et al [9] place CCN2 squarely in the limelight as critical for cartilage and bone formation from earliest developmental stages to later fetal and post-natal stages of skeletal growth. In fact, CCN2 expression persists in vascular endothelium, condensed connective tissue around bone and cartilage, and maturing layer VII neurons in the cerebral cortex. CCN2 knockout mice exhibit skeletal dysmorphisms as a result of impaired chondrogenesis. Thus CCN2 appears not to be rescued by other CCN members. So, although many macromolecules figure prominently in formation of cartilage and bone, specific CCN proteins appear to be key players in mediating development of cartilage and bone from first conception.

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