Review of: "The CCN Family of Proteins: A Critical Approach to the Multi-Modular Structure of the CCN Domains"

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The review and critical analysis by Prof. Bernard Perbal on the CCN family of proteins focused on structure-activity addresses important questions yet to be adequately answered. With the whole protein constituting modules IGFBP-VWC-TSP1-CT forming larger biologically active proteins, is it feasible to ascertain that individual modules would not be uniquely biologically active given the possibilities of 3D configurations that would be interactive with multiple types of receptors on other proteins in the matrix and at the cell surface? Thus, the challenge in the field has been to try to determine how and what the modules cooperate with to elicit biological functions.

Prof. Perbal, one of the pioneers of the CCN field, has had a long history of publishing leading papers on the molecular biochemistry of CCN proteins, tissue expression, regulation, and structure-activity properties. In particular, here Prof. Perbal examines the proposed basis and ongoing experimental evidence for the interactions and functions of the constitutive modules of CCN proteins. The paper very accurately lays out the historical basis and current evidence that supports a complex functional network inherent and governed by the modular construction of CCN proteins. When one considers that these CCN proteins are matricellular transmitters of molecular information from the extracellular environment through and into the cells that express these CCN proteins and operate in both physical and transcriptional modalities, the range of potential functions is greatly expanded. From older studies on CCN3 and current studies cited from the Attramadal group on the TSP1 domain of CCN6 and CCN5, it is somewhat clearer that modules unto themselves can subserve key biological functions, whereas previous studies have proposed that there is necessary functional cooperation amongst different modules.

An interesting and critical aspect of how CCN proteins may affect transcriptional activity in cells is the data showing that the TSP1 domain is essential for nuclear localization. Many studies on other proteins have also indicated that membrane proteins readily translocate into the nucleus after entering the cytoplasm. So for the CCN proteins, nuclear translocation is required for potential transcriptional activity to be realized. This is another area of biological functioning for CCN proteins to be elaborated.

The possible permutations and combinations of modular peptides, discussed by Prof. Perbal, can ascribe multiple interactions and biological functions aside from these modules combined into a whole protein. Although the inadequacy of experiments performed on isolated domains stands out, it is also evident that proteolysis at the hinge region and other susceptible sites can generate unique peptides competitive with the whole protein. Is this then a biologically conserved

other level of functional regulation of the CCN family of proteins? Then thrown into this complexity are the tissue and cell type-specific interactions and the temporal aspects, which then pertain to developmental and mature organ functions. Do these herald the biological diversity in functions required for optimizing physiological functioning within multiple tissues and organs?

One just has to peruse Figure 3 in the paper depicting all currently known interactions of the modules with a slew of well-studied factors that are functionally active in the body. It is really mind-boggling if considered at one time but should stimulate investigators, to quote Prof. Perbal, “develop future approaches that are comprehensive and based on spatial biology methodologies ....mandatory to reach successful biomedical applications based on a deep understanding of the unique multi-domain biology of the CCN proteins.” Since CCN proteins figure prominently in multiple diseases and pathological states, it definitely behoves investigators in the CCN (and in concert with other fields) to pick up on the arguments laid out by Prof. Perbal to bring to bear all the exciting new molecular and biophysical methodologies to get at the heart of CCN biology.

Prof. Perbal should be commended for raising this topic and suggesting possible approaches for dissecting the biological unknowns that still underlie the CCN field and that resurface at every CCN workshop.