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

Sourav Roy[1]

1 Independent researcher

Potential competing interests: No potential competing interests to declare.

In the current manuscript, Dr. Perbal has critically reviewed the studies associated with the structure and function of the CCN proteins. He has raised several interesting questions that need to be investigated in this field. The review is well-written; however, it can be improved if the following queries can be addressed.

1. In the last paragraph of the section on 'Tale of TSP1 and nuclear CCN addressing', Dr. Perbal has alluded to an article by Grotendorst and Duncan wherein the authors have reported the proteolytic digestion of CCN2, resulting in the N- and C-terminal domains with unique functions. Dr. Perbal has also mentioned that the conclusion in the article agrees with the hypothesis that four exons of CCN3 must have been brought together by evolution for 'coordinated level of expression, leading to the balanced production of all proteins.' If these are true, how were the isolated domains of CCN proteins expressed for binding studies?
2. The CCN proteins of *C. intestinali and C. gigas* contain the additional IGFBP and the CT domains, respectively. However, these are not present in *B. floridae* and *D. melanogaster*. Can the author comment on why these domains were lost during evolution? Do these domains have specific functions in *C. intestinalis* and *C. gigas*?
3. Do the IGFBP and the CT domains vary in length and sequence in the different organisms? What is the extent of sequence conservation in these domains in the different organisms?
4. What is the aggregation state of the individual domains of the CCN proteins? Do the individual domains associate in a specific aggregation state to form the functional CCN complex?