

Peer Review

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 article "The CCN Family of Proteins: A Critical Approach to the Multi-Modular Structure of the CCN Domains" presents a comprehensive and insightful perspective on the structural and functional complexity of CCN proteins. The manuscript is authored by a highly experienced researcher in the CCN field, and it successfully integrates historical context, structural biology, evolutionary perspectives, and functional interpretation of CCN domain organization. The review provides valuable conceptual discussion regarding domain cooperation, post-translational processing, and spatiotemporal regulatory models, which are important for understanding the multifunctional behavior of CCN proteins in cellular signaling, fibrosis, and tumorigenesis. The emphasis on the limitations of studying isolated domains and the advocacy for full-length protein and spatial biology approaches represents a strong and forward-looking scientific argument.

The manuscript demonstrates notable strengths. The evolutionary analysis of domain conservation is well articulated and supports the hypothesis that modular organization contributes to coordinated biological regulation. The discussion of TSP1 domain-mediated nuclear localization and antifibrotic activity provides an important synthesis of emerging literature. Additionally, the review successfully highlights unresolved mechanistic questions in CCN biology, which may stimulate future research directions.

However, several aspects could be improved to strengthen scientific rigor and clarity. The manuscript is largely narrative and opinion-driven, and while this provides valuable expert insight, it occasionally lacks systematic literature evaluation or a balanced presentation of conflicting experimental evidence. Some statements challenging established paradigms would benefit from stronger empirical support or more explicit referencing. The review would also gain clarity from improved structural organization, as

transitions between evolutionary, structural, and functional discussions are sometimes abrupt. Furthermore, the inclusion of summary tables or schematic diagrams synthesizing domain-specific biological roles and interacting partners would enhance readability and accessibility for readers outside the CCN research community. Expanding the discussion of translational implications, particularly in oncology, fibrosis, and regenerative medicine, would further increase the article's biomedical relevance.

Overall, this review provides an important conceptual contribution to CCN protein biology and offers valuable perspectives that challenge traditional reductionist approaches. With minor improvements in structural clarity and evidential balance, the manuscript represents a meaningful addition to the literature.

Recommendation

Accept with minor revisions.

Declarations

Potential competing interests: No potential competing interests to declare.