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EDITORIAL

Time has come to address the spatiotemporal combinatorial model for CCN proteins biological activitites by spatial transcriptomics and genome wide association studies

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Abstract
It is a renewed pleasure to wish our authors, editorial board members, and readership an excellent new year, full of professional and personal satisfactions. According to the Chinese Horoscope, 2023, the Year of Water Rabbit, is predicted to be quiet; a year to step back, assess the situation and make plans. It will be the time to carefully appraise, with the patience of the Water Rabbit, the future and scientific wealth of our Journal. Based on a few aspects of the CCN3 biology status that remain open questions, I am presenting below a short summary of a few CCN research directions that in my eyes, become necessary to undertake through wide-angle collaborative approaches.

Keywords CCN proteins · Spatiotemporal combinatorial model · Transcriptomics · Genome wide association studies

The 2022 ICCNS AWARD

The 2022 ICCNS award was presented to Professor Lester Lau for his significant contributions to the field of CCN biology. It was a mark of our willingness to renew with traditions that suffered from the COVID-19 pandemy.

Professor Lau, one of the founding members of the ICCNS, was a strong supporter for the adoption of a new unified nomenclature that would advantageously substitute for the misleading original names given to the CCN proteins (Perbal et al. 2018). His scientific recognition goes beyond the CCN field in which his work led to the description of critical interactions between CCN proteins and integrins. Lester recently shared with Annick and myself his conviction that indeed, future studies should not only address the interactions of CCN proteins with themselves, but also with their ligands at a spatiotemporal scale via emerging technologies.

On this occasion, Professor Lau gave a talk in which he presented the role of CCN1 in wound healing and tissue regeneration which is summarized in the upcoming scientific report of the 11th workshop on the CCN family of genes that was held last October in Nice, France.

Time for spatial transcriptomics and genome wide association studies

Even though CCN proteins have been studied for almost 35 years, they have not yet revealed all of their hidden biological properties.

In my introduction to the workshop, entitled “From Molecular to Functional: A wide angle Approach to Cellular Communication Networks Factors” I presented a review focusing on a few CCN3 features that could help the field to significantly expand should they be considered with a wider angle.

The goal to reach requires a shift from considering the CCN proteins as independent members of a small family of signaling regulators and addressing questions regarding only the physical and biological interactions of CCN proteins with themselves, to going a step beyond and focus, above all, on their connections within the realm of other « CCN» factors that belong to other superfamilies (manuscript in preparation). Among the questions that are still pending, I pointed out a few features of CCN3 which should be reconsidered with a wider angle.

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One of them addressed pieces of evidence suggesting that CCN proteins might be part of moonlighting proteins (Perbal B, *in* Brigstock et al. 2005).

CCN3 behaves both as a transforming factor ex vivo, and as an antiproliferative and tumor suppressor factor both in vitro and ex vivo (Joliot et al. 1992; Scholz et al. 1996; Gupta et al. 2001; Benini et al. 2005). The reasons for this dual activity remained a puzzle until it was shown that, while CCN3 is interfering with cell differentiation in various animal models, it is acting as a break in the normal cell cycle, resulting in an accumulation of cells in the S phase (Bleau et al. 2007).

A nuclear CCN3 species, which was not detected in resting cells, was selectively expressed both in normal proliferative undifferentiated cells and cancer cells, suggesting that CCN3 might have different functions in distinct cell compartments (Perbal 1999).

Whereas the N-terminal signal peptide drives CCN3 outside of the cells, the addressing of CCN3 directed by a nuclear localization sequence localized in its C-terminal module, CCN3 physically interacts with a few nuclear factors such the rpb7 subunit of the RNA polymerase III. Other CCN proteins showed a dual localization pattern but no studies addressed the biological functions of these nuclear proteins.

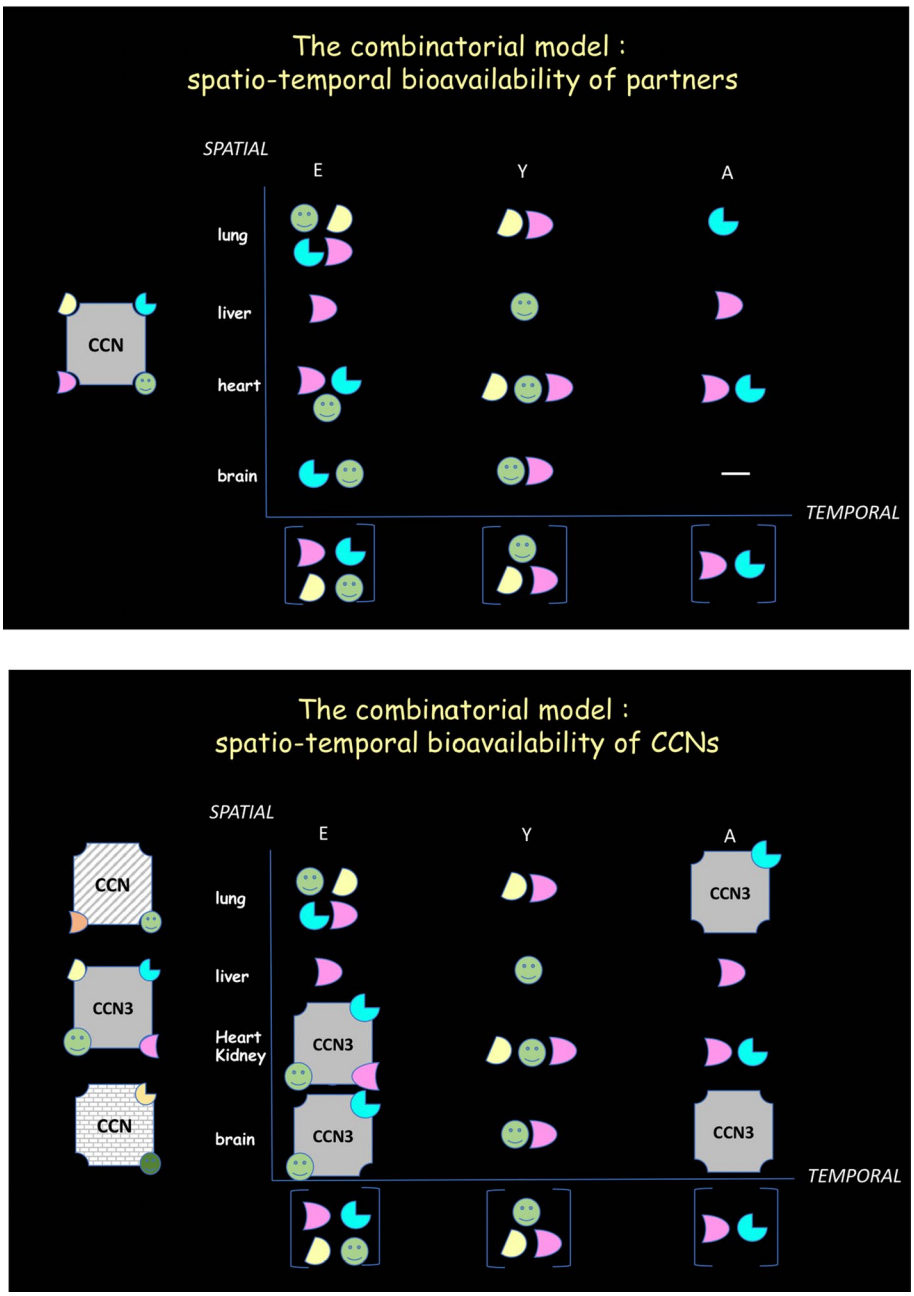

Fig. 1 The spatiotemporal combinatorial interactions model. The model is based on the CCN proteins (panel B) and partners (panel A) bioavailability, as a function of time and biological space

Based on the tetramodular structure of the CCN proteins I originally proposed that "*the different modules correspond to functional domains that can interact either sequentially or simultaneously with other partners, and that the final biological properties of the CCN proteins might be dependent upon different combinatorial effects*" (Perbal 2001). During my introduction, I presented a more elaborate version of the spatiotemporal combinatorial model that I originally proposed to account for the complex regulatory processes governing the wide array of CCN proteins biological activities (Perbal 2018 and Fig. 1).

In this model, the bioactivities of the CCN proteins depend upon the bioavailability of both the CCN proteins and their partners in various tissues at different developmental stages. The wide array of flexible combinations made possible by the time-and space- dependent expression of the CCN proteins and their partners translates into the vast variety of biological activities shown by the CCN proteins and their isoforms.

The biological power of these combinatorial events is directly dependent upon the complexity of the CCN partner pools and is amplified by the presence of the four CCN modules that were reported to bind independently several different ligands and regulatory factors.

I concluded that future research directions in the fields of CCN communication and signaling should aim at new technologies which recently proved to be effective in personalized molecular medicine. For example, understanding the various interconnected aspects of this spatiotemporal regulatory model requires the identification of all partners, their temporal localization and their expression levels, through global approaches such as Genome Wide Association Studies and Spatial transcriptomics which proved very powerful in the past few years (see my Commentary in this issue). Studying the circadian control of both the CCN proteins and their various partners, might also turn out to be a productive approach since anti-apoptotic roles of the master clock regulators BMAL1 and CLOCK were recently involved in promoting proliferation of liver cancer cells (Qu et al. 2023).

Since then, the recent report of a Drosophila CCN protein lacking the amino-proximal module (Garett et al. 2023), raised very exciting questions regarding the importance of the CCN 3D structural state influencing their biological properties in the nervous system through various interactions with their partners as previously suggested (Perbal 2004). The dCCN (drosophila CCN protein) might be a good system, among others, in which to assess the spatiotemporal combinatorial model proposed earlier to be a key step in controling the multifunctional biological properties assigned to CCN proteins.

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References

Benini S, Perbal B, Zambelli D, Colombo MP, Manara MC, Serra M, Parenza M, Martinez V, Picci P, Scotlandi K (2005) In Ewing's sarcoma CCN3(NOV) inhibits proliferation while promoting migration and invasion of the same cell type. Oncogene 24:4349–4361

Bleau AM, Planque N, Lazar N, Zambelli D, Ori A, Quan T, Fisher G, Scotlandi K, Perbal B (2007) Antiproliferative activity of CCN3: involvement of the C-terminal module and post-translational regulation. J Cell Biochem 101:1475–1491

Brigstock D, Lau L, Perbal B (2005) Report and abstracts of the 3rd International Workshop on the CCN Family of Genes. St Malo, France, 20–23 October 2004. J Clin Pathol 58:463–478

Garrett EC, Bielawski AM, Ruchti E, Sherer LM, Waghmare I, Hess-Homeier D, McCabe BD, Stowers RS, Certel SJ (2023) The matricellular protein drosophila cellular communication network factor is required for synaptic transmission and female fertility. Genetics. https://doi.org/10.1093/genetics/iyac190

Gupta N, Wang H, McLeod TL, Naus CC, Kyurkchiev S, Advani S, Yu J, Perbal B, Weichselbaum RR (2001) Inhibition of glioma cell growth and tumorigenic potential by CCN_3 (NOV). Mol Pathol 54:293–299

Joliot V, Martinerie C, Dambrine G, Plassiart G, Brisac M, Crochet J, Perbal B (1992) Proviral rearrangements and overexpression of a new cellular gene (nov) in myeloblastosis-associated virus type 1-induced nephroblastomas. Mol Cell Biol 12:10–21

Meng Q, Zhang G, Han Q, Alexander V, Raymond W, Tsukamoto H, Jia Z, Huang W, Lenz H-J, Rich JN, Kay SA (2023) Circadian regulator BMAL1::CLOCK promotes cell proliferation in hepatocellular carcinoma by controlling apoptosis and cell cycle. Proc Natl Acad Sci. https://doi.org/10.1073/pnas.2214829120

Perbal B (1999) Nuclear localisation of NOVH protein: a potential role for NOV in the regulation of gene expression. Mol Pathol 52:84–91

Perbal B (2001) NOV (nephroblastoma overexpressed) and the CCN family of genes: structural and functional issues. J Clin Pathol: Mol Pathol 54:57–79

Perbal B (2004) CCN proteins: multifunctional signalling regulators. Lancet 363:62–64

Perbal B (2018) The concept of the CCN protein family revisited: a centralized coordination network. J Cell Commun Signal 12:3–12

Perbal B, Tweedie S, Bruford E (2018) The official unified nomenclature adopted by the HGNC calls for the use of the acronyms, CCN1-6, and discontinuation in the use of CYR61, CTGF, NOV and WISP 1–3 respectively. J Cell Commun Signal 12:625–629

Scholz G, Martinerie C, Perbal B, Hanafusa H (1996) Transcriptional down regulation of the nov proto-oncogene in fibroblasts transformed by p60v-src. Mol Cell Biol 16:481–486