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EDITORIAL

CCN proteins are part of a multilayer complex system: a working model

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The international Workshop on the CCN family of Genes that was held this year at Niagara Falls marked the tenth anniversary of this biannual meeting series.

Twenty years ago, upon my invitation all leaders in the burgeoning field of CCN biology came together in Saint-Malo, France for what would later become a reference meeting in the field of intercellular communication.

At that time, the most important question circulating on all lips was regarding the biological functions of these six proteins which shared an amazing structural constitution with four modules showing a striking degree of homology and displayed a high degree of conservation throughout evolution.

Even though the quality of science reported in these workshops steadily increased over the twenty past years, the question of functionality of the CCN proteins remains an unsolved maize. As much progress as we have made into the identification of the signaling pathways in which the CCN proteins participate, we still do not have a clear picture of how these proteins functionally interact and govern key steps in the regulation of cellular biology from birth to death.

The workshop organized this year by Andrew Leask at Niagara Falls, marked a significant opening in a variety of new fundamental aspects of CCN protein biology leading to a better understanding of functional dysregulations responsible for pathological conditions that were the target of therapeutic approaches for quite some time now.

Studies on the participation of CCN proteins in a variety of cancers highlighted new connections with basal metabolism in normal and pathological conditions, whereas structure-function approaches pointed to novel aspects of post-translational regulation of CCN protein activity.

Emerging roles of CCN proteins in neuronal biology were also reported and their critical functions in fibrosis and inflammation were reinforced by the results of in vivo studies.

In a special educational session financially supported by the University of Saskatchewan, the role of exosomes in cancer was reviewed by specialists in the field whose presentations were greatly appreciated by the whole audience.

Thanks to the efforts of Andrew Leask, the venue chosen for this celebration meeting provided a unique opportunity for researchers in the field to enjoy good science in a wonderful environment.

Details about the scientific content of the meeting will appear as usual in a report that will be published shortly in the Journal of Cell Communication and Signaling.

The workshop was also a unique opportunity to honor Professor Cynthia Kenyon, recipient of the seventh ICCNS-Springer award for her outstanding contribution to the field of aging. In her very inspiring and brilliant presentation, Cynthia Kenyon reviewed the evolution of the aging concept over the past decade since her discovery of mutations involved in the modification of lifespan. Once more, the organizers of the workshop were extremely pleased to host a very talented worldwide renowned scientist who accepted to come among us and discuss her views on a field that is the object of intense research and holds great promise for the future of mankind.

Having Cynthia Kenyon accepting to participate in our workshop also provided both the young and senior researchers the opportunity to interact in a very simple and direct manner with someone who I believe represents a genuine model, both on scientific and human grounds, for the younger generation to come and work in such an exciting field.

As many of our participants and readers know, our international workshops are also the time to critically review the achievements of our society and the progress made in the

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The progress in interest shown by the JCCS audience has resulted in a marked increase in its impact factor. The significance of this metrix has previously been discussed. Thanks to the commitment of the whole editorial board and dedication of Andrew Leask, JCCS has now reached a higher level of scientific recognition that is demonstrated by the widening of its readership. Within a few years, the number of JCCS downloads has increased in a significant way, and the journal has now established itself as a unique niche for manuscripts dealing with translational and molecular aspects of extracellular and intracellular communication in various normal and pathological contexts.

A great satisfaction for the ICCNS was provided by the official recognition of the CCN acronym by the HUGO nomenclature committee (Perbal et al. 2019). I believe that the choice of a common acronym in which is embodied the concept of a family of communication factors working as a network (CCN calls for Cellular Communication Network factors), represents a significant unification step in a field that has suffered from researchers ignoring the work and achievements of others because of an obsolete, misleading nomenclature. Furthermore, the acronym also conveys the idea that the six proteins that belong to this family share a great level of structural organization that allows them to functionally interact.

As a keynote speaker of the workshop, giving an introductive presentation, I was provided with the great opportunity to propose an extension of the communication network model that I had first introduced a few years ago (Perbal 2013, 2018).

The working model that I discussed stems from the concept of complex functional system biology, and the hierarchy of complexity levels in biological organization that is presently widely accepted.

The tetramodular organization of the CCN proteins provides a unique ground for complex functional interactions with other complex systems involved in the command of several other critical pathways that must function in a coordinated manner to allow a harmonious and balanced set of developmental steps permitting responsive communication with the external environment.

Each module of the CCN proteins is derived from exon shuffling that distributed four module-encoding sequences in a set of proteins that evolved separately, as shown by the fact that they are not playing redundant functions and are not expressed at the same time in the same tissues.

Yet, the modules contained in each of the proteins, have maintained the capacity to interact with some common ligands and receptors. Furthermore, other regulatory proteins functionally unrelated to the CCN family of proteins, do contain the same type of module, albeit showing significant physical differences.

Two modules in the CCN proteins contain motifs that have been involved in dimerization (cystine knot within the C-terminal module), and mutimerization (VWC motif in the second module). It is therefore possible that the modules present in CCN proteins not only allow the CCN protein to dimerize, as experimentally shown, but also to engage into heterotypic dimers and multimers with other regulatory proteins (Perbal 2013).

As previously discussed the combination of modules from CCN proteins with functionally similar modules in other proteins might influence, or modulate the activities of the complex. Furthermore, the CCN5 protein that is lacking the CT module, present in the other CCN proteins, might play the role of a dominant inhibitor, by combining with other CCN proteins or other CCN-like-containing regulators.

Altogether, the temporal regulation of CCN protein expression added to the potential to interact with others in a homotypic or heterotypic fashion, constitutes a very flexible set of combinatorial events that likely dictate the robust functionality of these protein complexes.

There are several examples of interactomes underlying different levels of biological complexity. Each set of interactions might represent one of the many functional layers in a complex assembly, in a similar way as multimeric enzymatic complexes combine singular activities in a single architecture (e.g. the ATCase/OTCase family protein family that is made of evolutionary related enzymes: aspartate carbamoyltransferase and ornithine carbamoyltransferase).

From the point of view of quantum mechanics, a group of Qubits that can exist simultaneously in multiple states provides way more processing power when they are connected than the same number of binary bits. Similarly, the hierarchy of complexity levels supplied by the CCN protein layers would provide significantly more regulatory biological power than the same number of individual activities.

The complexity of CCN biological properties needs to be tackled from this kind of new angle.

Although it may seem a wish made to Santa Clause, I strongly believe in the strength of the combinatorial events within this kind of integrated system.

One can predict that global approaches that will take into account the six CCN proteins as a whole integrated system, should prove much more fruitful than the present way of considering isolated CCN proteins on their own.

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