Preface

CCN is an acronym that is derived from Cyr61, CTGF, and Nov, the names originally given to the first three proteins to be identified in what is now a six-member family. These proteins comprise a fascinating and important group of homologous proteins that have not received the attention that they deserve from cell and molecular biologists. The publication of this book should do much to rectify this oversight.

In their excellent overview (Chapter 1) Perbal and Takigawa describe the early history of these proteins and the various names that were assigned to them, most of which were based on their perceived functions. As might be expected for proteins with multiple, diverse functions that were discovered almost simultaneously by different investigators, several names were often assigned to the same protein. In some cases, as with CCN2 for which the term connective tissue growth factor (CTGF) did not accurately describe its function, these names were a potential source of confusion. It is therefore a tribute to the field, and of substantial assistance to investigators in related areas of research with an interest in CCN proteins, that agreement on a systematic nomenclature was reached.

The practice of categorization in biology is a time-honored one that can be traced to Carolus Linnaeus, the father of taxonomy. In the case of CCN proteins, a grouping on the basis of homologous genetic structure is sensible, and is in keeping with the principles of protein evolution. There are, in addition, many other similarities among the six CCN proteins, which are summarized in Chapter 1, and are considered in greater detail in other Chapters throughout the book.

A common feature of CCN proteins is that they are all secreted proteins and are therefore present in the extracellular milieu. Since there is currently no evidence that any of the CCN proteins functions as an integral component of a structural entity such as a fibril or a basement membrane, it is presumed that these proteins function predominantly by interaction with cell-surface receptors. Indeed, as discussed by Lau and Lam (Chapter 3), there is good

evidence for functional interactions of CCN1, 2, and 3 with many integrins, and this property is likely to extend to the other CCNs. Several members of the CCN family have been shown to influence the Wnt signaling pathway, which includes the receptor LRP6 (Latinkic, Chapter 8), and interactions with LRP1 and Notch have also been demonstrated. In addition to cell-surface receptors, CCN proteins can interact with many different cytokines, growth factors, and extracellular matrix proteins.

The similarity of CCN proteins to matricellular proteins has not escaped the notice of several authors in this book. The term 'matricellular' was coined to call attention to the unusual properties of a group of proteins that, while resident in the extracellular space, do not appear to play a structural role in the matrix, at least postnatally in vertebrates, but rather serve to modulate cell-matrix interactions and cell function (Bornstein, 1995). The realization that the extracellular matrix contains regulatory proteins that are distinct from growth factors and cytokines grew from an initial consideration of the properties of thrombospondin (TSP)-1, SPARC, and tenascin-C (Sage and Bornstein, 1991). This notion was later supported by studies of TSP-2, osteopontin, and tenascin-X (Bornstein, 2001; Bornstein and Sage, 2002). There are many similarities between the functions of members of the CCN and matricellular protein families. These include the regulation of angiogenesis, cell adhesion, migration, and proliferation, and control of collagen fibrillogenesis. Their fundamental mode of action is also similar in that it results from interactions with bioeffector molecules (cytokines, growth factors, and in some cases proteases), and with a multitude of cell-surface receptors.

However, matricellular and CCN proteins differ in that the latter are grouped on the basis of protein homology, whereas matricellular proteins include structurally dissimilar proteins that are functionally analogous. Within the matricellular family, TSPs 1 and 2 are also closely related structurally, and lessons learned from the studies of these two proteins may be particularly relevant to the CCN family. Despite their very similar structures and almost identical properties when the purified proteins are tested *in vitro*, the phenotypes of the TSP1- and TSP2-null mice are very different. This finding very likely reflects the different spatial and temporal patterns of expression of the two proteins, and the fact that their functions, as well as that of other matricellular proteins, are contextual and depend on the cell-surface receptors and bioeffector molecules with which they interact. Both the phenotypes of the TSP1- and TSP2-null mice, and the fact that there is no evidence in these mice for compensation of one TSP by the other, are consistent with the very different sequences of the promoters in the two genes. Thus far, only the phenotypes of

CCN1- and CCN2-null mice have been published. It will be of interest to determine the degree of overlap, or lack thereof, among the six mouse knockouts and to correlate this information with studies of the promoters of the relevant genes. Nevertheless, with the data that are currently at hand, it is probably safe to say that the information that is gained from experiments *in vitro* with purified CCN proteins can only serve as a rough guide to the physiological functions of these proteins.

On balance, it would seem advantageous for scientists in both fields to consider CCN proteins as members of the matricellular family. However, it should be remembered that categorization of proteins on the basis of function, and the resulting assumptions that are made, are human tendencies that Nature does not necessarily share.

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