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> ONE MONTH, ONE PROTEIN <

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relay

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Life is a powerful force. From the moment it appeared on Earth – which is estimated at roughly 4.5 billion years ago – it has never ceased to find ways of continuing, plucking from Nature what it needs to create offspring. Rich soil broken down by earthworms feeds the emerging buds of flowers. Grains shed by fruit provide hatchlings with food, and the planet's oceans stock up with plankton to sustain their schools of fish and pods of whales. This team spirit, if you like, is also found on the molecular scale. When mothers lactate, for example, their bodies draw calcium from their own bones to build the bones of their newborn. In the same vein, scientists discovered another relay at work further upstream where maternal factors are activated to replace the calcium that has been removed from the mother's bones. In this way, the mother's bones are not weakened while the baby's bones are strengthened – and life carries on. A maternal brain hormone that is directly involved in rebuilding maternal bone during lactation has recently been discovered. Its name: CCN3. CCN3 is not new to biologists, but its role in fortifying the bones of lactating mothers is.

Nursing mother

Paula Modersohn-Becker (1876-1907)

CCN3 belongs to the CCN family of proteins that is composed of six members: CCN1 to CCN6. CCN3 is one of the founding members and was initially called NOV (for Nepthroblastoma Overexpressed). The two other founding members are CCN1 and CCN2, first named CYR61 (for Cystein Rich) and CTGF (for Connective Tissue Growth Factor), respectively. These three proteins were discovered in the early 1990s. When scientists realised that not only were they closely related but they also shared a similar domain structure, they were renamed CCN1-CCN3, where CCN was the acronym of CYR61, CTGF and NOV in that order. Based on their structural features and partial identity, three other proteins soon joined the family – WISP-1, WISP-2 and WISP-3 which were renamed CCN4, 5 & 6 accordingly. This is the field of nomenclature. It is not fun to read, but giving the right names to things can be a real time saver for biologists who are frequently faced with identical proteins, or proteins that belong to one same family, which carry such contrasted names that, unless you are aware, you would never think they were related. Funnily enough and perhaps not surprisingly, like a cat moving silently from one room to another, over the years, the meaning of the acronym CCN has slowly shifted from the first initials of its three founding members to those of Cellular Communication Network.

What do CCN proteins have in common? They are probably multimeric complexes and expressed in a wide variety of both adult and embryonic tissues, at highly variable levels. They are cysteine-rich proteins, secreted into the extracellular matrix and, so far, have only been found in vertebrates. It is thought that the six members of the CCN family act together, or sequentially, at given times and locations throughout an organism's life. What do they do? Like switchboard operators, CCN proteins are at the heart of a communication network between

cells. Once activated, CCN proteins bind directly to various factors that trigger off multiple signals which, in turn, prompt numerous signalling pathways. Studied in the framework of osteogenesis and angiogenesis, CCN proteins are known to influence cell communication, cell adhesion, cell migration, cell proliferation, cell growth, cell differentiation, cell survival as well as protein production in cells involved in the formation of bone and blood vessels – all things essential for healthy embryonic development, but also for adults.

How can six members of one family be at the heart of such an astounding variety of biological functions? They owe this to their modular structure and, perhaps also, to the presence of linker regions and a hinge. Indeed, CCN proteins are made up of four modules – 1) an insulin-like growth factor binding protein (IGFBP) motif, 2) a von Willebrand factor (VWC) domain, 3) a thrombospondin type 1 (TSP1) domain and a 4) carboxy-terminal (CT) domain – linked to one another by supple linker domains. Each module can interact independently, or in concert, with several effectors (extracellular matrix proteins, transmembrane proteins, growth factors…). Consequently, CCN proteins engage with a large range of effectors – even larger when considering multimeric complexes of CCN proteins. Together they form a centralized communication network that regulates key signalling pathways leading to cell differentiation, growth, proliferation and so on. It is likely, too, that the four modules communicate with each other in a combinatorial manner to fashion yet other functions – possibly thanks to the presence of those supple linker domains and a hinge between the second and the third modules which could facilitate inter-domain communication.

CCN3, as mentioned earlier, is one of the founding members of the CCN family. It is known to be involved in skeletal development and cartilage metabolism where it represses chondrocyte cell proliferation when energy levels are low – thus promoting cell quiescence while environmental conditions are not favourable. As such, CCN3 can be regarded as a metabolic regulator that prevents cells from overworking if conditions are not good. Found in the adrenal gland and in blood, researchers suggest that CCN3 is an adrenal hormone.

An intriguing find was made recently. When mothers lactate, calcium is extracted from their bones to produce milk and help build the bones of their newborn. It is estimated that bone loss in rodents – who have large litters – can reach 30% while in humans loss can reach 10%. Under normal circumstances, oestrogen deals with calcium deficiency by promoting bone formation. However, mothers suffer a severe drop in oestrogen levels shortly after delivery – so there must be another mechanism dedicated to lactation to keep calcium levels balanced. This is when scientists noticed a surge in CCN3 expression in lactating mothers. Where? In neurons belonging to a part of the hypothalamus known as the arcuate nucleus which is involved in transmitting appetite signals, themselves reflected by energy stores. So there must be a system that senses low maternal calcium levels. CCN3 is then synthesized and flung, in the manner of a hormone, into the mother's blood to bind to its receptor – probably a growth factor.

So in one instance, CCN3 hinders bone formation (cartilage metabolism) while in another (lactation) it promotes bone formation. This seemingly conflicting situation may explain the fact that the roles of CCN proteins are not only defined by a given combination of modules and possible interactions between them but also possibly by proteolytic processing, gene expression regulation – or they may even be susceptible to where they are synthesized – a given tissue or organ – and when – a certain stage of development for instance. Certainly, CCN3 seems to be involved one way or another with bone formation and could prove to be an ideal therapeutic candidate for people suffering from bone diseases among which osteoporosis. Meanwhile, it will continue to relay strength between a mother and her progeny.

Cross-references to UniProt

CCN family member 3, *Homo sapiens* (Human) : P48745
CCN family member 3, *Rattus norvegicus* (Rat) : Q9QZQ5

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