MULTIFUNCTIONAL PROTEINS OF THE SMALL LEUCINE-RICH PROTEOGLYCANS (SLRP) FAMILY. THE MATRIKINES OF EXTRACELLULAR MATRIX

Y. WEGROWSKI, F. –X. MAQUART

Laboratoire de Biochimie, Medical Faculty, Reims, France

Extracellular Matrix (ECM) constitutes a compartment elaborated by all multicellular species, from sponges to mammals. For a long time, many data indicated the role of ECM proteins in the embryonic development, for example the formation of mesenchyme or neuron guidance. However, in adult organism, ECM was though to play rather passive role, serving as a support to the cells and, eventually, reconstituting tissue stiffness in wound healing process. This is no more truth. First, ECM is necessary for normal cell function. For example, epithelial cell polarisation is only obtained when the cells are seeded on matrix substratum. Second, the most of pathologic process, including inflammation and tumor growth, take place in extracellular space. Also pathogens (viruses, bacteria) use the ECM for propagation and invasion. How ECM can control these events?

During inflammation or tumor growth ECM undergoes intensive remodelling. The liberated proteins, glycoconjugates or protein fragments, acquire new physiological properties to play an informative role for surrounding cells. These fragments are called matrikines or, when not active in mother protein: matricryptins. For example different types IV collagen fragments (endostatin, canstatin, arresten...) possess strong anti-angiogenic properties. On the contrary, elastin fragments have pro-angiogenic potential.

Our works are presently focused on Small, Leucine-Rich Proteoglycan (SLRP) family of ECM macromolecules. This family is composed of, at last, 16 gene products. All of these proteins posses the leucine-rich region which imposes the conformational stringency of repetitive beta sheet-alpha helix cluster. The whole protein adopts arch or banana shape and exposes the concave face for the reaction with other proteins. The SLRPs are characterised by extremely rapid turn-over, as compared with collagen or elastin. Their principal role is to control and organise collagen and elastin fibrillar network. Indeed, the mouse knock-out of several SLRPs (decorin, biglycan, lumican or fibromodulin) showed the impairment of fibrillogenesis and, in consequence, fragile skin, bone or tendon tissue.

SLRPs are member of the matrikine family. Over 15 years ago, Ruoslahti's group shown that decorin inhibits cell growth in culture. Subsequently, it was shown that decorin and some other SLRPs sequestrate and inactivate serum growth factors like TGF-beta or TNF-alpha.

Recent studies demonstrated the anti-tumoral properties of the SLRPs. Decorin is an agonist for EGF receptor, inhibiting the EGF-dependent signal transduction and increasing the expression of cycline-dependent kinase p21 inhibitor in tumor cells. Our studies showed that lumican inhibits melanoma progression and growth as well in cell culture as in the mouse model. We partially elucidated the mechanism of the inhibition. Lumican is able to increase the fixation of FAS ligand on its cognate receptor to induce the extracellular pathway of apoptosis in tumor cells. In the apoptosis-resistant cells, lumican rapidly clusters at focal adhesion contacts *via* beta-1 integrin receptor, increasing adhesion and reducing cell migration without stimulation of FAK kinase phosphorylation. In this manner SLRPs is a non-permissive check point for non-mesenchymal cells and may constitute a natural agent for some solid tumor therapy.