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Extracellular matrix: understanding the complexity

R. Borojevic

Departamento de Histologia e Embriologia, Instituto de Ciências Biomédicas, and Programa Avançado de Biologia Celular Aplicada à Medicina, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil

Correspondence
R. Borojevic
Caixa Postal 68021
21941-970 Rio de Janeiro, RJ
Brasil
Fax: +55-21-590-8736
E-mail: radovan@iq.ufrj.br

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The Brazilian Symposia on Extracellular Matrix (SIMEC) have become a forum for a broad discussion of cell and extracellular matrix biology, including structural studies on intercellular environment and cell interactions within it. A review of the Symposia during the last ten years shows an increasing understanding of the complexity of cell-matrix interactions.

The 5th Brazilian Symposium on Extracellular Matrix (SIMEC 98) was held in Angra dos Reis in September 1998, ten years after the first SIMEC meeting, whose scope and organization were proposed by Ricardo Brentani and Wilson Savino. The original proposal of the SIMEC meetings was to open a discussion in a broad field of studies on the intercellular environment involving the extracellular matrix proper, as well as the cell membrane-associated molecules. Within this scope, the Symposia also covered cell-cell and cell-matrix adhesion, adhesion-mediated cell communication, matrix-dependent proliferation and differentiation control in normal and pathologic tissues, extracellular messengers and their interaction with intercellular environment, etc. - covering a vast area of cell and tissue biology. Traditionally, each Symposium is organized by two scientists who are entirely free to define the scope, prepare the program, select a particular filed (or fields) to be discussed, and invite the speakers. The Symposia have been biased towards different fields such as cancer research, neurobiology, parasitology, immunology or pathobiology according to the scientific profile of the organizers. In addition to the traditional fields of cell biology dealt with in previous meetings, SIMEC 98 has introduced studies on mechanical aspects of bio-materials and bio-engineering that are likely to develop into an important field of study related to the extracellular environment in the near future (1).

Notwithstanding the particularity of each meeting, the participation of the best local and international scientists who work on the frontiers of the selected fields has permitted a

permanent follow-up of the evolution of studies on the intercellular environment. In the late eighties and early nineties, the structural, biochemical and molecular characterization of the major proteins of extracellular matrix represented a large part of the reports. Traditionally, the adhesive properties of the host-parasite cell interactions have attracted great interest, as also has the adhesion-mediated cell differentiation in the immune system, due to a large local community working in these fields. The last SIMEC meeting has necessarily maintained the overall profile of the scientific content, but the approach and the scope of the studies now point towards the more challenging goals. Earlier analytical studies have revealed the major members of the molecular families involved in the composition of the intercellular environment. Although new minor components are still to be described, we have a rather consistent idea of the major elements present in the extracellular matrix. However, due to the potent analytical tools in defining gene expression, the isoforms produced, and the post-translational modifications of the extracellular proteins, we have advanced far more rapidly in the understanding of the types and the quality of extracellular molecules than in the understanding of their function. We are now confronted by several fields that are lagging behind in terms of our overall knowledge and understanding of the molecular composition of the matrix.

Recent studies have increasingly stressed the specificity of the molecular interactions within the intercellular environment. This specificity involves a very precise recognition of particular molecular territories within tissues, which are the basis of the concept of cell homing or ecotaxis, well defined as the concept of cell recognition of the "self within self" inside the organism (2). This concept is now being extended to the recognition of the physiologic (or pathologic) state of a precise site in a tissue, at a precise moment in life. This extends the cell capacity to recognize and specifically interact with the microenvironment into the time dimension. Moreover, we now know that molecular systems retain the memory of the molecular assemblage pathways. The self-organization of an extremely complex system such as the extracellular matrix can retain the memory of the preceding periods in its own organization, which can subsequently be determinant for the constitution of functional multicellular units (3).

The flux of the genetic information is essentially controlled at the nucleo-cytoplasmic level, and we have now a very coherent conceptual frame to understand it and to work within. The spatial and the temporal content of information within the extracellular matrix is more difficult to understand. Extending earlier studies, we are now aware that complex glycoconjugates can contain a quasi-unlimited quantity of variables. Glycidic chains, potentially composed of a relatively long series of monosaccharides with unevenly distributed covalent modifications, fit well Schrödinger's postulate for the molecular basis of information by having an aperiodic crystal structure (4). However, in contrast to the beauty and simplicity of the genetic code, supported by two purine and two pyrimidine bases, the glycidic chains, albeit shorter, can contain a much broader number of informative variables. At the same time, whilst the double helix grants the straightforward transmission of the information content from one molecule to the other, the glycidic chains are synthesized and subsequently covalently modified by a series of ordered enzymatic reactions that involve substrate recognition, adding, trimming and covalent modification of the individual components. Each of these steps is dependent upon the availability of specific enzymes, substrates and donor molecules, and upon complex controls of the kinetics of each enzyme. Moreover, the flow of information is bidirectional: the cell behavior is determined by the structure and quality of extra-

cellular glycoconjugates, which in turn are modulated by the intrinsic cell programs or undergo specific stimulation of a selected set of cell functions (5,6). We also know now that, besides the classical structural glycoproteins, the pivotal molecules in the cell-matrix interactions, such as integrins, can have complex and variable patterns of glycosylation, including their conversion to facultative proteoglycans, that are relevant for their behavior (7,8). The full biological significance of such a phenomenon remains to be established. The understanding of a) the intercellular controls that determine the composition of such molecular information, b) the mechanisms used by the target cells or molecules to read the information, and c) the pathways that transduce the received information and transform it into modifications of the cell or molecular behavior are the challenges for future studies to be discussed at subsequent SIMEC meetings.

The second question is the increasing awareness of the fact that the biochemical reactions at the basis of cell and tissue biology and pathology, and in particular the cell interactions with the intercellular environment, involve an enormous quantity of interactive elements. As an example, we may cite the conceptually simple system of the interaction of a peptide cytokine with the corresponding transmembrane receptor, giving a punctual informative input to the cell. We are now aware that the activity of a vast series of growth factors depends in qualitative and quantitative terms upon their binding to the membrane or matrix-associated glycoconjugates such as heparan-sulfate proteoglycans (5,9). This binding can be itself dependent upon the cell membrane molecular background. The biology and the potential function of the major membrane elements, such as phospholipids, glycolipids and other membrane components, are not less complex than those of glycoproteins, with which they share the dynamic participation of the Golgi system and the associated enzymes in their synthesis, turnover and secondary biochemical modifications. The importance of these molecules has been already emphasized in earlier SIMEC meetings (10), but the development of this field still requires great effort.

A beautiful natural environment, massive participation of young students and scientists, highly informative and prospective lectures and stimulating discussions have been the hallmarks of the SIMEC meetings, and we are eagerly waiting for future reports on the developments in this increasingly complex field of cell biology.

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