

Grinnell F. Cellular adhesiveness and extracellular substrata.

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This review article presented a unified model of cell-substratum adhesion that included both methodological and theoretical considerations and attempted to unify the diverse literature in the cell adhesion field. [The *SCF*® indicates that this paper has been cited in over 495 publications.]

Cell-Substratum Adhesion

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April 9, 1990

Neither Paul Sreer nor I knew much about cell adhesion in 1970 when, as a postdoctoral fellow, I joined his laboratory at the Veterans Administration Hospital in Dallas. Like many research projects, my studies on cell adhesion began with an unexpected observation. I discovered that sulfhydryl binding reagents inhibited hepatoma cell attachment. Before joining Sreer's laboratory, I had been studying inhibition of succinyl-CoA synthetase by sulfhydryl binding reagents, and I guessed that formation of the cell-substratum complex was analogous to formation of an enzyme-substrate complex.

My thinking was reinforced when I read Saul Roseman's paper in which he proposed an enzyme-substrate model to explain cell-cell adhesion.¹ Unlike cell-cell adhesion, however, it was not obvious what molecule on the substratum might be recognized by cells. Sreer was emphatic on this point: "Cells don't have receptors for plastic!" His intuition set the agenda for the next six years of my research, first in his laboratory and later in the Department of Cell Biology at the University of Texas Southwestern Medical School.

By 1976 I had developed what I thought was a reasonably complete model of cell-substratum adhesion. Consequently, when Jean Paul Revel suggested that I write a review for the *International Review of Cytology*, I was ready and willing. My goal was to put together an overview of the cell-substratum adhesion problem that included methodological and theoretical considerations—an overview that would unify the diverse literature in the field and help establish the thought style² on which subsequent adhesion research would rely. I think that the review's inclusiveness was one feature that accounted for its popularity.

The model that I presented divided cell-substratum adhesion into a series of separate steps: cell contact, attachment, spreading. I emphasized the role of cooperative ligand-receptor interactions and summarized the evidence that there was more than one type of adhesion ligand (e.g., fibronectin and collagen). I pointed out that cells could use adhesion ligands from exogenous sources (e.g., serum) or produced by their own by biosynthetic activity. Finally, I described the significant similarities between diverse cell types in their mechanisms of adhesion.

The general details of my model have held up despite the dramatic growth of the cell adhesion field. Now there are almost a dozen adhesion ligands, the integrin family of receptors, and peptide recognition sequences.³⁻⁵ As the number of ligands and ligand receptors keeps increasing, the problem has become one of understanding what specificity underlies the apparent redundancy.

As for me, I have become interested in cell adhesion to three-dimensional substrata composed of extracellular matrix components. I hope to model aspects of the *in vivo* situation that could not be realized in studies with planar substrata. For instance, fibroblast responsiveness to growth factors differs depending upon the organization of the matrix in which the cells reside.⁶ Our understanding of the chemical specificity of adhesion has advanced remarkably, but we are just beginning to appreciate geometric specificity.

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