

Nicolson G L. Transmembrane control of the receptors on normal and tumor cells. I. Cytoplasmic influence over cell surface components. *Biochim. Biophys. Acta* 457:57-108, 1976.

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This paper (and its companion article<sup>1</sup>) reviews the emerging data indicating that the plasma membrane is not an autonomous cell organelle; it is one in which cell surface integral membrane glycoproteins are coupled by transmembrane linkages to various cytoplasmic structures and other organelles inside the cell. Complicated events, such as cell capping, adhesion, locomotion, endocytosis, exocytosis, and signal transduction mediated by the binding of ligands to specific cell surface receptors, appear to require transmembrane communication and structural linkages of components expressed on the outer plasma membrane surface with structural components inside cells. [The SCJ® indicates that this paper has been cited in over 500 publications.]

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My interest in membranes, particularly plasma membranes, began during my graduate studies with S.J. Singer at the University of California, San Diego, in the late 1960s. At that time it was becoming increasingly clear that plasma membranes were dynamic structures made up of fluid lipid bilayers containing asymmetrically intercalated globular proteins and glycoproteins.<sup>2</sup> Although it was briefly mentioned in our contribution, there was scant evidence, however, indicating that the mobilities and distributions of plasma membrane components were under any restraints by transmembrane interactions.

After moving to the Salk Institute, I became interested in how transmembrane interactions might influence the mobilities and topographic distributions of cell surface components. The first studies on this topic utilized red blood cell membranes and transmembrane perturbations by antibodies and plant lectins.<sup>3</sup> Richard G. Painter and I found that antispectrin antibodies bound to spectrin at the inner membrane surface could mediate transmembrane changes in the distribution of sialoglycopro-

teins at the outer membrane surface,<sup>4</sup> and Tae H. Ji and I showed that perturbation or clustering of erythrocyte cell surface glycoproteins with lectins could result in changes in the distribution and susceptibility to cross-linking of components expressed at the inner membrane surface.<sup>5</sup> An even more complex situation existed in certain highly specialized cells, such as spermatozoa, and Ryuzo Yanagimachi and I discovered that in these highly asymmetric cells discrete membrane domains of differing lectin-binding site mobilities could be distinguished along the same mammalian spermatozoan cell membrane.<sup>6</sup> These studies, and additional ones by other researchers who are cited in the paper, stimulated me to write an article on transmembrane regulation of mammalian cell surface receptor distribution and dynamics and the role that the cell cytoskeleton might play in this process.

This publication, my third to become a *Citation Classic*,<sup>2,3</sup> was written during a transition period, as I was moving my laboratory from the Salk Institute to the University of California, Irvine. I decided to use both addresses, because in the transition I actually held positions at both institutions. When I first submitted my manuscript to *Biochimica Biophysica Acta*, it was not in two parts. One of the associate editors insisted that such a lengthy manuscript (containing over 1,300 references) be divided. After the initial horror at the prospect of redoing the entire manuscript wore off, I decided to split off about 60 percent of the text and references to a second part<sup>1</sup> that concentrated on possible mechanisms underlying the differences in cell surface receptor mobilities of untransformed and transformed cells and other properties that defined cellular transformation and malignancy. This latter topic (cancer malignancy and metastasis) would eventually become my primary research focus.

This paper is probably highly cited because of its comprehensive coverage of the literature. It was not the only contribution in the field that year, however, to receive extensive citations. Gerald M. Edelman published an excellent review dealing with aspects of transmembrane signaling and cell growth control,<sup>7</sup> and G.F. Schreiner and E.R. Unanue<sup>8</sup> contributed a superb review on transmembrane events in lymphocyte plasma membranes. As additional data have become available, more recent reviews have dealt with these subjects in much finer detail.<sup>9</sup>

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