CC/NUMBER 11
MARCH 18, 1985

This Week's Citation Classic™

Blobel G & Dobberstein B. Transfer of proteins across membranes. I. Presence of proteolytically processed and unprocessed nascent immunoglobulin light chains on membrane-bound ribosomes of murine myeloma. *J. Cell Biol.* 67:835-51, 1975. [Rockefeller University, New York, NY]

The paper contains a detailed formulation of a hypothesis (termed signal hypothesis) for the translocation across or integration into specific cellular membranes of distinct proteins. The hypothesis proposes a zip-code mechanism and corresponding receptor-effector systems each localized to distinct cellular membranes [The *SCI*® indicates that this paper has been cited in over 1,460 publications since 1975]

Günter Blobel
Rockefeller University
1230 York Avenue
New York, NY 10021-6399

February 4, 1985

What has become the main attraction of this paper, namely, the theoretical consideration collectively called the signal hypothesis, was properly disguised by a lengthy and highly technical title. The signal hypothesis deals with the problem of how numerous newly synthesized and distinct proteins are targeted to specific intracellular membranes either for translocation across them or for asymmetric integration. A less detailed version of some of the ideas in this paper had been proposed in 1971 with my colleague David Sabatini[1] and in 1972, independently, also by Milstein and his colleagues.[2] Finally, in 1980, a more updated and extended version of the signal hypothesis was published.[3]

Among the first experimental landmarks was the discovery in 1972 by Milstein and his colleagues of a transient sequence at the amino terminus of a secretory protein, the light chain of IgG. This transient sequence could have represented the specific sequence predicted earlier.[1] However, other transient sequences had already been described (the pro sequence of proinsulin being the first example), and it was conceivable that the transient sequence of the light chain of IgG served some function other than targeting the light chain for translocation across the endoplasmic reticulum membrane. That this transient amino terminal sequence was indeed a strong candidate for such a targeting function was established in the experimentally much more important (but apparently less quoted) companion[4] to the signal hypothesis paper. It was shown there that the first step in the secretory pathway,[5] namely, unidirectional translocation across the endoplasmic reticulum membrane, can be reconstructed faithfully in a reconstituted *in vitro* system. Using this system, it was shown that the transient sequence of the IgG light chain is cleaved during the translocation process; that this sequence can express its function only cotranslationally, not posttranslationally; and that proteins that do not contain such a sequence (such as the globin chain) are not translocated. This reconstituted system then became the prototype of similar systems for the study of protein import into chloroplasts and mitochondria and protein export in bacteria.

Subsequent experimental landmarks in support of the signal hypothesis were the discovery of the signal recognition particle (SRP), an 11S ribonucleoprotein, and of the SRP receptor, an integral membrane protein of the endoplasmic reticulum (reviewed in reference 6).

Altogether then, it turned out that the signal hypothesis was a fertile working hypothesis. It stimulated a lot of experimental work as well as the formulation of alternative hypotheses. Like any other hypothesis, it underwent modification in detail as new experimental data became available. Its basic tenets, however, have so far withstood the test of time, although many of the predictions remain to be proved or disproved.

1 **Blobel G & Sabatini D D.** Ribosome-membrane interaction in eukaryotic cells (Manson L A, ed) *Biomembranes* New York Plenum, 1971 Vol 2 p 193-5 (Cited 245 times)
2 **Milstein C, Brownlee G G, Harrison T M & Mathews M B.** A possible precursor of immunoglobulin light chains *Nature New Biol* 239 117-20, 1972 (Cited 485 times)
3 **Blobel G.** Intracellular protein topogenesis *Proc Nat Acad Sci US* 77 1496-1500, 1980 (Cited 230 times.)
4 **Blobel G & Dobberstein B.** Transfer of proteins across membranes II Reconstitution of functional rough microsomes from heterologous components *J Cell Biol* 67 852-62, 1975 (Cited 555 times)
5. **Palade G.** Intracellular aspects of the process of protein secretion *Science* 189 347-58, 1975 (Cited 1,265 times)
6 **Walter P, Gilmore R & Blobel G.** Protein translocation across the endoplasmic reticulum *Cell* 38 5-8, 1984.

