CC/NUMBER 50
DECEMBER 15, 1986

This Week's Citation Classic®

Ashwell G & Morell A G. The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. *Advan. Enzymol.* 41:99-128, 1974.

A novel procedure for labeling serum glycoproteins led to the serendipitous discovery that galactose, exposed by enzymatic removal of the terminal sialic acid residues, constitutes a cryptic signal for hepatic recognition and catabolism of the resulting asialoglycoprotein. [The *SCI*® indicates that this paper has been cited in over 965 publications.]

Gilbert Ashwell
Laboratory of Biochemistry
and Metabolism
National Institute of Arthritis, Diabetes,
and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, MD 20892

September 23, 1986

In the fall of 1965, while on sabbatical leave in the laboratory of Elvin Kabat at Columbia University in New York City, I had the rare good fortune to spend many stimulating evenings at the home of Anatol and Halina Morell, warm friends and colleagues for many years. At that time, Anatol was working on a problem concerning the role of ceruloplasmin in Wilson's disease in the laboratory of I. Herbert Scheinberg at the Albert Einstein College of Medicine in the Bronx. One evening, after a pleasant and relaxing dinner at their home, Anatol raised a question that had concerned him for some time. The only method then available to monitor the metabolism of ceruloplasmin involved the use of copper-64, a short-lived isotope, and he wondered whether an alternate method might be devised. Since my background was largely in the area of carbohydrate rather than protein chemistry, I promptly teased him that he would never make any progress in this problem so long as he considered ceruloplasmin a metaloprotein rather than a glycoprotein.

Although the definitive carbohydrate structure of most proteins was largely unknown at that time, we postulated that some of the well-known enzymatic reactions of monosaccharide chemistry might be applied successfully to the generally more labile glycoproteins. Thus, by removing the then-presumed terminal sialic acid residues with the enzyme neuraminidase, we hoped to expose galactose, which in turn could be oxidized with galactose oxidase and sequentially reduced with sodium borotritide. We expected the product to be a minimally altered and highly radioactive protein that would be eminently suitable for studies *in vivo*. After several weeks of intense telephone consultations between the Bronx and Manhattan, Anatol informed me excitedly that the preparation was completed and that the product was highly labeled with tritium.

Our joy, however, was short-lived. Although the half-life of ceruloplasmin in the rabbit was known to be in excess of two days, the first blood sample, taken several hours after injecting the labeled material, was essentially devoid of radioactivity. It was only when the sampling time was reduced to 10 minutes that even trace amounts of the product could be recovered. Among the numerous potential artifacts that had to be considered, denaturation of the protein appeared to be the most probable and the most discouraging. However, with the subsequent demonstration that the rapid clearance from the serum was reversible either by removing the terminal galactose residues or by restoring the missing sialic acid with the enzyme, sialyltransferase, it became clear that the protein was not denatured and, more importantly, that the intact terminal residues of galactose constituted a cryptic signal initiating removal of the entire protein and its eventual catabolism in the liver.

The broader significance of these findings became abundantly clear when it was shown that the above phenomena were valid for all glycoproteins in which galactose, or N-acetylgalactosamine, could be exposed as the terminal sugar residue. In the intervening years, these observations have served as a stimulus for the identification of a host of carbohydrate-specific receptors on various cell surfaces[1,2] and have inaugurated the current concept of a "cellular lectin."[3,4]

1. Ashwell G & Harford J. Carbohydrate specific receptors of the liver. *Annu. Rev. Biochem.* 51:531-54, 1982.
2. Stockert R J & Morell A G. Hepatic binding protein: the galactose-specific receptor of mammalian hepatocytes. *Hepatology* 3:750-7, 1983.
3. Stockert R J, Morell A G & Scheinberg I H. Mammalian hepatic lectin. *Science* 186:365-6, 1974. (Cited 105 times.)
4. Ashwell G. A functional role for lectins. *Trends Biochem. Sci.* 2:N186, 1977.

/A -18