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Watkins W M. Blood-group substances. *Science* 152:172-81, 1966.
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This paper reviews the limited knowledge available in 1966 concerning the serology, genetics, and biochemistry of the blood-group ABH and Lewis blood-group systems and delineates the proposed biosynthetic pathways for the formation of the antigens. [The *SCI*® indicates that this paper has been cited in over 445 publications.]

Carbohydrate Antigens, Glycosyltransferases, and Blood-Group Genes

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After obtaining my PhD with Arthur Wormall in the Biochemistry Department at St. Bartholomew's Hospital Medical School, London, in 1950, I joined Walter Morgan's laboratory at the Lister Institute of Preventive Medicine, London. Work on human ABO blood-group antigens had begun in this laboratory in the early 1940s and, as attempts by others to extract blood-group active materials from red-cell membranes had met with little success, attention was focussed on the water-soluble glycoproteins in secretions that carry the same specific structures. By 1950 the overall compositions of A, B, H, and Lewis active glycoproteins had been established, but their similarity made it apparent that chemical analysis alone would not reveal the basis of blood-group specificity.[1] This realisation led us to try a series of indirect methods to obtain clues to the nature of the determinants.

In 1952, employing the Landsteiner principle that simple substances with structures related to the immunological determinant groups of an antigen can act as competitive inhibitors of antigen-antibody reactions, we tested the constituent sugars of the blood-group active glycoproteins for inhibition of agglutination with an array of human and animal anti-A, anti-B, and anti-H sera. A positive answer was obtained with only one reagent: a naturally occurring anti-H in the serum of the eel *Anguilla anguilla* was inhibited by L-fucose.[1,2] Tenuous though the inference was, we believed this result had given us the first indication that one sugar might be more important for H specificity than the others. A year later similar tests with the recently discovered anti-H and anti-A plant lectins confirmed the role of L-fucose in H structures and indicated the importance of *N*-acetylgalactosamine in A specificity. Shortly after, the use of exoglycosidases pointed to the role of D-galactose in B specificity.

Even more complete structural information about the Lewis antigens was obtained in 1957 through the availability of a series of fucose-containing oligosaccharides isolated from human milk by Professor R. Kuhn and colleagues in Heidelberg. These compounds enabled us to pinpoint the trisaccharide structure responsible for Le^a specificity with remarkable precision and to deduce that a difucosylated tetrasaccharide structure was involved in Le^b specificity. Parallel studies on the sequential action of exoglycosidases on the blood-group active glycoproteins led to the revelation that loss of one immunological specificity following the removal of a single sugar from an oligosaccharide chain was accompanied by the development of a new specificity as a different end-group was exposed. By 1959 sufficient information on the chemistry, genetics, and serology of the ABH and Lewis antigens was available to warrant speculation on their genetic interrelationships and pathways of biosynthesis.[2] In the ensuing years, oligosaccharide fragments carrying the complete A, B, H, Le^a, and Le^b determinants were isolated and structurally characterised.[2,3]

Therefore, when this review article was written in 1966, the genetic regulation of blood-group antigenic expression was rapidly becoming clearer, and it had been possible to predict that the primary protein products of the *A*, *B*, *H*, and *Le* genes were glycosyltransferases concerned with the final stages of the biosynthesis of the carbohydrate antigens.

I believe that this paper has been frequently cited because it appeared at a time when the collective evidence providing an explanation for the differences between the A, B, H, and Lewis blood groups at a chemical level, and for the interrelationships of the ABO, Lewis, and Secretor genes, was just emerging as an exciting and coherent story. In the next decade it was shown by S. Hakomori in the US and J. Koscielak in Poland that, although the carrier molecules differed, the blood-group determinant structures on the red-cell membrane were identical to those established for the secreted glycoproteins.[4] The predicted enzymic basis of the blood-group specificity was confirmed in our laboratory and by Ginsburg in the US, and the discovery of these glycosyltransferases provided new genetic markers for forensic studies and for investigations of rare blood-group phenotypes.[5] With the advent of molecular genetic techniques, identification of the DNA encoding the enzymes has become the next exciting chapter to be explored in the blood-group antigen saga.[6]

1. **Morgan W T J.** A contribution to human biochemical genetics; the chemical basis of blood group specificity. *Proc. Roy. Soc. London Ser. B* 151:308-47, 1960. (Cited 150 times.)
2. **Watkins W M.** Blood group specific substances. (Gottschalk A, ed.) *Glycoproteins, their composition, structure and function.* Amsterdam, The Netherlands: Elsevier, 1972. p. 830-91. (Cited 175 times.)
3. **Kabat E A.** Immunochemical studies on the carbohydrate moiety of water soluble blood group A, B, H, Le^a and Le^b substances and their precursor I antigens. *Advan. Chem. Ser.* (117):334-61, 1973. (Cited 35 times.)
4. **Hakomori S & Kobata A.** Blood group antigens. (Sela M, ed.) *The antigen.* New York: Academic Press, 1974. Vol. 2. p. 79-140. (Cited 155 times.)
5. **Watkins W M.** Biochemistry and genetics of the ABO, Lewis and P blood group systems. *Advan. Hum. Genet.* 10:1-136, 1980. (Cited 210 times.)
6. **Greenwell P, Edwards Y H, Williams J & Watkins W M.** Approaches to cloning the genes at the human blood group *ABO* locus. *Biochem. Soc. Trans.* 15:601-3, 1987.

