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P1PK, GLOB, and FORS Blood Group Systems and GLOB Collection: Biochemical and Clinical Aspects. Do We Understand It All Yet?

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ABSTRACT

Antigens belonging to the P1PK, GLOB, and FORS blood group systems and the GLOB blood group collection represent a closely related set of 13 glycosphingolipids (GSLs). They are synthesized by the coordinated action of glycosyltransferases, encoded by at least 7 different loci. Three of these enzymes show either different activity or a different mRNA expression profile due to genetic polymorphisms, resulting in blood group diversity. In recent years, significant progress has been made in understanding the molecular background and biological functions of these GSLs. Their medical significance is often related to the existence of natural antibodies, as they may cause complications after transfusions and during pregnancies. In addition, GSLs belonging to these blood group systems are receptors for several pathogens. This review summarizes the present knowledge about the complicated network of enzymatic interactions leading to synthesis of these GSLs, as well as their clinical implications.

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Antigens belonging to the P1PK, GLOB, and FORS blood group systems and the GLOB blood group collection are glycosphingolipids (GSLs), which are related with respect to their structure and biosynthesis. Among human blood group systems, P1PK seems to be the most complicated and elusive. Its discovery started in 1927, when Landsteiner and Levine found that rabbits immunized with human erythrocytes produce antibodies reacting with an antigen that is now called P1 [1]. The presence of this antigen or its absence on erythrocytes gave rise to the P_1 and P_2 blood groups, respectively. Initially, the P blood group system also included 2 other GSLs: globoside (the major glycosphingolipid of erythrocytes, called P antigen), and the P^k antigen, first described by Matson et al [2] in 1959. These antigens were grouped together in the P blood group system because P1 and P^k show serological cross-reactivity. Evaluation of the structure of these GSLs revealed that P^k is a precursor of the globoseries GSLs including globoside and its derivatives [3]. In turn, the P1 antigen belongs to the different neolactoseries of GSLs but shares with P^k the same terminal disaccharide unit, Galα1,4Gal-.

Glycosphingolipids are synthesized by the sequential addition of monosaccharides to precursor substrates by specific glycosyltransferases. The antigens of the P1PK, GLOB, and FORS blood group systems arise as a result of a coordinated action of glycosyltransferases originating from at least 7 different loci. These are *A4GALT, B3GNT5, B3GALNT1, B4GALT1, GBGT1, B3GALT5,* and *ST3GAL1* (Fig 1). In addition to the *B4GALT1*, glycosyltransferases from 3 other loci (*B4GALT2*, *B4GALT3*, *B4GALT4*) may be involved in the synthesis of paragloboside, depending on the tissue-specific expression profile [4,5]. Three of these genes reveal nucleotide polymorphisms leading to synthesis of different blood group antigens: P1/P^k synthase (α1,4-galactosyltransferase, also known as Gb3/CD77 synthase, encoded by the *A4GALT* gene), P synthase (β1,3-*N*-acetylgalactosaminyltransferase, encoded by the *B3GALNT1* gene), and Forssman synthase (α1,3-*N*-acetylgalactosaminyltransferase, encoded by the *GBGT1* gene). P1/P^k synthase was previously known to be responsible for the synthesis of P^k antigen only. P^k antigen is present in all erythrocytes, except the rare null phenotype called *p*; but P1 antigen is present only in a fraction of the population. For a long time, the biosynthesis of the P1 antigen was a puzzle. However, neither the concept of 2 different galactosyltransferases nor the existence of allelic variants of P1/P^k synthase in P_1 and P_2 individuals has been confirmed. The results of recent studies, which showed that the P1/P^k synthase is responsible for the synthesis of both P1 and P^k antigens and which shed new light on the problem of genetic difference between P_1 and P_2 phenotypes, are described later in this review. Presently, the International Society of Blood Transfusion considers that the P^k and P1 antigens, which are directly dependent on the presence of active P1/P^k synthase, belong to the blood group system called P1PK [6]. Recently, a new rare variant antigen NOR, which was found by us to arise because of a single mutation in the P1/P^k synthase gene, has been added to the P1PK blood group system [7]. The presence of P antigen is dependent on the activity of β1,3-*N*-acetylgalactosaminyltransferase, and so P antigen was reclassified into the GLOB blood group system [8,9]. Antigens LKE (a derivative of globoside) and PX2 (a derivative of paragloboside) are included in the GLOB collection because their genetic background is not clear yet. The Forssman antigen, named after its discoverer [10], was known to be present in animals but not in humans. The human FORS blood group system has been acknowledged after a single point mutation was found in the *GBGT1* gene that makes the human Forssman synthase active and gives rise to a rare phenotype that was previously misclassified as an ABO subgroup [11].

The first in-depth review summarizing all data available at the time on the (then) P blood group system and closely related GSL antigens was published in 1995 by Spitalnik and Spitalnik [12]. Since then, an enormous amount of new data has been gathered, which led to a thorough revision of the way these antigens are classified today; and 2 short reviews devoted to the newly established P1PK and GLOB blood group systems have been published [13,14]. Here, we attempt to summarize all of the present knowledge on the complex and intertwined nature of the P1PK, GLOB, and FORS blood group systems and the GLOB collection in one article, including their biochemical, genetic, serological, and medical aspects.

Biochemistry of P1PK, GLOB, and FORS Blood Group Antigens

Structures and Biosynthesis of Antigens

The current classification of the antigens belonging to the P1PK, GLOB, and FORS blood group systems and the GLOB collection is

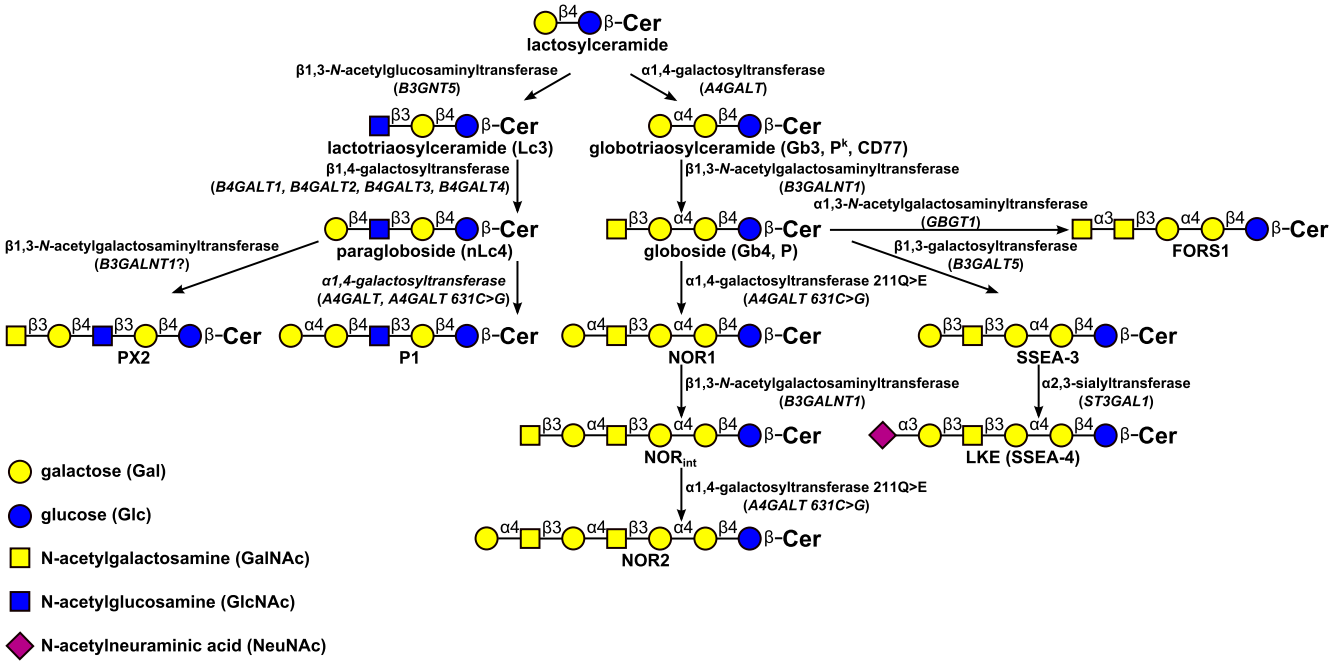

Fig 1. Schematic representation of biosynthesis of P1PK, GLOB, and FORS blood group antigens. The symbols are as recommended by Varki et al (2009) [29]. Cer, ceramide.

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