

compartmentalization of this enzyme in particular membrane microdomains in which the enzyme functions, as has been reported for the interaction between sPLA₂ and HSPG.

However, why does it have to take place in apoptotic cells? More important, it is critical to determine whether the event can occur *in vivo*. It also would be interesting to know whether other sPLA₂ isozymes can use the same machinery to interact with apoptotic cells. Clarifying these issues will contribute to our understanding of the physiologic function of sPLA₂ in the immune response.

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The ABO gene— more variation!

The polymorphism of the ABO antigens was largely responsible for the discovery of blood groups by Landsteiner¹ about 100 years ago. The ABO blood group system is clinically one of the most important because the A- and B-glycan epitopes it expresses are strongly immunogenic.

Functional alleles at the ABO genetic

locus encode glycosyltransferases that participate in the assembly of glycan units of glycoproteins and glycolipids of the membranes of erythrocytes and other cells and of glycoproteins of certain secretions. All products arise as a result of mutations in the single *ABO* gene; however, only 3 specific mutations, which show a high frequency in the population, indirectly lead to changes in the epitope structures resulting in A, B, or O specificities. Two of the mutations (substitutions) affecting the recognition and binding of donor nucleotide sugar substrates change the specificity of the enzyme from an N-acetylgalactosaminyltransferase (the A enzyme) to a galactosyltransferase (the B enzyme). These glycosyltransferases, in turn, introduce an α 1,3 N-acetylgalactosamine (A) or an α 1,3 galactose (B) at the ends of type H glycan chains. The third mutation is a deletion within the 5' region of the catalytic domain that results in a frameshift and inactivates the enzyme altogether, leaving the H glycan unmodified. These different glycans define the A, B, or O epitopes.

The molecular basis of the ABO system was elucidated by Yamamoto and colleagues² over 10 years ago. In an elegant series of experiments, they cloned the gene and identified the mutations responsible for the A, B, or O specificities.² Subsequently, this group and others identified a large number of additional mutations on the background of the A, B, or O alleles around the active site and in other regions of the coding sequence. Today, 88 allelic variants of the *ABO* gene are documented.³ Except for several major allelic variants, the functional significance of many of those mutations is not known. However, the corresponding amino acid changes probably lead to changes in activities of the glycosyltransferases. In turn, changes in specificity and activity of these variant enzymes affect the structures of epitopes, allowing serologists

to detect variant ABO blood group phenotypes.

In this issue, Seltsam and colleagues (page 3035) identify many additional mutations within the *ABO* gene. In contrast to previous studies that focused on mutations within exons 6 and 7 (encoding the catalytic segments), they address mutations across essentially the entire *ABO* gene in DNA from 55 individuals that show a variety of common and rare ABO blood group phenotypes. This paper illustrates the need for full-length nucleotide sequencing of each allele. The authors confirm the presence of already-known mutations in coding regions and introns, document 3 new mutations within coding regions, and describe many new mutations within introns. Interestingly, a large number of intron mutations are recurrent (ie, nucleotide changes of the same type occur at the same sites in a number of alleles), resulting in patches of identical patterns of mutations across sets of alleles. Patches of recurrent mutations are also a hallmark of mutations in the coding regions of the *ABO* gene. The new data provide additional parameters for understanding the paths and mechanisms for the diversification of the *ABO* gene and help answer questions as to when and how diversification occurred. Like others, the authors begin to tackle these questions by examining correlations among alleles and by presenting a phylogenetic analysis of the new and previous data.

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