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American Liver Foundation Research Award: Epigenetics of X-Linked Genes in Primary Biliary Cirrhosis: Does X Mark the Spot?

by Carlo Selmi, MD, PhD

The project was designed to dissect the epigenetics (i.e. DNA changes not requiring modification of the sequence) of the X chromosome that might contribute to the susceptibility to primary biliary cirrhosis (PBC). The hypothesis was based on the previous data on the importance of X chromosome major defects in women with PBC. In particular, we would take advantage of a unique set of monozygotic twin and similar-age sisters all discordant for PBC (i.e. only one of the two sisters had the disease) to compare the expression (i.e. the amount of RNA product derived from their translation) of 125 genes located on the X chromosome. Importantly, it is currently thought that the vast part of one X chromosome is silenced through epigenetic changes (methylation in particular) in women (who would otherwise have a double dosage of those genes compared to men). The 125 genes were chosen since they undergo variable degrees of methylation, type of chemical modification of DNA that can be inherited and subsequently removed without changing the original DNA sequence, and can be expressed (not methylated) or silenced (methylated) on both X chromosomes also in healthy women.

Although preliminary, interesting results have been obtained with the study of a regulatory region of one of these genes, i.e. the promoter region, which includes several CpG islands. CpG islands are short regions of DNA in which the frequency of the CG sequence is higher than in other regions. "p" indicates that "C" and "G" are connected by a phosphodiester bond. CpG Islands are often located around the promoters of housekeeping genes (which are essential for general cell functions) or other genes frequently expressed in a cell. Our preliminary analysis demonstrates that a nucleotide change in this region (called a polymorphism) might change a CpG island thus influencing the methylation of the region. This specific polymorphism, having multiple alleles of a gene within a population, is quite uncommon in the US population and is now being studied for an association with the disease.

The potential implications of our study are quite important. Indeed, it is already well established that genetic predisposition contributes to the onset of PBC, yet the genetic bases of the disease are remain largely unknown, mostly due to the relative rarity of the disease. Our current study and preliminary results broaden this idea and support the hypothesis that the candidate gene could be one of the genes involved in the development of PBC even though further analyses need to be completed. In particular, the specific function of the polymorphism of this gene may explain also the incomplete concordance in identical twins by its related methylation changes. Ultimately, we are convinced that all our efforts will lead to a solid definition of the individual susceptibility to PBC, thus making the diagnosis possible before any sign or symptom, particularly in first-degree relatives of patients.

Dr. Selmi is an Assistant Professor of Medicine at the University of California, Davis. He received a \$225,000 Seed Grant Primary Biliary Cirrhosis Award from the American Liver Foundation in 2006.