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To the editor:

X-linked clonality testing and autoimmune diseases

In their *Blood* First Edition paper, Drs Chen and Prchal[1] review X-linked clonality testing: interpretation and limitations. I believe that there is an important error in interpreting the data regarding skewed X-chromosome inactivation patterns (XCIPs) in autoimmune disorders.[2,3]

Chen and Prchal skilfully review clonality detection based on XCIPs and their implications; however, they incorrectly state ". . . age-related X-chromosome inactivation skewing has been implicated in the pathogenesis of scleroderma, autoimmune thyroid diseases (AITD; including Graves disease and Hashimoto thyroiditis), and primary biliary cirrhosis. . . . "[1] First, the cited reference on primary biliary cirrhosis[4] reports the frequency of monosomy X and not XCIPs. Furthermore, neither new data from the same group[5] nor our unpublished observations (T.O., April 2006) support that primary biliary cirrhosis is associated with skewed XCIPs. Second, and more importantly, the extremely skewed XCIPs in scleroderma[2] and AITDs[3,6] do not appear to be age related. In fact, many patients with extremely skewed XCIPs were in the second or third decades of their lives, and a shift toward the skewed range in older patients and controls was not observed. There is also new data suggesting that skewed XCIPs could be associated with childhood autoimmune diseases as exemplified by juvenile idiopathic arthritis.[7]

Aging is an important issue in XCIP studies, particularly in formulating hypotheses to design studies that will investigate extremely skewed XCIPs in female predisposition to autoimmunity. Two possibilities could be considered in assessing the nature of the relationship between skewed XCIPs and autoimmune disease susceptibility. Skewing may arise as a result of break down in self-tolerance, or break down in self-tolerance could be the result of skewing. We believe the latter is more likely, simply because the degree of skewing is at the extreme of 95:5 or 100:0 in most patients. If the skewing were to arise as a result of aging and/or an autoimmune reaction in the body, then these ratios would more likely be in the milder ranges (ie, 80:20 to 90:10). Circumstantial evidence in favor of this proposition was presented in our AITDs study.[6] Skewed X-inactivation cosegregates with the disease in at least 2 families with multiple affected members. Also, recurrent spontaneous abortions, which have been shown to be associated with skewed XCIPs[8,9] and X-chromosome abnormalities,[10] are elevated in the skewed group. Based on these considerations, we propose that germ-line X-linked mutations or X-chromosome rearrangements and their differential expression patterns could provide a disadvantage to affected blood cells and lead to skewed XCIPs. This could mean that female predisposition to autoimmunity could be initiated by a variety of X-chromosomal events in a very rich repertoire of genes. Therefore, it is probably time to consider "loss of mosaicism" for X-linked gene expression as the first step of the cellular events that lead to breakdown of self-tolerance in females.

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