human dendritic cells. Biochem Biophys Res Commun 2002;296: 194–200.
6. Fukuzawa M, Satoh J, Sagara M, Muto G, Muto Y, Nishimura S, et al. Angiotensin converting enzyme inhibitors suppress production of tumor necrosis factor-α in vitro and in vivo. Immunopharmacology 1997;36:49–55.
7. Hernandez-Presa M, Bustos C, Ortego M, Tunon J, Renedo G, Ruiz-Ortega M, et al. Angiotensin-converting enzyme inhibition prevents arterial nuclear factor-kappa B activation, monocyte chemoattractant protein-1 expression, and macrophage infiltration in a rabbit model of early accelerated atherosclerosis. Circulation 1997; 95:1532–41.
8. Hall FC, Dalbeth N. Disease modification and cardiovascular risk reduction: two sides of the same coin? Rheumatology (Oxford) 2005. Epub ahead of print.

DOI 10.1002/art.21508

Skewed X chromosome inactivation in scleroderma: comment on the article by Özbalkan et al

To the Editor:

Özbalkan et al (Ozbalkan Z, Bagislar S, Kiraz S, Akeyerli CB, Ozer HTE, Yavuz S, et al. Skewed X chromosome inactivation in blood cells of women with scleroderma. Arthritis Rheum 2005;52:1564–70), using a polymerase chain reaction (PCR) involving the androgen receptor locus for the assessment of methylation status, have determined that there is skewing of X chromosome inactivation in blood cells from women with scleroderma. Based on recent disclosures following the sequencing of 99% of the human X chromosome, their conclusion may be unwarranted; it may be the androgen receptor locus and not the inactivated X chromosome that is skewed.

One or the other of the 2 X chromosomes is suppressed in each cell of a woman's body. However, sequencing of 99% of the human X chromosome (Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 2005;434:400–4) revealed that ~15% of genes escape this X inactivation, and those genes that escape vary from woman to woman. The genes that escape X inactivation are expressed from both X chromosomes. Therefore, the level of expression of such genes is higher than that of genes expressed from only one X chromosome. If the androgen receptor gene was among those that escape and are expressed from both chromosomes, the PCR would detect increased expression of the androgen receptor gene in that chromosome. Rather than skewing X chromosome inactivation, this would reflect skewed expression of the androgen receptor gene locus.

Although skewed expression of the androgen receptor gene could, in some instances, account for the apparent skew of X chromosome inactivation, that happenstance might remain significant or become even more significant. The increased expression of the androgen receptor gene, if observed primarily in patients with scleroderma, may mean that the androgen receptor gene has a role in the disease etiology.

Hugh McGrath, Jr., MD
Louisiana State University Health Sciences Center
New Orleans, LA

DOI 10.1002/art.21509

Reply

To the Editor:

Dr. McGrath questions the conclusion of our study of X chromosome inactivation in women with scleroderma in light of a recent study that revealed extensive variability in X-linked gene expression in females (1). He raises 2 issues: first, that the androgen receptor locus and not the inactivated X chromosome could be skewed, and second, that the androgen receptor locus could escape from X chromosome inactivation, and biallelic expression of this gene could be involved in disease pathogenesis. Indeed, ~15% of X-linked genes escape inactivation to some degree, and an additional 10% of X-linked genes show variable patterns of inactivation. However, androgen receptor is not one of them. The report by Carrel and Willard (1; supplementary Table 3) and numerous previously published studies firmly establish that at least 214 X-linked genes, including the androgen receptor locus, are subject to X chromosome inactivation. With respect to the isolated skewing of the androgen receptor locus, this is also highly unlikely. It is well known that inactivation occurs early in development, leading to silencing that is mitotically stable, so that females are mosaics for cell populations in which either the paternal or the maternal X is silenced (2). It is also well-established that DNA methylation is involved in the maintenance of the inactive X chromosome silencing, and the well-established human androgen receptor assay used in our study determines the methylation status of the androgen receptor (3). In conclusion, we could not identify any experimental data that support the points raised by Dr. McGrath.

Zeynep Özbalkan, MD
Sedat Kiraz, MD
Meral Çalgüneri, MD
Hacettepe University Medical School
Ankara, Turkey
Sevgi Bağişlar, BSc
Cemaliye Boylu Akyerli, PhD
Bilkent University
Ankara, Turkey
Hüseyin T. C. Özer, MD
Çukurova University Medical School
Adana, Turkey
Şule Yavuz, MD
Marmara University Medical School
Istanbul, Turkey
A. Merih Birlik, MD
Dokuz Eylül University Medical School
Izmir, Turkey
Tayfun Özçelik, MD
Bilkent University
Ankara, Turkey
and Ayhan Sahenk Foundation
Istanbul, Turkey

1. Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 2005;434: 400–4.
2. Plath K, Mlynarczyk-Evans S, Nusinow DA, Panning B. Xist RNA and the mechanism of X chromosome inactivation. Annu Rev Genet 2002;36:233–78.