

Partial Hormone Resistance in Mice With Disruption of the Steroid Receptor Coactivator (SRC-1) Gene

The authors demonstrate that in mice inactivation of the steroid receptor coactivator (*Src-1*) leads to decreased growth of the gonads and sex hormone-dependent structures (uterus, prostate) but does not impair fertility. *Src-1* influences gene transcription by increasing histone acetyltransferase activity and other mechanisms, thus enhancing receptor-mediated nuclear gene transcription. The investigators inactivated *Src-1* by deleting ~9 kb of its genomic sequence (446 amino acids) from embryonic stems and then inserting these cells into blastocysts of a strain of C57 mice, thus generating chimeric founders. They then bred heterozygous and homozygous *Src-1*-deficient mutant animals. Heterozygous animals were normal. Homozygous *Src-1*-deficient animals were phenotypically normal, but responded subnormally to several steroid hormones. Uterine growth in response to estrogen was significantly attenuated when compared with normal animals, as was testosterone-induced prostate growth. Testicular size was decreased and breast development impaired in homozygous mutants. Serum concentrations of estradiol and testosterone were slightly elevated in the *Src-1*^{-/-} animals. Surprisingly, fertility was normal. In part, the defect in *Src-1* expression was compensated for by increased synthesis of related steroid receptor coactivators such as *TIF2*. The writers concluded that *Src-1* is important for efficient steroid hormone action in vivo.

Xu J, et al. *Science* 1998;279:1922-1925.

Editor's comment: Nuclear estrogen receptor (ER)-associated proteins help mediate the transcription-activating effects of the estrogen-ER complex.¹ Flanking the DNA binding domain (DBD) of the ER are 2 independent transcription-activating domains (AF-1 on the amino terminal side of the DBD and AF-2 on the carboxyl terminal side of the DBD, overlapping but distinct from the hormone binding domain). Transcription activated through the AF-2 site is mediated by several coactivating proteins that bind to the AF-2 site after the change in conformation of the ER that accompanies its binding to ligand estrogen occurs.¹ One wonders how soon it will be until patients with partial insensitivity to steroid hormones due to inactivating mutations of steroid receptor coactivating proteins are identified clinically and genomically.

Allen W. Root, MD

Halachmi S, et al. *Science* 1994;264:1455-1458.

2nd Editor's comment: Could these ER-associated proteins or similar augmentors contribute to the variations in breast size among women of similar body size and/or adiposity?

Robert M. Blizzard, M.D.

Of Fingers, Toes, and Penises*

Hox genes encode DNA-binding transcription factors that regulate and coordinate the relative positioning of structures during embryologic development.¹ There are 4 *Hox* complexes in vertebrates. Experimental mutations in *Hox* genes alter the position of the regulated skeletal structures (limbs, digits) as well as their size. Kondo et al developed mice with compound mutations in different *Hox* genes: (1) the hypodactyly allele, which is a deletion of *Hoxa-13*; and (2) null alleles in *Hoxa-13* or *Hoxd-11*, *-12*, and *-13*. These compound mutant mice had total digital agenesis and agenesis of the genital eminence with absence of the penis in male animals and absence of the bladder and urethra in females. The authors concluded that *Hoxa* and *Hoxd* genes regulate development of the morphogenetic ends of the body—digits at the ends of limbs and genital structures at the end of the trunk.

Kondo T, et al. *Nature* 1997;390:29.

*Capital letters (*HOX*, *HOXA*, *HOXD*) designate human genes; small letters (*Hox*, *Hoxa*, *Hoxd*) represent animal genes.

Editor's comment: These experimental findings shed light on the genetic mechanisms that are aberrant in clinical human malformation syndromes involving the

HOX genes.¹ Mutations in *HOXD-13* are associated with synpolydactyly, an autosomal dominant disorder characterized by duplication of the 3rd and 4th fingers and syndactyly of the 3rd, 4th, and/or 5th toes. The mutation in *HOXD-13* (chromosome 2q31) involves expansion of a sequence of 15 consecutive alanine residues in the N-terminal region of the normal gene to one with 22 to 29 alanine residues and is thought to be associated with gain-of-function of this protein. A dominant-negative mutation (deletion of 20 amino acids necessary for DNA binding) in *HOXA-13* (chromosome 7p14-p15) has been associated with the hand-foot-genital syndrome, a disorder characterized by hypoplasia of the thumbs and great toes, clinodactyly of the 5th fingers, abnormalities of the carpal and tarsal bones, penile hypospadias in males, and abnormal urethras and ureters and malformed uteri in females. It is likely that mutations in 1 or more *HOX* genes may be found in patients with minor skeletal malformations (clinodactyly, brachydactyly, brachymetacarpia, brachymetatarsia).

Allen W. Root, MD

Innis JW. *Curr Opin Pediatr* 1997;9:617-622.