

## CHAIRPERSON'S INTRODUCTION

### Clues from other animals and theoretical considerations

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In the first two papers of this volume, the genetic control of sex determination in *Caenorhabditis* and *Drosophila* is reviewed by Hodgkin and by Nöthiger & Steinmann-Zwicky, respectively. Sex determination in both cases depends on the ratio of X chromosomes to autosomes, which acts as a signal to a cascade of regulatory genes located either on autosomes or on the X chromosome. The state of activity of the last gene in the sequence determines phenotypic sex. In the third paper, Erickson & Tres describe the structure of the mouse Y chromosome and the polymorphisms that have been detected in different mouse species and strains. As in all mammals, the Y carries the primary male-determining locus; autosomal genes may also be involved in sex determination, but they must act down-stream from the Y-linked locus. In the mouse, these loci may be responsible for the development of XY females, i.e. the failure of the Y chromosome to induce maleness, but XX male mice that carry no Y chromosomal material have not been detected. In contrast, de la Chapelle describes evidence for a human autosomal locus, TDFA, located on an autosome or pseudo-autosomally on the X, defects in which can give rise to true masculinization, i.e. to XX men as well as to hermaphrodites.

To begin a symposium volume on the mammalian Y chromosome with two papers on animals that are not mammals and do not possess a Y chromosome might seem perverse, but the reason is not far to seek. Since sex is so pervasive in the animal kingdom, it seems unlikely that the evolution of sex-determining mechanisms would have been totally independent in different groups of animals. The elegant and detailed genetic analysis that has proved feasible in insects and nematodes may therefore be expected to shed light on the genetics of mammalian sex determination also.

However, some of the complexity of the sex-determining mechanisms in *Caenorhabditis* and *Drosophila* appears to be involved with the interactions between sex determination and dosage compensation. Using the X:autosome ratio as a signal requires that the presence of two X chromosomes in a

female be detectably different from the presence of one X in a male; yet dosage compensation requires that they be equivalent. In *Drosophila*, reconciliation of these conflicting aims appears to be brought about by using the X:autosome ratio very early, at the blastoderm stage, to set the state of a single 'master control gene', *Sxl*, which controls dosage compensation as well as the cascade of genes that regulate sex determination. Once set, the state of *Sxl* is maintained by an autoregulatory mechanism independent of the X:autosome ratio. Dosage compensation is achieved by increasing the level of transcription from the single X chromosome of male flies to match the total output of the two X chromosomes in female flies. A similar mechanism probably operates in nematodes.

In mammals, sex determination depends on the presence or absence of the Y chromosome, for which no dosage compensation is required. The sex difference in the number of X chromosomes that is consequent upon the X/Y pairing mechanism does require dosage compensation, which is achieved by inactivation of one of the two X chromosomes early in female development. This is quite independent of sex determination, so in mammals there is no need to postulate a 'master control gene' regulating both sex determination and dosage compensation, a requirement that may underlie the 'disturbingly complex' transcriptional pattern attributed by Nöthiger & Steinmann-Zwicky to the *Sxl* gene in *Drosophila*.

A separate issue, not dealt with in detail in the present volume, is germ cell sex determination. In mice, whether a germ cell enters the male or female pathway of development depends only on whether it is exposed to a testicular environment, rather than on a direct effect of the Y chromosome. XY germ cells can develop as oocytes, while germ cells lacking any Y chromosomal sequences can embark on spermatogenesis. Dosage compensation is negated, as the second X chromosome in XX germ cells is reactivated before birth, and the number of X chromosomes plays an important role: continuation of spermatogenesis past the time of birth is impossible in the

presence of two X chromosomes, while germ cells with a single X are at a disadvantage during oogenesis. The Y chromosome plays a role only in the later stages of spermatogenesis (Burgoyne, this symposium). In *Drosophila* and in nematodes, the cascade of genes that regulate somatic sex determination may also be expressed in germ cells and may be involved in germ cell sex determination.

Nöthiger & Steinmann-Zwicky postulate a common genetic strategy for sex determination, distributed widely in the animal, and even the plant, kingdom. A primary signal (which could be chromosomal, e.g. the X:autosome ratio; or genetic, e.g. expression of a locus on the Y chromosome; or environmental, e.g. temperature) is recognized by a key gene, whose state of activity then regulates the expression of a cascade of subordinate control genes, which finally serve to repress either the male or the female differentiation genes, producing a female or a male respectively. While a general schema of this sort may be widely applicable, it is of the essence of those systems that have been analysed that they are highly labile. As Hodgkin points out, the *C. elegans* sex-determining system could be modified by introducing a null and a gain-of-function mutation at the final locus of the cascade (*tra-1*), which would make it very similar to the dominant-gene mechanism of birds or mammals. All genes in the cascade upstream of *tra-1* would then become irrelevant. Similarly, Nöthiger & Steinmann-Zwicky describe a temperature-sensitive mutation of the *tra-2* locus in *Drosophila* that could

well form the basis of a temperature-controlled, environmental mechanism of sex-determination, as seen in certain reptiles. Erickson & Tres stress the evolutionary flexibility of sex-determining mechanisms: closely related species may have a chromosomal or an environmental mechanism, the heterogametic sex may be the male (as in mammals) or the female (as in birds), or both options may be encountered in a single population (as in platyfish). It seems that relatively minor genetic changes can convert one system into another.

Thus the underlying logic of sex-determining mechanisms may have been conserved in evolution even though the details, including perhaps the nucleic acid sequences, may change rather rapidly. At present, we know little of the basis of sex determination in mammals at the genetic level, nothing at the molecular level. The mammalian Y-chromosome-based mechanism could prove to be very much simpler than what we see in nematodes and *Drosophila*: perhaps much of their observed complexity is indeed associated with reconciling dosage compensation and recognition of the X-autosome ratio, or perhaps some of the gene cascade is replaced in mammals by the intricate feedback systems of sex-hormone interaction. Among vertebrates, mammals have the most rigidly canalized sex-determining mechanism. The next few years should show whether this has been achieved by secondary simplification or at the cost of increased levels of regulatory complexity.