Protection from X inactivation

SIR — Davies in News and Views[1] draws attention to the growing literature on genes on the X chromosome that are not subject to inactivation, and to the now established finding that such genes are not confined to a single contiguous region extending from the telomere of the short arm. This distribution cannot be accounted for by arrest of a spreading inactivation process. The finding that this class of genes includes some that are also present (although with minor sequence differences) on the Y chromosome suggests a possible solution to the problem of the mechanism of local and distributed protection from inactivation.

A widely accepted explanation[2] for inactivation of one X chromosome is that inactivation ensures that the dosage of genes is the same in the female (with an XX complement) as in the male (who with an XY complement carries only one copy of X-linked genes). A similar dosage problem can be seen to exist for any Y-linked genes not involved in sex determination. Such genes may be presumed to have an active homologue on the X-chromosome, and to maintain dosage equilibrium they would be expected not to be subject to inactivation in the female.

How could such protection of X-linked Y-homologous genes be achieved? A possible answer is that they might be protected by sequence specific pairing in male meiosis from a process of genomic imprinting. Pairing of X and Y chromosomes in male meiosis is known to extend well beyond the 'pseudoautosomal region' within which there is strict sequence homology and recombination between X and Y (ref. 3). Genes outside this region present only on the X chromosome would be subject to imprinting, whereas those with homologous (although perhaps not identical) sequences on the Y chromosome would be protected.

The hypothesis predicts the following: (1) protection from inactivation will occur when the X chromosome that is preferentially inactivated in the female is the unpaired paternal X. In marsupials and for trophectoderm and primitive endoderm (but not for primitive ectoderm and its embryonic derivatives[4,5]) in the mouse it is the paternal X that is consistently inactivated. However in primitive ectoderm in the mouse, and in man, which X chromosome is inactivated is apparently random. A test of the hypothesis therefore is whether X–Y homologous genes remain active on an inactivated X chromosome that is maternal in origin. (2) Pairing of X–Y homologous genes (for example, ZFY and RPS4Y in Yp11.3 with ZFX in Xp21 (ref. 6) and RPS4X in Xq13 (ref. 7), respectively) requires an unusual configuration in male meiosis. If such a configuration occurs it might be detected by electron microscopic examination of surface spread synaptonemal complexes.

According to this hypothesis genes on the Y chromosome (other than those that determine sex) are predicted in each case to have a homologue on the X chromosome that is not subject to inactivation. Conversely, genes that are not inactivated on the X chromosome will be expected to have a homologue on the Y. An apparent exception to this rule is A1S9T, a gene that lacks a Y homologue and had been thought[8] to escape inactivation. It now seems, however, that this gene is susceptible to the normal inactivation process[9]. Therefore, the principle that X-linked genes that escape inactivation are also represented on the Y chromosome is preserved, and X–Y pairing in male meiosis deserves consideration as a possible mechanism.

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Chitin and nodulation

SIR — In the yeast *Saccharomyces cerevisiae*, the *CSD2* gene is required for chitin synthase III activity and for synthesis of 90% of the cellular chitin[1]. A FASTA search of the TRANSGEN protein database using the deduced amino-acid sequence of *CSD2* reveals significant similarities to chitin synthases, as expected, to *nodC* proteins from several species of *Rhizobium* bacteria (initn=280 for *R. meliloti*[2]), and to the DG42 protein of the amphibian *Xenopus laevis*[3] (initn=173). DIAGON comparisons of each of these proteins to the *CSD2* protein identify a common region of ~180 amino acids.

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DG42   SVDYVQ-VCD SDTKLDELAT VEMVKVLESN DMYGAVGGDV RILNPYDSF- ----ISFMSS
nodC   SGDLVL-NVD SDSTIAFDVV SKL-ASKMRD PEVGAVMGQL TASNSGDTW- ----LTKLID
CSD2   FYETVL-MVD ADTKVFPDAL THMVAEMVKD PLIMGLCGET KIANKAQSW- ----VTAIQV
CHS2   LQPTVVTLVD VGTRLNNTAI YRLWKVFDMD SNVAGAAGQI KTMKGKWGLK LFNPLVASQN

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DG42   LRYWMAFNVE RACQSYFDCV SCISGPLGMY RNN------- ------ILQV FLEAWYRQKF
nodC   MEYWLACNEE RAAQSRFGAV MCCCGPCAMY RRS------- ------ALAS LLDQYETQLF
CSD2   FEYYISHHQA KAFESVFGSV TCLPGCFSMY RIKSPKGSDG YWVPVLANPD IVERYSDNVT
CHS2   FEYKISNILD KPLESVFGYI SVLPGALSAY RYRALKNHED GTGPL--RSY FLGETQEGRD

          .   .  *****·*·  *·**  ·· · ··**··*   * ·*·  ·  *·*··** ·*
DG42   LGTYCT---- LGDDRHLTNR -VLS--MGYR TKYTHKSRAF SETPSLYLRW LNQQTRWTKS
nodC   RGKPSD---- FGEDRHLTI- LMLK--AGFR TEYVPDAIVA TVVPDTLKPY LRQQLRWARS
CSD2   NTLHKKNLLL LGEDRFLSS- LMLKTFPKRK QVFVPKAACK TIAPDKFKVL LSQRRRWINS
CHS2   HDVFTAN-MY LAEDRILCWE LVAKRDAKWV LKYVKEATGE TDVPEDVSEF ISQRRRWLNG
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Alignment of the sequences of the *CHS2*, *CSD2* (GenBank accession number M73697) nodC and DG42 proteins. The region displayed exhibits 30% identity between *CHS2* and *CSD2* (11.5 s.d. above random), 32% identity between *CSD2* and *nodC* (6.0 s.d. above random), and 25% identity between *CSD2* and *DG42* (8.2 s.d. above random). The program BESTFIT was used. The marks above the sequences indicate the number of identical amino acids: a dot indicates two, an asterisk three, and a bold asterisk four.

The functions of the *nodC* and DG42 proteins are unknown: *nodC* is required for nodulation in all species of *Rhizobium*[4] and for synthesis of the extracellular nodulation factor, NodRm-1, a sulphated *N*-acyl-tri-*N*-acetyl-β-1,4-D-glucosamine tetrasaccharide[5]. The relationship of this molecule to chitin (poly-*N*-acetyl-β-1,4-D-glucosamine), together with the similarity between the *nodC* and *CSD2* gene products, suggest that *nodC* encodes an *N*-acetylglucosaminyltransferase that synthesizes the oligosaccharide backbone of NodRm-1. The similarity of the *nodC* protein to DG42, a gastrulation-specific protein[3], is noteworthy (FASTA initn=342). Could oligosaccharides like NodRm-1 serve as signals during embryogenesis?

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