DOSAGE COMPENSATION IN HUMAN

Dosage Compensation Prevents Excessive Expression of X-Linked Genes in Mammals

In this section, we will describe research findings regarding X-linked gene expression that demonstrate a genetic mechanism of d**osage compensation that balances the dose of X chromosome gene expression** in females and males.

Barr Bodies

i)A Barr body (named after discoverer Murray Barr) is an inactive X chromosome in a cell with more than one X chromosome, rendered inactive in a process called lyonization, in species with XY sex-determination (including humans).

Murray L. Barr and **Ewart G. Bertram's** experiments with female cats, as well as **Keith Moore** and **Barr's** subsequent study in humans, demonstrate a genetic mechanism in mammals that compensates for X chromosome dosage disparities. **Barr and Bertram** observed a darkly staining body in interphase nerve cells of female cats that was absent in similar cells of males. In humans, this body can be easily demonstrated in female cells derived from the buccal mucosa (cheek cells) or in fibroblasts (undifferentiated connective tissue cells), but not in similar male cells. **(Figure1)**

This highly condensed structure, about 1 mm in diameter, lies against the nuclear envelope of interphase cells. It stains positively in the Feulgen reaction, a cytochemical test for DNA.

ii)**Susumu Ohno** was the first to suggest that the Barr body arises from one of the two X chromosomes. This hypothesis is attractive because it provides a possible mechanism for dosage compensation.

iii)If one of the two X chromosomes is inactive in the cells of females, the dosage of genetic information that can be expressed in males and females will be equivalent.

Example- No Barr body is seen in the somatic cells of Turner 45,X females; one is seen in Klinefelter 47,XXY males; two in 47,XXX females; three in 48,XXXX females; and so on. Therefore, the number of Barr bodies follows an N - 1 rule, where N is the total number of X chromosomes present.

Q.What do you mean by The Lyon Hypothesis ? **Q.Which X-chromosome is inactivated? Is the inactivation random? Is the same chromosome inactive in all somatic cells**?

In mammalian females, one X chromosome is of maternal origin, and the other is of paternal origin. In 1961, **Mary Lyon and Liane Russell** independently proposed a hypothesis that answers these questions.

i)They postulated that the inactivation of X chromosomes occurs randomly in somatic cells at a point early in embryonic development, most likely sometime during the blastocyst stage of development. Once inactivation has occurred, all descendant cells have the same X chromosome inactivated as their initial progenitor cell controlled by an X-linked gene.

Numerous mutant alleles of this gene have been detected, and their gene products can be differentiated from the wild-type enzyme by their migration pattern in an electrophoretic field.)Fibroblasts have been taken from females heterozygous for different allelic forms of **G6PD** and studied.

ii)The Lyon hypothesis predicts that if inactivation of an X chromosome occurs randomly early in development, and thereafter all progeny cells have the same X chromosome inactivated as their progenitor, such a female should show two types of clones, each containing only one electrophoretic form of G6PD, in approximately equal proportions.

iii)The Lyon hypothesis is generally accepted as valid; in fact, the inactivation of an X chromosome into a Barr body is sometimes referred to as **lyonization.**

One extension of the hypothesis is that mammalian females are mosaics for all heterozygous X-linked alleles—some areas of the body express only the maternally derived alleles, and others express only the paternally derived alleles. An especially interesting example involves red-green color blindness, an X-linked recessive disorder. In humans, hemizygous males are fully color-blind in all retinal cells. However, heterozygous females display mosaic retinas, with patches of defective color perception and surrounding areas with normal color perception. In this example, random inactivation of one or the other X chromosome early in the development of heterozygous females has led to these phenotypes.

The Mechanism of Inactivation

i)The least understood aspect of the Lyon hypothesis is the mechanism of X chromosome inactivation.

ii)Either DNA, the attached histone proteins, or both DNA and histone proteins, are chemically modified, **silencing most genes** that are part of that chromosome.

iii)Once silenced, **a memory is created** that keeps the same homolog inactivated following chromosome replications and cell divisions.