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Dosage compensation of the sex chromosomes and autosomes

Christine M. Disteche [a,b,*]

[a] Department of Pathology, School of Medicine, University of Washington, 1959 NE Pacific St. Seattle, WA 98115, USA
[b] Department of Medicine, School of Medicine, University of Washington, 1959 NE Pacific St. Seattle, WA 98115, USA

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ABSTRACT

Males are XY and females are XX in most mammalian species. Other species such as birds have a different sex chromosome make-up: ZZ in males and ZW in females. In both types of organisms one of the sex chromosomes, Y or W, has degenerated due to lack of recombination with its respective homolog X or Z. Since autosomes are present in two copies in diploid organisms the heterogametic sex has become a natural "aneuploid" with haploinsufficiency for X- or Z-linked genes. Specific mechanisms have evolved to restore a balance between critical gene products throughout the genome and between males and females. Some of these mechanisms were co-opted from and/or added to compensatory processes that alleviate autosomal aneuploidy. Surprisingly, several modes of dosage compensation have evolved. In this review we will consider the evidence for dosage compensation and the molecular mechanisms implicated.

Contents

1. Introduction

The adaptive advantages of recombination favor sexual reproduction [1], which is often accompanied by differentiation of sex chromosomes. In mammals, males are XY and females XX, while in birds, males are ZZ and females ZW. These systems evolved because sex is genetically determined [2,3]. Other vertebrates such as reptiles rely on temperature-sensitive systems for sex determination. Muller hypothesized that differentiation of the sex chromosomes would inevitably arise from lack of recombination due to the appearance of a sex-determining gene on the Y or W chromosome [4]. Ohno expanded these ideas by proposing the concept of ancestral sex chromosomes (proto-sex chromosomes) that progressively evolved to the present-day sex chromosomes by degeneration of the Y or W. [5].

Sex chromosomes have evolved independently multiple times: for example, mammalian and avian sex chromosomes derive from different ancestral autosomes. It has been proposed that some chromosomes may be better suited to become sex chromosomes based on their gene content [3,6]. Both Muller and Ohno predicted that sex chromosome divergence would lead to dosage compensation of the natural type of aneuploidy caused by degeneration of one chromosome in the heterogametic sex. Indeed, a variety of dosage compensation mechanisms that regulate the sex chro-

* Corrresponding author at: Departments of Pathology, School of Medicine, University of Washington, 1959 NE Pacific St. Seattle, WA 98115, USA.
E-mail address: cdistech@uw.edu

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mosomes have evolved, resulting in a dazzling array of systems throughout the plant and animal kingdoms. The evolution of vertebrate sex chromosomes and of dosage compensation were recently comprehensively reviewed by us and by others [3,7–9]. In addition, X chromosome inactivation, one of the main form of X regulation in mammals is discussed in detail by others in this issue.

Here, we summarize salient features of dosage compensation of sex-linked and autosomal genes with a focus on molecular mechanisms of dosage regulation. Two major types of sex chromosome dosage compensation, often confounded in the literature, can be recognized; one type balances gene expression throughout the genome by changing the relative expression of X-linked or Z-linked genes versus autosomal genes or vice versa, and the other equalizes sex-linked gene expression between homogametic and heterogametic sexes. The former type of dosage regulation is critical to maintain fitness. Finally, a narrower definition of dosage compensation has been proposed as representing evolutionary adaptive changes in expression of ancestral autosomal genes that evolved into sex-linked genes [10]. Such definition is necessarily based on a restricted number of conserved genes in different species.

Dosage regulation of the sex chromosomes can be viewed as either global, i.e. employing mechanisms that modify most – but not all – genes on an entire chromosome, or local, i.e. acting on individual genes. This distinction is somewhat fluid as the number of dosage-compensated genes on a given sex chromosome varies between tissues, and also depends on methods of analysis. Intuitively, not all genes need to be regulated by either type of dosage compensation mentioned above. Indeed, balanced expression throughout the genome may be critical only for dosage-sensitive genes implicated in protein complexes and functional networks, but may not apply to dosage-insensitive genes unless they are swept in a global regulatory system. Deleterious effects of copy-number changes may be subtle at the individual gene level, but cumulative effects of large chromosomal imbalance are often severe and yet to be fully understood. Conversely, patchy dosage compensation may be advantageous and selected for in terms of sex-specific traits important in male/female conflicts. This is particularly relevant for testis- or ovary-specific genes abundant on the sex chromosomes.

2. Evolutionary differentiation of the sex chromosomes

Dosage compensation of sex-linked genes should be considered in light of sex chromosome evolution. One of the best studied systems in which progressive evolutionary steps have been deciphered is represented by the human sex chromosomes that have evolved for about 300 million years [11–14]. Based on DNA sequence analyses of genes retained on the human sex chromosomes it is apparent that the Y underwent inversions that progressively prevented large regions from undergoing X/Y recombination. This may have been helped by a gradual spread of regions with reduced recombination [15]. Detailed sequence analyses led to the definition of six evolutionary strata on the X chromosome, each containing genes that diverged from their Y paralogs for a similar length of time [13]. Evolutionary strata have also been found in other mammals and in birds [11,14,16].

The Y chromosome in mammals and the W chromosome in birds are gene-poor, having lost many functional genes [17]. It is estimated that the human Y retains about 3% of the genes originally located on the proto-sex chromosomes, whereas the X retains about 98% of genes [14]. Among the X/Y genes retained is a subset of dosage-sensitive genes (see below). The human Y is rich in palindromic duplicated sequences that may help retention of specific Y-linked genes important in male fertility, but also facilitate deletions and gene loss [18]. Such deletions are often associated with male infertility [19,20], in which case they would not be transmitted, thus preserving some integrity of the Y chromosome.

When comparing sex chromosomes in divergent mammalian species such as marsupials (metatherian) it is evident that the eutherian sex chromosomes acquired a large piece of chromosome that is autosomal in marsupials [21]. Graves proposed that successive cycles of addition and attrition have shaped the sex chromosomes [3]. Small regions have also been added or deleted more recently to the eutherian sex chromosomes, reshaping the pseudoautosomal region (PAR) but rarely changing the content of the rest of the X [22,23]. Altogether, the X chromosome in eutherian mammals is highly conserved, probably because it is subjected to complex mechanisms of dosage regulation [5].

3. Specialized gene content of the sex chromosomes

When studying dosage regulation of the sex chromosomes one must consider their gene content. For example, male-biased genes often expressed in testis are abundant on the Y chromosome, a location predicted to be favorable to the accumulation of sexually antagonistic genes with a male benefit [24]. Interestingly, the X chromosome is also highly enriched in male-biased genes [25]. Hemizygosity in males favors the accumulation of male-advantageous mutations at both X and Y locations. In addition to being enriched in male-biased genes the X chromosome is also enriched in female-biased genes expressed in ovary [26]. Of special interest is the accumulation of brain expressed genes on the X chromosome, possibly a by-product of sexual reproduction [27–29].

Some of the male-biased genes located on the sex chromosomes were recently and independently acquired in different clades [30]. The convergent evolution of the bird Z and mammalian X chromosomes, both of which demonstrate massive enrichment in multi-copy genes expressed in testis, shows striking similarities between the two types of heterogametic systems [31]. The mouse Y represents an extreme case of specialization with accumulation of hundreds of copies of fertility genes. In this case, both Y- and X-linked paralogs are amplified, suggesting meiotic driver/suppressor pairs with cycles of amplification in response to interchromosomal X/Y conflict [32].

The mammalian sex chromosomes also carry genes essential for survival of human embryos. Over 95% of 45, X embryos die during development and those that survive are often mosaic for a normal XX or XY line [33]. A subset of highly conserved dosage-sensitive X/Y paralogs with essential functions (see dosage-sensitive genes below) are the main candidates in the context of embryo survival [11,14]. These genes usually escape X inactivation in females and thus are bi-allelically expressed in both sexes [34–36]. Note that even though many of the X/Y paralogs retain apparently similar functions their sequence has in some cases diverged, suggesting that the Y-linked paralog may be acquiring a male-specific function. An early example of concerted divergence between X/Y paralogs and acquisition of X inactivation is represented by the gene pairs ZFX/ZFY and Zfx/Zfy1-2 in human and mouse. In human, which would represent the more primitive condition, both ZFX and ZFY are ubiquitously expressed and ZFX escapes X inactivation, ensuring similar expression between sexes. In mouse, Zfy1-2 have acquired a testis-specific function, while the ubiquitously expressed Zfx is subject to X inactivation [37–39].

The specialized gene content of the sex chromosomes results in phenotypic sex differences manifested in health and disease susceptibility. Specific mouse breeding schemes including the four-core genotype to generate sex-reversed animals have helped sort out the roles of X- and Y-linked genes versus those of sex hormones [40,41]. The complicated dosage regulation of the sex chromosomes, for example escape from X inactivation, may have evolved