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Review

The X factor: X chromosome dosage compensation in the evolutionarily divergent monotremes and marsupials

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ABSTRACT

Marsupials and monotremes represent evolutionarily divergent lineages from the majority of extant mammals which are eutherian, or placental, mammals. Monotremes possess multiple X and Y chromosomes that appear to have arisen independently of eutherian and marsupial sex chromosomes. Dosage compensation of X-linked genes occurs in monotremes on a gene-by-gene basis, rather than through chromosome-wide silencing, as is the case in eutherians and marsupials. Specifically, studies in the platypus have shown that for any given X-linked gene, a specific proportion of nuclei within a cell population will silence one locus, with the percentage of cells undergoing inactivation at that locus being highly gene-specific. Hence, it is perhaps not surprising that the expression level of X-linked genes in female platypus is almost double that in males. This is in contrast to the situation in marsupials where one of the two X chromosomes is inactivated in females by the long non-coding RNA *RSX*, a functional analogue of the eutherian *XIST*. However, marsupial X chromosome inactivation differs from that seen in eutherians in that it is exclusively the paternal X chromosome that is silenced. In addition, marsupials appear to have globally upregulated X-linked gene expression in both sexes, thus balancing their expression levels with those of the autosomes, a process initially proposed by Ohno in 1967 as being a fundamental component of the X chromosome dosage compensation mechanism but which may not have evolved in eutherians.

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1. Introduction

In mammals, sex is determined by heteromorphic sex chromosomes with male heterogamety (XY male, XX female). The sex chromosomes evolved from ancestral autosomes, and in the common therian ancestor of both the placental mammals (eutherians) and marsupials (metatherians), it is estimated that the X and Y chromosomes emerged approximately 181 million years ago, just prior to the divergence of the two lineages [1] (Fig. 1). In contrast, monotremes (prototherians) possess multiple X and Y chromosomes that appear to have arisen independently of, and yet concomitantly with, the therian sex chromosomes around 175 million years ago [1] and which display partial homology to the sex chromosomes of birds [2,3] (Fig. 1). Given that monotremes and ancestral therians evolved their sex chromosomes independently of each other, between 175 and 181 million years ago, the mechanism by which their common mammalian ancestor determined sex, around 200 million years ago, is a fascinating enigma.

A defining feature of the evolution of the sex-determining Y chromosome is its progressive degradation, such that in humans it

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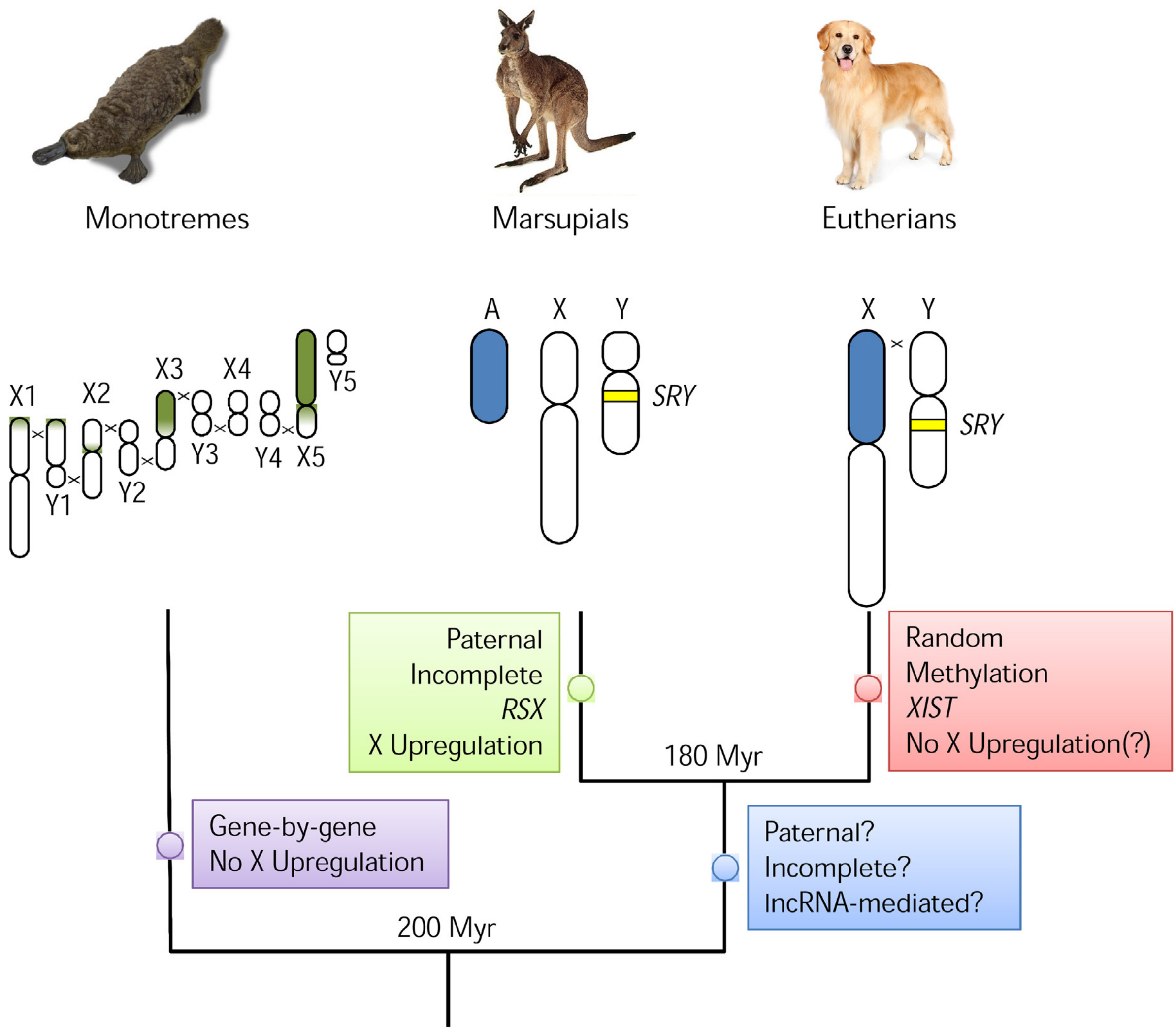

Fig. 1. Evolution of X chromosome inactivation in mammals. Monotremes have a 5X, 5Y sex chromosome system that forms a translocation chain in meiosis (homologous regions are denoted with crossed lines). The X chromosomes contain regions of homology to the bird Z chromosome (green shading). Therians evolved an XY sex chromosome system. In eutherians, the X contains a large added region derived from an autosomal gene in the therian ancestor (blue shading) and that has remained autosomal in marsupials (blue; A). The monotreme lineage (purple box) does not show chromosome-wide X chromosome inactivation (XCI); rather, for each gene, one locus is silenced at a specific frequency within a population of cells. Monotremes show no indication of global X upregulation. XCI evolved in the therian ancestor (blue box) and was likely paternal, incomplete and mediated by a long non-coding RNA (lncRNA). This mechanism of XCI has persisted in marsupials (green box) and is controlled by *RSX* expression. Marsupials display global upregulation of X-linked genes, restoring parity with expression levels of the autosomes. In eutherians (red box), XCI has become random, involves DNA methylation and is controlled by the *XIST* gene. Eutherians appear not to have upregulated the expression of X-linked genes, although the data are still conflicting on this point. (Myr: million years ago).

contains less than 3% of its original gene content [4], in contrast to the X chromosome which has recruited and retained large numbers of genes [5]. A consequence of Y chromosome decay is an imbalance between the expression of X-linked genes in the male (equivalent to a monosomy) and those in the female. Hence, in 1967, Ohno [6] proposed a mechanism whereby a two-fold increase in the expression of X-linked genes in both sexes, followed by an inactivation of one of the X chromosomes in females, would both balance the expression of X-linked genes between males and females in addition to restoring the level of expression of genes on the X chromosome relative to those on the autosomes. While in eutherians the phenomenon of X chromosome inactivation (XCI) has been extensively characterised, studies into Ohno's premise of X chromosome upregulation have yielded data that are conflicting and the results inconclusive [7–14]. Given their evolutionary divergence from eutherians, monotremes and marsupials are well placed to provide insight into the evolution of X chromosome dosage compensation.

2. Monotremes

Monotremes are egg-laying mammals whose extant representatives include two genera of echidna (the Australian species *Tachyglossus aculeatus* and several species of *Zaglossus* that are endemic to Papua New Guinea) and the Australian platypus (*Ornithorhynchus anatinus*). Monotremes diverged from the therian lineage approximately 200 million years ago [1] (Fig. 1) and sequencing of the platypus genome [15] provided genetic evidence in support of the observational suspicion that they are indeed an extraordinary amalgam of ancestral reptilian and derived mammalian traits, perhaps best exemplified by the fact that although young hatch from eggs, they are nourished post-hatching with milk. The female platypus and echidna have five pairs of distinct X chromosomes (X_1–X_5), while male platypus have five X chromosomes (X_1-X_5) and five Y chromosomes (Y_1-Y_5); the male echidna similarly has five X chromosomes (X_1–X_5) but only four Y chromosomes (Y_1–Y_4) due to a fusion of Y_3 and Y_5 [2,16,17]. During meiosis in the male, X and Y chromosomes form an alternating chain