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Minireview

When X-inactivation meets pluripotency: An intimate rendezvous

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ABSTRACT

The integration of X-inactivation with development is a crucial aspect of this classical paradigm of epigenetic regulation. During early female mouse development, X-inactivation reprogramming occurs in pluripotent cells of the inner cell mass of the blastocyst and in pluripotent primordial germ cells. Here we discuss the developmental strategies which ensure the coupling of the regulation of X-inactivation to the acquisition of pluripotency through the regulation of the master of X-inactivation, the non-coding *Xist* gene, by the key factors which support pluripotency Nanog, Oct4 and Sox2.

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1. A historical perspective of X-inactivation regulation during early mouse development

In mammals, the emergence of a Y chromosome virtually entirely devoted to male sex determination has been associated during evolution with the appearance of a dosage compensation mechanism that equalizes the level of X-linked gene expression between XY males and XX females. Mary Lyon proposed, based on cytological and genetic evidence, that to achieve dosage compensation of the X-chromosomes between males and females, one of the two X-chromosomes is inactivated early in female embryogenesis [1,2].

Following Lyon's seminal work, the idea that X-inactivation occurs during cell differentiation became a long-standing concept. The first signs of X-inactivation in the female embryo were thought to appear early in the first tissue to differentiate, the trophoblast, and only later in tissues of the embryo proper [3]. This schema was compatible with data suggesting that in the early blastocyst both X-chromosomes were active in cells of the undifferentiated inner cell mass (ICM) [4], while in the trophectoderm one X-chromosome in each cell was in an inactive state. Two distinct processes characterize X-inactivation: in the extra-embryonic lineages, X-inactivation is imprinted with the paternal X-chromosome always being chosen for inactivation [5], whereas in cells of the embryo proper both X-chromosomes are targeted at random by the inactivation process, through the so-called random X-inactivation. Cellular differentiation therefore appeared to drive X-inactivation either through imprinted or random mechanisms depending on the cell lineage in question. A developmental stem-cell model for X-inactivation was proposed by Monk [6], with X-inactivation occurring, albeit in different forms, at different times and in different cell populations as they differentiate from a pluripotent state. This model was supported by ex vivo X-inactivation studies, initially exploiting the differentiation of female embryonic carcinoma (EC) cells [7], the stem cells of teratocarcinomas, later the differentiation of female embryonic stem (ES) cells [8], the stem cells derived from the ICM. In both ex vivo systems, activity of the two X-chromosomes in the female cell is maintained until cellular differentiation is initiated and random X-inactivation established, highlighting the existence of a close relationship between the regulation of lineage commitment and the establishment of X-inactivation. For over 25 years, the view in the field that prevailed based on such results was that during blastocyst formation, imprinted X-inactivation occurs first in the trophectoderm and, subsequently, in the primitive endoderm, whereas both X-chromosomes remain active in those cells of the ICM that remain pluripotent. A corollary of this view is that at the onset of the multi-lineage differentiation of the epiblast that generates the embryo proper, X-inactivation is established for the first time

Abbreviations: ICM, inner cell mass; TE, trophectoderm; PE, primitive endoderm; EPI, epiblast; PGCs, primordial germ cells; EC, embryonic carcinoma; ES, embryonic stem; iPS, induced pluripotent stem; Xic, X-inactivation center; Xist, X-inactive specific transcript; Tsix, Xist antisense; Xi, inactive X; ChIP, chromatin immunoprecipitation

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and that this random X-inactivation is then stably maintained throughout development and the entire life of the organism, with reactivation of the inactive X occurring exclusively in the female pluripotent germ line [9,10].

Reprogramming experiments further reinforced the idea that X-inactivation is intimately linked to differentiation. Reactivation of the inactive X-chromosome carried by female somatic nuclei has been observed after cell fusion with male EC [11] and ES cells [12], as well as after nuclear transfer into the enucleated egg [13]. Importantly, the recent generation of induced pluripotent stem (iPS) cells by forced expression of ES cell regulators [14] has also been shown to be accompanied by the reactivation of the inactive X-chromosome of female somatic cells [15]. Based on such experiments it appears that X-inactivation is established when the loss of pluripotency occurs and, reciprocally, that X-inactivation is reversed following the acquisition of pluripotency.

The recent discovery that imprinted X-inactivation takes place much earlier than predicted by the stem-cell model demonstrates that the simple association of X-inactivation with cellular differentiation no longer holds. In a clear paradigm shift, three independent articles convincingly argued against the conventional view by demonstrating that X-inactivation initiates several cell divisions prior to the formation of the blastocyst [16,17]. Imprinted X-inactivation, associated with the exclusive inactivation of the paternal X-chromosome, was shown to be implemented in all cells of the cleavage-stage embryo. This initial form of imprinted X-inactivation was shown, however, to be labile and at the blastocyst stage, the paternal X is reactivated in the ICM [16,17]. This results in both X-chromosomes being active in undifferentiated cells of the ICM during a short time-window. Subsequently, random X-inactivation is initiated with either the paternal or the maternal X being chosen for inactivation. In contrast, X-inactivation remains imprinted in extra-embryonic tissues. Therefore, the critical developmental regulation of X-inactivation is based on the reactivation of the paternally-inherited inactive X-chromosome in the ICM, rather than in a simple coupling of the inactivation and differentiation processes. Although it is now clear that imprinted X-inactivation is not per se associated to differentiation, it remains true that random X-inactivation is linked to the differentiation of the epiblast, as illustrated by differentiating female ES cells.

In summary (Fig. 1), during early female mice development, X-inactivation reprogramming occurs in pluripotent cells of the inner cell mass of the blastocyst, when imprinted X-inactivation is replaced by random inactivation, via a transient stage characterized by the presence of two active X-chromosomes. Reactivation of the inactive X also occurs in pluripotent primordial germ cells (PGCs) and is also observed in vitro, during the reprogramming of female somatic cells mediated by nuclear cloning, by fusion with EC and ES cells, and during the generation of iPS cells. Reprogramming of X-inactivation is therefore associated with the acquisition of pluripotency both in vivo and in vitro [18].

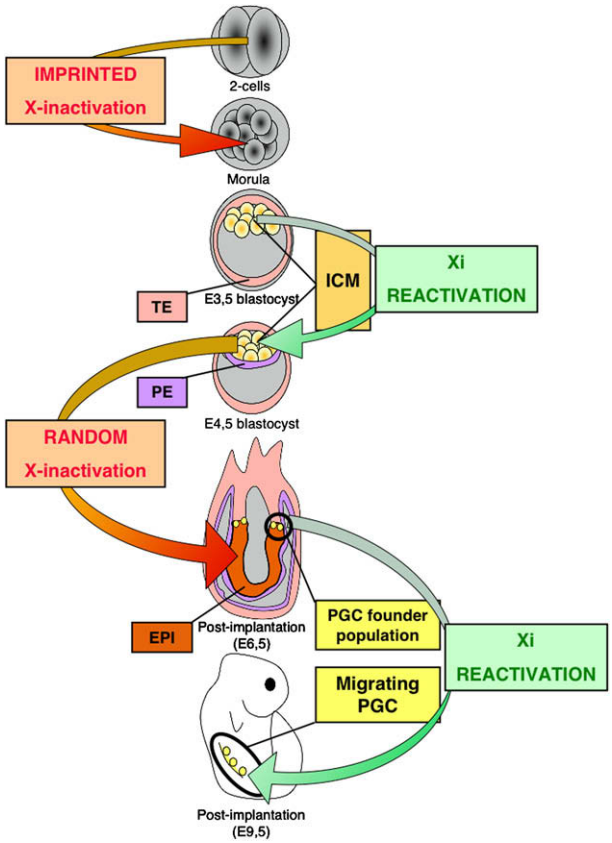

Fig. 1. Developmental dynamics of X-inactivation. Imprinted X-inactivation of the paternal X-chromosome is first established at the 2–4-cell transition of early female embryogenesis. This initial form of X-inactivation is maintained during the cleavage-stages of the morula, as well as during the differentiation of the extraembryonic tissues such as the trophectoderm (TE, in pink) and the primitive endoderm (PE, in purple). The paternal inactive X (Xi) is then reactivated in the pluripotent cells of the inner cell mass (ICM, in light yellow) of the blastocyst which allows the establishment of random X-inactivation in the differentiating epiblast (EPI, in orange). This is the form of X-inactivation that will be maintained in somatic tissues of the post-implantation embryo and in the adult. The randomly chosen Xi is reactivated in migrating pluripotent primordial germ cells (PGC, in yellow).

2. Developmental regulation of *Xist*, the trigger of X-inactivation

The initiation of X-inactivation is controlled by the X-inactivation center (*Xic*), a complex X-linked locus responsible for the inactivation of a single X in female cells and an absence of inactivation in male cells [19]. The *Xist* gene lies within the *Xic* and produces an essential non-coding RNA with the unique property of coating and silencing the X-chromosome in *cis* [20]. Given that only high levels of *Xist* RNA can induce X-inactivation, *Xist* expression has to be tightly regulated in order to ensure the dynamics of X-inactivation during development. In pre-implantation embryos, *Xist* expression is imprinted and high *Xist* RNA levels are exclusively produced from the paternal X-chromosome. Drastic changes in *Xist* expression pattern take place in the ICM, where paternal *Xist* expression is efficiently repressed and this correlates with the reactivation of the paternal X-chromosome [16,17]. At the onset of random X-inactivation, *Xist* is upregulated specifically on the future inactive X, irrespectively of its parental origin. Accordingly, in undifferentiated female ES cells, both X-chromosomes produce low levels of *Xist* RNA. As the cell differentiates, *Xist* is mono-allelically upregulated at random to induce X-inactivation in *cis*, whilst the second *Xist* allele of females and the single *Xist* allele of males are turned off.

The randomly chosen inactive X-chromosome is also reactivated in the female germ line. Similarly to what has been described in the ICM, the initial step of the reversion of X-inactivation appears to be the repression of *Xist* which occurs in migrating PGCs [21,22]. Thus, in the germ line, the repression of *Xist* expression which leads to the reactivation of the inactive X is again correlated with the acquisition of pluripotency.

Two aspects of *Xist* regulation, the levels of *Xist* RNA and its chromosomal-origin, appear to be crucial for the developmental regulation of X-inactivation. In particular, the repression of *Xist* expression that characterizes the reprogramming events which takes place in pluripotent cells appears as a key developmental event in X-inactivation regulation. This notion is further supported

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