Chromatin remodelling proteins and cell fate decisions in mammalian preimplantation development

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Abstract

The very first cell divisions in mammalian embryogenesis produce a ball of cells, each with the potential to form any cell in the developing embryo or placenta. At some point the embryo produces enough cells that some are located on the outside of the embryo, while others are completely surrounded by other cells. It is at this point that cells undergo the very first lineage commitment event: outer cells form the trophectoderm, and lose the potential to form embryonic lineages, while inner cells form the Inner Cell Mass, which retain embryonic potential. Cell identity is defined by gene expression patterns, and gene expression is largely controlled by how the DNA is packaged into chromatin. A number of protein complexes exist which are able to use the energy of ATP to remodel chromatin: that is, to alter the nucleosome topology of chromatin. Here we summarise the evidence that chromatin remodellers play essential roles in the successful completion of preimplantation development in mammals, and describe recent efforts to understand the molecular mechanisms through which chromatin remodellers facilitate the successful completion of the first cell fate decisions in mammalian embryogenesis.

1. Introduction

Within the first five days of mouse development, a single celled zygote progresses, by an ordered series of cleavage divisions and successive differentiation events to the specification of three lineages: trophectoderm (TE), epiblast and primitive endoderm (PrE) within the developing embryo (Rossant and Tam 2009). The TE is the first lineage to become specified and forms the outer epithelial layer which contributes to the placenta and is required for implantation into the uterus (Carson et al. 2000). The inner cells go on to segregate into epiblast or PrE. The epiblast forms the embryo proper while TE and PrE lineages give rise to extra-embryonic structures that support the development of the embryo (Rossant and Tam 2009; Chazaud and Yamanaka 2016). This developmental progression is

highly reproducible and these three lineages are defined by specific gene expression programs which must be carefully established and controlled.

Although this descriptive information about embryo development has been long known, many questions are still unanswered as to exactly how these lineages are formed. A cell's identity is defined by the genes it expresses and those it represses, so to understand cell fate decisions we must understand how gene expression is controlled. Every cell in an organism contains the same genome, and yet there are multiple distinct cell types, all of which exhibit different dynamic gene expression profiles. Therefore, when we consider cell fate choices, we are actually witnessing the re-wiring of these gene regulatory networks (GRN) to create new stable cell types. For this to occur, each cell must respond appropriately to stimuli and ensure the correct expression of specific genes. Understandably, chromatin modifiers and remodellers are key in this context: they facilitate transcription factor and RNA Polymerase II access to those genes required in the new cell state, and prevent aberrant expression of those that are undesirable. Recent evidence indicates that cell signalling creates the environment for appropriate decision-making, while specific changes in gene expression cement a cell fate transition. This model prompts questions such as: How are the signals decoded by the cells at the chromatin level? How are specific genes brought 'into play' by the signalling machinery? Whether a gene is transcribed or silent is largely dependent upon its chromatin environment. In this review, we will focus on the role of chromatin remodellers in forming the required chromatin environment for each cell decision in mammalian preimplantation development.

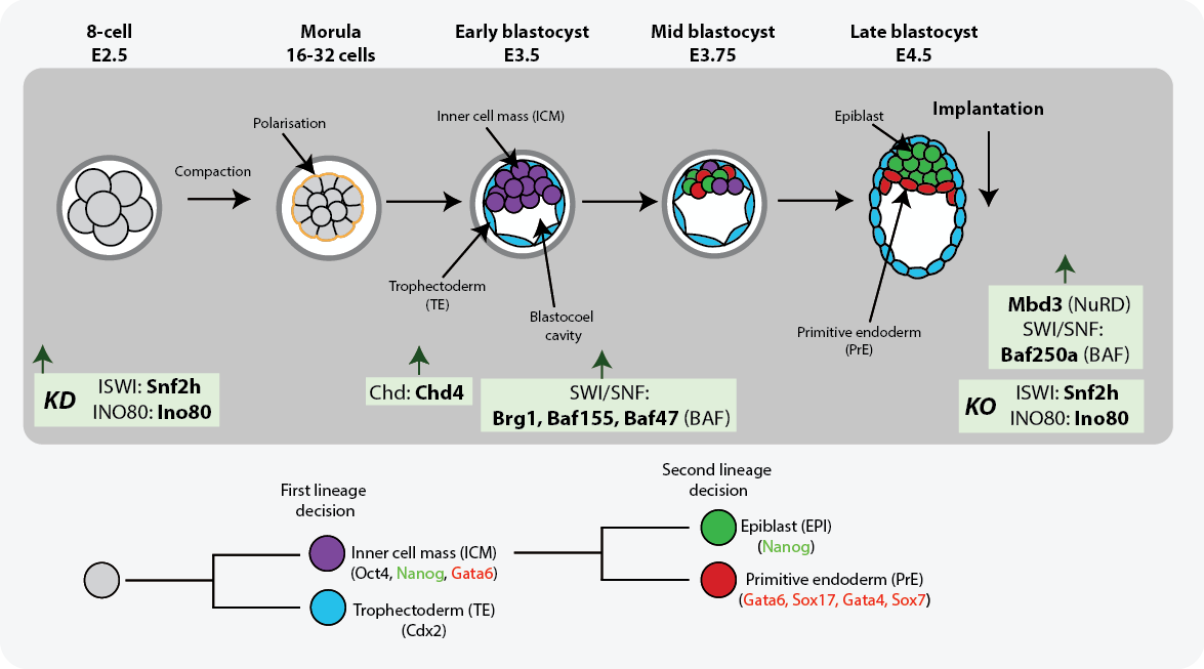

Figure 1 - Diagram to illustrate mouse pre-implantation development and the stages specific chromatin remodellers are required

From the 8-cell stage the blastomeres undergo polarisation and compaction to form a morula. By E3.5 the embryo has cavitated to form a blastocyst and there is a polarised epithelium of cells on the outside of the embryo (trophectoderm) enclosing the ICM. By the mid-blastocyst stage, some cells show up-regulation of epiblast or PrE factors, and this decision is completed by E4.5. Here the ICM cells have segregated into epiblast and PrE cells, and shortly after this point, implantation occurs. Green boxes indicate the stage at which certain chromatin remodellers are required and the family and/or complex to which these proteins belong.

2. Events associated with the first lineage decision: TE vs ICM

Initial rounds of cell division, from fertilisation until approximately the 8-cell stage, result in an increase in cell number without any overall increase in size of the embryo (Aiken et al. 2004). Although the exact time when the first lineage decision begins is a matter of some debate (Piotrowska-Nitsche et al. 2005; Dietrich and Hiiragi 2007; Torres-Padilla et al. 2007; Ralston and Rossant 2008; Dietrich et al. 2015), it is after the 8-cell stage that the first signs of loss of symmetry occur. At the 8 cell stage cell-to-cell adhesion increases and the cells undergo a process called compaction (Johnson and Ziomek 1981). The cells flatten and the embryonic surface becomes smooth. Concomitant with compaction, the cells acquire apical-

basal polarity (Figure 1). This is characterised by the re-organisation of the cytoplasm (Reeve and Kelly 1983; Fleming and Pickering 1985; Maro et al. 1985), the formation of an apical domain (Pauken and Capco 2000; Plusa et al. 2005; Vinot et al. 2005) and the presence of microvilli on the apical domain (Ducibella et al. 1977). Other polarity proteins are also localised basolaterally (Vinot et al. 2005). From this point on outer cells retain these polarised features and go on to form TE, while inner cells (which become ICM) become apolar. During the next two rounds of cell division, blastomeres either divide symmetrically or asymmetrically, passing down either all or part of the apical cytoplasm to their daughter cells.

3. The second lineage decision: Epiblast vs PrE

Once the TE and ICM decisions have been made the embryo has formed a cavitated structure known as the blastocyst, with the TE cells forming an outer layer and ICM cells forming a tight ball to one side of the inside structure (Kunath et al. 2004; Chazaud and Yamanaka 2016). The ICM cells then undergo the second lineage decision: epiblast versus PrE. Whereas cell position plays a large part in TE specification, it seems the reverse is true for PrE: cell fate commitment both precedes and facilitates cell positioning (Rossant and Tam 2009). The PrE cells form an epithelial layer between the epiblast cells and blastocoel cavity (Figure 1). Any presumptive PrE cell not positioned in this layer migrates towards it, switches fate to epiblast or undergoes apoptosis (Plusa et al. 2008). By E4.5, the specification of the PrE is complete, and epiblast and PrE cells show distinct fates (Gardner and Rossant 1979). Finally, following PrE specification, the embryo implants, and progresses to the early egg cylinder stage (E5.5). At this point, the embryo undergoes gastrulation and forms all three primary lineages: definitive endoderm, ectoderm and mesoderm.

4. The role of chromatin modifiers in the formation of the early embryonic lineages

ATP-dependent chromatin remodelling complexes can be divided into four distinct classes based upon the chromatin remodelling subunit, which fall into the SWI/SNF, ISWI, INO80 and CHD families (Hargreaves and Crabtree 2011). Their ATPase subunits use the energy derived from ATP hydrolysis to move, eject or slide nucleosomes along the DNA (Clapier and Cairns 2009).

Studies of these remodelling proteins *in vitro* have provided clear pictures of how these proteins function biochemically. Connecting these biochemical activities to the alterations in gene expression and developmental progression seen *in vivo* using genetic mutants has often been difficult. While chromatin remodellers may all appear to possess similar biochemical activities, each complex clearly controls distinct aspects of chromatin biology.

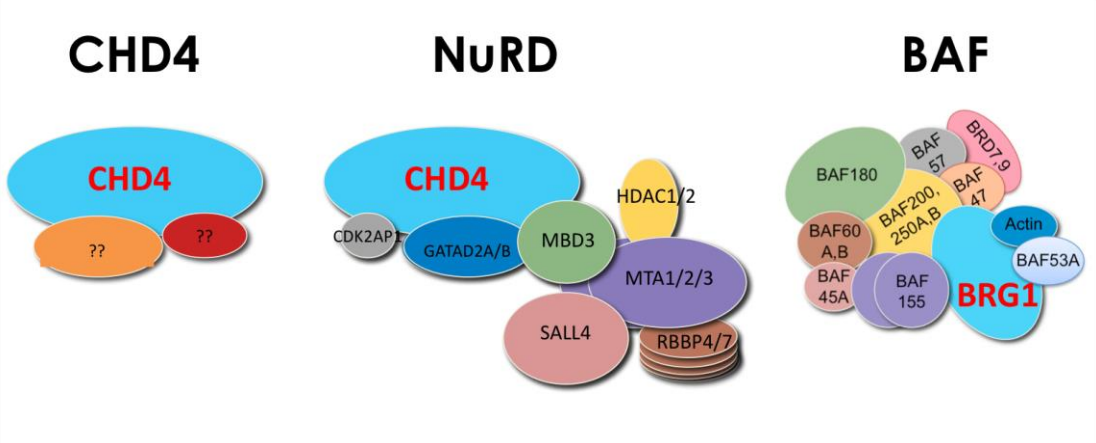

Figure 2. CHD4, NuRD and BAF Complexes. *Protein components of the NuRD and esBAF complexes. Whether CHD4 associates with other proteins when it is not part of NuRD is not known. The component of the BAF complex shown correspond to the ES-cell specific complex, esBAF (Hargreaves and Crabtree 2011).*

5. CHD4: A precise subtle regulator of fate

CHD4 is a founding member of the NuRD (Nucleosome Remodelling and Deacetylation) complex (Figure 2). The NuRD complex regulates transcription and has long been assumed

to be a transcriptional repressor, in part due to the presence of histone deacetylase (HDAC) proteins within the complex. While NuRD certainly is capable of mediating transcriptional repression (Ahringer 2000; McDonel et al. 2009), the advent of genome-wide analyses has led to the realisation that CHD4 and NuRD are just as likely to be associated with transcriptional activation (Gunther et al. 2013; Reynolds et al. 2013; Shimbo et al. 2013; Kim et al. 2014) . As well as containing a chromatin remodelling protein (either CHD4 or CHD3) and HDAC proteins (HDAC1/2), NuRD contains zinc-finger proteins GATAD2A/B, SANT domain proteins MTA1/2/3, histone chaperones RBBP4/7, structural proteins MBD2/3 and the small CDK2AP1 protein (Le Guezennec et al. 2006; Allen et al. 2013). Although CHD4 is the founding member of the complex (Tong et al. 1998; Wade et al. 1998; Xue et al. 1998; Zhang et al. 1998), there is accumulating evidence that CHD4 can also function independently of the NuRD complex (O'Shaughnessy and Hendrich 2013).

CHD4 function is critical for the first lineage decision in mouse pre-implantation development. Although embryos lacking CHD4 form a morphologically normal blastocyst, they are unable to form functional TE (O'Shaughnessy-Kirwan et al. 2015). Single cell gene expression analysis was used to show that CHD4 is required for embryos to establish exclusive lineage-appropriate gene expression programmes at the 16-cell stage, before the formation of the morphological blastocyst. Cells of 16-cell embryos express markers of PrE, TE and epiblast in a stochastic manner, in a process that resembles lineage priming (Enver et al. 2009). In the absence of CHD4, these cells express lineage markers at increased frequency. The consequence of this increased transcriptional ‘noise’ is that cells are unable to accurately specify the TE lineage, and, despite forming an embryo that resembles a blastocyst, they lack trophectoderm function in that they are unable to maintain the integrity of the blastocoel or to implant *in vivo* or *ex vivo* (O'Shaughnessy-Kirwan et al. 2015). The activity of CHD4 in restricting gene expression probability, rather than gene expression levels per se, is thus essential for successful completion of the first lineage decision.

Although CHD4 binds broadly to active chromatin, this study did not find global dysregulation of gene expression in *Chd4*-mutant blastocysts (O'Shaughnessy-Kirwan et al. 2015). Instead, the essential function of CHD4 in the developing embryo is focused on lineage specific genes. This work highlights two important points; that the essential targets of a chromatin remodeller may vary depending on the tissue and/or developmental stage, and that while the developing embryo is fairly robust, only small changes in gene expression can be enough to culminate in developmental failure. It remains to be seen whether this function of CHD4 is specific to the TE lineage, or whether CHD4 function similarly controls the PrE vs epiblast lineage decision.

Surprisingly this function of CHD4 was exerted independently of the NuRD complex (O'Shaughnessy-Kirwan et al. 2015), indicating that despite the majority of chromatin remodelling proteins forming multi-protein complexes, their role isn't necessarily restricted to that within complexes. Impairment of NuRD activity through deletion of the gene encoding MBD3, an important NuRD structural component, results in developmental failure of the epiblast (Kaji et al. 2007). These observations lead to a model in which CHD4 functions on its own to facilitate the first lineage decision, it subsequently functions as part of NuRD to enable the development of epiblast cells during implantation (Kaji et al. 2007). This raises the interesting question of whether the biochemical activity of CHD4 is somehow altered when it is incorporated into NuRD, or alternately whether NuRD acts to target CHD4 activity to specific sites in vivo.

6. BRG1/BAF chromatin remodellers

BAF complexes, which belong to the SWI/SNF family of remodellers, are large polymorphic complexes that contain at least 15 different subunits, the precise composition of which is cell type-specific (Ho and Crabtree 2010; Kadoch and Crabtree 2015) (Figure 2). Loss of many of the BAF complex subunits are incompatible with successful completion of early mammalian development, often resulting in pre- or peri-implantation lethality (Hota and

Bruneau 2016). Loss of either the ATPase subunit (BRG1/SMARCA4), or of two other major components (BAF47 and BAF155) in embryos results in similar phenotypes: embryos develop to the blastocyst stage but fail to progress further. Neither trophectoderm nor ICM outgrowths are viable in these mutants indicating that BAF function is essential for the continued proliferation of both lineages *ex vivo* (Bultman et al. 2000; Klochendler-Yeivin et al. 2000; Guidi et al. 2001; Kim et al. 2001; Kidder et al. 2009; Panamarova et al. 2016). Loss of the BAF250A subunit results in developmental arrest later in development, shortly after implantation (Gao et al. 2008).

Although the ES cell-specific BAF complex has been extensively studied (Ho et al. 2009a; Ho et al. 2009b; Ho et al. 2011) and the requirement for various BAF complexes in embryo viability are well known, the essential molecular mechanisms though which BAF activity sustains viability in the early mouse embryo are less well characterised. While initial work showed that zygotic deletion of *SMARCA4* resulted in a peri-implantation lethality, it was not clear how development failed in these mutants (Bultman et al. 2000). The fact that null blastocysts were morphologically normal at embryonic day 3.5 and were able to attach to plastic substrate (after removal of the zona pellucida) was an indication that the TE-ICM decision may not require zygotic BRG1 activity. Knockdown of *SMARCA4* in zygotes, which would deplete both maternally-supplied and zygotic mRNA, did not prevent formation of a morphological blastocyst, however antibody staining indicated evidence for specification defects in trophectoderm. Specifically, TE cells were found to inappropriately express OCT4 and NANOG, two proteins which should only be expressed in epiblast cells (Wang et al. 2010; Carey et al. 2015). While BRG1 and CHD4 appear to exert opposing effects on chromatin accessibility (Morris et al. 2014; de Dieuleveult et al. 2016), it appears that both activities are necessary for complete silencing of epiblast lineage genes during TE specification, and/or for maintaining the silent state of these genes.

More recent work has demonstrated that the BAF155 subunit is essential for accurate lineage specification in early mouse embryos (Panamarova et al. 2016). This study found that loss of BAF155 resulted in ectopic expression of the epiblast marker NANOG in the TE, while increased *BAF155* expression resulted in upregulated expression of differentiation genes *CDX2* and *SOX17*. This study further showed that BAF155 acted to control the levels of stable BAF complex formation, and that extra-embryonic lineages showed increased complex formation or stability compared to embryonic lineages (Panamarova et al. 2016). This study raises the possibility that quantitative changes in the abundance or stability of chromatin remodellers could be play an important role in cell fate transitions.

7. INO80 and ISWI chromatin remodellers

Two more chromatin remodelling ATPase proteins that have been implicated in early embryonic development are the INO80 DNA helicase and the SNF2H (SMARCA5) ATPase (Lazzaro and Picketts 2001; Bao and Shen 2007; Gerhold and Gasser 2014), although what their functions might be in preimplantation development are not yet clear. Knockdown of *INO80* in zygotes severely impaired blastocyst formation after in vitro culture (Wang et al. 2014), but zygotic deletion of *INO80* had no detrimental effects until gastrulation, with zygotic *INO80*-null blastocysts appear morphologically normal and appropriately express markers of epiblast and PrE (Lee et al. 2014; Qiu et al. 2016). These observations indicate either that maternally-contributed INO80 plays an essential role in early cleavage stages, or that the embryo is able to compensate for a genetic deficiency, but cannot similarly compensate for a knockdown (Rossi et al. 2015). Similarly, a large proportion of zygotes injected with siRNA against *SMARCA5* displayed developmental failure prior to reaching the blastocysts stage (Torres-Padilla and Zernicka-Goetz 2006), whereas embryos homozygous null for *SMARCA5* showed no defects prior to implantation (Stopka and Skoultchi 2003). *SMARCA5* knockdown embryos showed reduced expression of a number of genes, indicating that the observed embryonic lethality is indeed due to changes in gene expression (Torres-Padilla and Zernicka-Goetz 2006). These studies demonstrate that in contrast to BRG1 and CHD4,

neither zygotic INO80 nor zygotic SNF2H are necessary for successful completion of the first cell fate decisions or for implantation. Rather, protein derived from maternally-supplied mRNA from both *INO80* and *SMARCA5* is essential for viability of early cleavage stage embryos.

8. Concluding remarks

Chromatin remodelling proteins play key roles in ensuring cell fate decisions occur correctly throughout mammalian development. While CHD4 and BAF proteins are essential for the first cell fate decision, zygotic SNF2H and INO80 are required only after implantation. In contrast, while maternally-derived BRG1 is dispensable for the viability of cleavage stage embryos, both INO80 and SNF2H made from maternally-deposited mRNA play essential roles. This simple relationship illustrates the separation of function that exists between these very different chromatin remodelling proteins.

Until recently genetics was the only concrete method of determining whether a specific chromatin remodeller was necessary during preimplantation development, but this provided little mechanistic information, if any. The recent explosion in the abundance of single cell analysis methods allows us to better understand how cell fate decisions are made, and to determine why, at the molecular level, specific proteins are necessary for cell fate decisions (Nimmo et al. 2015). Such work has demonstrated that both CHD4 and the BAF complex are indispensable for ensuring that only the appropriate gene expression programme is active in cells undergoing the ICM vs TE cell fate decision, and that complex abundance or stability could be an important factor in successful completion of the first cell fate decision. As the limits of molecular analyses continue to recede, so the molecular details of exactly how each remodeller exerts its functions in early embryos will come into increasingly sharper focus.

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