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Epigenetics
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/kepi20

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Published online: 01 Jan 2010.

To cite this article: Myriam Hemberger (2010) Genetic-epigenetic intersection in trophoblast differentiation: Implications for extraembryonic tissue function, Epigenetics, 5:1, 24-29, DOI: 10.4161/epi.5.1.10589

To link to this article: http://dx.doi.org/10.4161/epi.5.1.10589

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Epigenetics 5:1, 24-29; January 1, 2010; © 2010 Landes Bioscience

Genetic-epigenetic intersection in trophoblast differentiation

Implications for extraembryonic tissue function

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Recent years have seen considerable advances in our understanding of early mammalian development leading up to the establishment of the first cell lineages, with important implications for the behavior of stem cells derived from the early embryo. Dramatic new insights have also propelled the field of epigenetics with the identification of 5-hydroxymethylcytosine as an additional base modification and the pervasiveness of asymmetrical non-CG DNA methylation specifically in ES cells. Prompted by our findings on the role of DNA methylation in cell lineage commitment, this review highlights recent insights into the genetic-epigenetic intersection in the establishment of the placental trophoblast lineage that is essential for embryo implantation, nutrition and survival. The unique trophoblast epigenotype is instrumental for normal trophoblast differentiation and placental function, and consequently trophoblast is particularly susceptible to regrogramming failures.

Key words: cell lineages, DNA methylation, early development, placenta, reprogramming, stem cells, trophoblast

Abbreviations: ES cells, embryonic stem cells; TS cells, trophoblast stem cells; LTR, long terminal repeats

Submitted: 11/09/09

Accepted: 11/09/09

Previously published online: www.landesbioscience.com/journals/epigenetics/article/10589

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The Importance of Trophoblast Differentiation for Early Mammalian Development

The first differentiation event in mammalian development gives rise to two distinct cell populations of the early blastocyst, the outer trophectoderm that gives rise to all trophoblast subtypes of the later placenta and the inner cell mass that will form the embryo proper. The instructions imposed during this process are instrumental for the behavior of stem cells derived from the early embryo, namely embryonic (ES) and trophoblast (TS) stem cells.[1,2] Specification of the first cell lineages occurs in a tight interplay between genetic and epigenetic factors, cell position and polarization events as well as cellular signalling cascades.[3] With regards to extraembryonic development, insights from mouse mutants have established a hierarchical network of transcription factors that are required for the specification of the trophoblast lineage (**Fig. 1**). Currently on top of the trophoblast differentiation cascade is the TEA domain transcription factor TEAD4, that is required, directly or indirectly, to activate the caudal-type homeodomain transcription factor *Cdx2*.[4-7] Although the TEAD4-CDX2 axis is a major pathway in trophoblast differentiation, *Cdx2* cannot fully substitute for *Tead4* in the trophoblast lineage, suggesting the involvement of other, *Cdx2*-independent factors.[6] One such factor may be GATA3 that can also directly activate *Cdx2*.[8,9] CDX2 in turn is required for expression of the T-box gene *Eomes* that is equally necessary for normal specification and proliferation of the trophoblast lineage.[10,11] Other transcription factors such as TCFAP2C, ETS2, ELF5 and ESRRB may further regulate this cascade and act in parallel or slightly downstream pathways to correctly define the trophoblast compartment.[12-16]

A compelling phenomenon in early development is the scenario of mutually interacting transcription factors with antagonizing function, most notably CDX2 and OCT4.[17] This principle demonstrates that it is not absolute presence or absence of lineage-specific factors, but the relative abundance of transcription factors

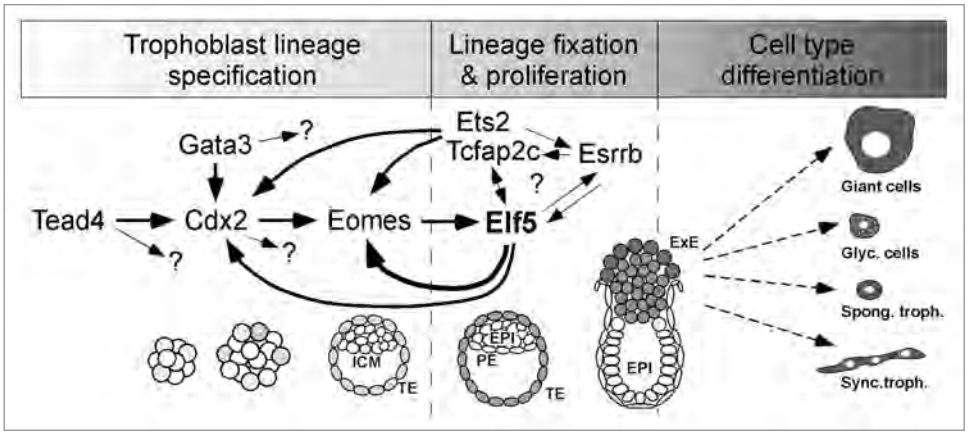

Figure 1. Schematic diagram of the hierarchical transcription factor network that is critical for specification, commitment and maintenance of the trophoblast lineage. Increasing gray shade levels indicate loss of cellular plasticity and progression towards terminal differentiation. Question marks indicate the presence of other, yet unknown target factors (e.g., for Tead4, Cdx2 and Gata3) and the possible crosstalk of transcription factors in the trophectoderm and extraembryonic ectoderm to promote trophoblast proliferation and onset of differentiation. Note that epigenetic fixation of lineage fate occurs at the late blastocyst stage through DNA methylation of *Elf5* (bold). Differentiation into main trophoblast cell types (giant cells, glycogen cells, spongiotrophoblast, syncytiotrophoblast) is indicated. ICM, inner cell mass; TE, trophectoderm; EPI, epiblast; PE, primitive endoderm; ExE, extraembryonic ectoderm.

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in proportion to each other that ultimately leads to the establishment of the embryonic and trophoblast cell lineage at the blastocyst stage.[18] An important implication of this finding is that the function of individual transcription factors may change depending on their relative expression level, and this may lead to differing roles in distinct cell types and compartments.

Epigenetic Regulation of Cell Lineage Differentiation

It is interesting to consider at what stage in development the epigenetic state of a cell affects its developmental potency. The relative distribution of some histone modifications varies between individual blastomeres already at the 4-cell stage and can predispose or bias a blastomere towards its future lineage fate.[3,19] Arguably the most important role of epigenetic modifications, however, is to ensure the stable maintenance of cell lineage fate once the lineages have been established. This epigenetic fixation of cell lineage fate occurs at the late blastocyst stage, coinciding perfectly with the loss of developmental plasticity and lineage cross-over that is observed at this time.[20,21] A major epigenetic barrier between the embryonic and trophoblast lineages is established by DNA methylation of the transcription factor *Elf5*.[21] *Elf5* is hypomethylated and expressed in the trophoblast compartment where it forms a positive feedback loop with CDX2 and EOMES to reinforce trophoblast fate and TS cell proliferation. By contrast, *Elf5* is methylated and stably repressed in the embryonic lineage from the late blastocyst stage onwards thereby aborting trophoblast differentiation within cells of the embryo proper. This epigenetic regulation of *Elf5* provides a molecular mechanism for the canalization of developmental pathways that was famously suggested by C.H. Waddington.[22]

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Promoter-Specific versus Global DNA Methylation Levels

The differential DNA methylation pattern of the *Elf5* locus reflects the global epigenetic asymmetry between the embryonic and trophoblast lineage. Thus the trophectoderm is relatively hypomethylated compared to the inner cell mass at the blastocyst stage and this methylation difference persists into later development in the placenta and embryo proper.[23-26] However, recent whole-genome approaches have revealed that gene promoters on the whole escape this global hypomethylation and exhibit similar, or even higher, DNA methylation levels in TS cells compared to ES cells.[27] This is the case, for example, for the embryo-specific genes *Oct4/Pou5f1* and *Nanog* that become methylated and repressed in the trophoblast lineage, thus exhibiting a methylation pattern reciprocal to that on the global level.[28,29] The *Elf5* methylation pattern (that follows the global trend) therefore represents a rare exception to the overall behavior of gene promoters pointing to the importance of the irreversibility of *Elf5* repression in early development. These data indicate that the epigenetic asymmetry observed between the embryonic and trophoblast lineage on the global level is due, in large, to DNA methylation differences in intergenic regions, repeat sequence families and satellite repeats which comprise centromeric heterochromatin.

DNA Methylation Patterns may Relate to the Self-Renewing State of Stem Cells

DNA methylation mostly affects CG dinucleotides in a symmetrical manner. Reflecting the importance of this sequence context, CGs are globally underrepresented but specifically enriched at gene promoters. Methylation of the cytosine base in other sequence contexts has not been investigated in much detail in mammals, although non-symmetrical CHG and CHH methylation is a prevalent and well-studied occurrence in plants. Results from recent deep-sequencing

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approaches of bisulfite treated genomic DNA (bisulfite-seq) from human ES cells and fibroblasts, however, trigger a reevaluation of the significance of asymmetrical non-CG DNA methylation in mammals.[30,31] Corroborating previous reports that identified the occurrence of CHG and CHH methylation in mouse ES cells but not somatic tissues, the unbiased detection of methylated cytosine residues genome-wide identified around 25% of non-CG methylation specifically in ES cells and in induced pluripotent stem (iPS) cells, whereas methylation in fibroblasts was almost exclusively confined to the CG context.[30] Overall, CHG and CHH methylation is specifically enriched on the antisense strand of gene bodies but is excluded from interaction sites with transcription factors such as the pluripotency factors NANOG, KLF4, SOX2 and OCT4 in human ES cells. These insights shed new light onto the potential role of non-CG methylation in ES cells where it may regulate the accessibility of transcription factor binding sites and may therefore determine the activity of the stem cell-specific transcriptional network.

This—in its extent is rather surprising—prevalence of non-CG methylation in ES cells indicates the potential importance of asymmetrical methylation for the pluripotent state and self-renewal of stem cells. It also emphasizes that the regulation of DNA methylation in mammals may be more similar to that in plants than previously appreciated. This similarity may allow us to translate some aspects of the well-studied mechanisms of DNA methylation in plants to the early mammalian embryo.

DNA Methylation Types and Patterns—Lessons from the Plant

The apparent specificity of asymmetrical non-CG methylation to the ES cell epigenome in both mice and humans raises the obvious question whether this type of methylation is an important feature of the stem cell state per se and whether it also occurs in other types of stem cells such as those representative of the trophoblast lineage. This is where we may borrow from lessons learned from insights into the plant epigenome. Reproduction in flowering plants requires a structure analogous to trophoblast cells and the placenta in mammals, the endosperm, that is equally adapted to nourish the embryo during early development. Like the placenta, the endosperm is characterized by global hypomethylation. Recent extensive bisulfite-seq data have revealed that this epigenetic asymmetry extends to all types of methylation, i.e., CG as well as CHG and CHH methylation.[32] Reduced DNA methylation levels of the maternal endosperm have been implicated in the allele-specific expression of imprinted genes in plants. However, the genome-wide methylome analysis in Arabidopsis shows that demethylation is a rather universal process not restricted to imprinted genes but affects the entire endosperm genome.[32]

From these data it is tempting to speculate that CHG and CHH methylation may also be globally reduced in trophoblast cells, similar to the situation in endosperm. It remains to be seen whether these types of methylation retain their enrichment at open reading frames as seen in ES cells and possibly mark alternative exons of lineage-specific transcript isoforms. It will be equally interesting to see whether the ES cell-specific methylome will be reset to a trophoblast-specific pattern when ES cells are induced to transdifferentiate, for example by downregulation of OCT4 or overexpression of CDX2.[17,33]

DNA Hypomethylation as a Requirement for Trophoblast Differentiation

What is the reason for global hypomethylation of the extraembryonic compartment in both plants and mammals? Here again, we may be able to learn from the plant world. In plants, CHH and to a lesser extent CHG methylation are important for silencing of repeats and transposable elements, mediated through active targeting by the RNA interference (RNAi) machinery.[34] Establishment of imprinting by demethylation of the maternal endosperm thus comes at the cost of general activation of transposons in the endosperm. It is possible that this is an acceptable, low-risk side effect because the endosperm genome is not transmitted to the next generation. An alternative possibility is, however, that transposon activation and RNAi accumulation is the original selective driving force of global demethylation (and that, vice versa, imprinting is an evolutionary bystander) since siRNA transport from the central cell (the precursor of the endosperm) into the egg cell might contribute to enhanced methylation and silencing of transposable elements in the embryo proper.[35]

Whether or not similar transport mechanisms for small RNA species exist between trophoblast tissues and the mammalian embryo remains to be seen. It is clear, however, that a co-evolution between imprinting and transposable element activation has also taken place in the placenta. In contrast to the situation in plants, genomic imprinting in mammals arises from the specific setting of DNA methylation marks in the germ line.[36] Imprinting is certainly a prevalent phenomenon in the placenta as the majority of all known imprinted genes are expressed in this organ and several genes are imprinted in the placenta in a tissue-specific manner.[37,38] At the same time, a hypomethylated trophoblast epigenome is essential for normal placentation. Hypomethylation leads to the placenta-restricted activation of endogenous retroviruses, and retrovirally-derived sequences play a particularly important role in placental development. Long terminal repeat (LTR) sequences, for example, can serve as enhancers and promoters to drive placenta-specific expression of neighbouring genes or to create placenta-specific transcript isoforms.[39,40] In addition, several retrotransposon-related sequences such as the imprinted genes *Peg10* and *Peg11/Rtl1* are essential for trophoblast differentiation and formation of a functional nutrient exchange surface.[41,42] Perhaps the most striking example for the cooption of retroviral elements in placental development are the Syncytins. Syncytins are endogenous retrovirus envelope proteins that are crucial for the differentiation of syncytiotrophoblast cells, a cell type that forms the placental exchange interface.[39,43,44] More specifically even, the two syncytiotrophoblast layers that separate fetal and maternal blood circulations in the mouse each rely on a specific Syncytin

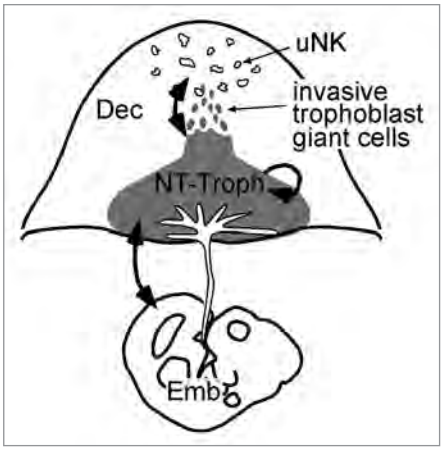

Figure 2. Possible sites of defects in nuclear transfer (NT)-derived conceptuses as indicated by bold arrows. Certain aspects of placental abnormalities are intrinsic to NT trophoblast. Tetraploid complentation assays revealed placenta-embryonic interactions as an important component of placentomegaly. NT conceptuses also evoke an abnormal feto-maternal communication that may contribute to the etiology of placentomegaly. In the mouse, the most likely site of interaction is between invasive trophoblast giant cells and uterine natural killer cells (uNK) that recognize trophoblast antigens that may be mis-expressed due to insufficient epigenetic reprogramming of the trophoblast compartment. Dec, decidua; uNK, uterine natural killer cells; NT-Troph, nuclear transfer-derived trophoblast; Emb, embryo.

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gene, thereby providing an explanation for how the two layers of syncytiotrophoblast cells can form in intimate proximity yet remain distinct.[45] Syncytins as well as retroviral LTR elements are regulated by DNA methylation and are hypomethylated in trophoblast where they are active.[46,47] At present it is not clear whether these retrovirally-derived sequences have been coopted into a placental function due to low methylation levels in trophoblast tissues or whether they are the driving force for placental hypomethylation.

Trophoblast hypomethylation may have also been selected for because the reduced genomic stability (and associated loss of proliferative capacity) that results from hypomethylation of pericentromeric heterochromatin may help to protect the mother from invasive, pro-angiogenic trophoblast cells that represent a liability to tumour formation.[48] In support of this argument, continued demethylation promotes differentiation of TS cells into the invasive trophoblast subtype and is associated with increasing degrees of polyploidization.[21] These examples provide interesting sources for comparison and speculation as to the reasons of placental hypomethylation. The characterization of the trophoblast methylome will provide important insights into these mechanisms and allow a closer analysis of similar and discrepant roles of DNA methylation in the plant endosperm and the mammalian placenta.

Trophoblast Differentiation upon Reprogramming by Nuclear Transfer

The highly specialized epigenetic environment required for trophoblast differentiation is a possible reason for the placental defects observed in conceptuses derived by nuclear transfer (NT) that are generally associated with placentomegaly.[49] In the mouse, these placental abnormalities become mostly obvious in the second half of gestation and are characterized by the enlargement of one specific placental layer, the spongiotrophoblast, and the overabundance of so-called glycogen cells.[50,51]

The extent to which an insufficient reprogramming of trophoblast cells contributes to these placental abnormalities has gained a substantial amount of attention recently. TS cell lines can be successfully derived from NT blastocysts at normal or even increased frequency compared to fertilized embryos.[52,53] Moreover, one study finds that these NT-TS cells grow faster and exhibit a decreased growth factor dependence than control TS cell lines which may account, at least in part, for the observed placentomegaly of NT conceptuses.[53] However, individual cells of NT blastocysts exhibit a greater epigenetic heterogeneity than normal fertilized embryos.[24,54] Therefore, the stem cell potential of NT embryos does not exclude the possibility that a proportion of insufficiently reprogrammed trophoblast cells causes trophoblast and placental defects (**Fig. 2**). Such an increased epigenetic heterogeneity may indeed be reflected by the higher rate of aneuploidies that has been reported for both NT-derived ES and TS cells.[52,55]

Important insights into the origins of placental defects of NT conceptuses have also been gained from reciprocal complementation assays with tetraploid embryos.[56,57] In this constellation the tetraploid cell population contributes preferentially to the trophoblast compartment but is generally excluded from the embryo proper.[58] These experiments suggested that the later-onset placentomegaly phenotype may be a non-cell autonomous defect that originates mostly in the embryo proper thus pointing towards an altered signalling from the NT embryonic compartment to the extraembryonic tissues as the cause of placental overgrowth (**Fig. 2**).[59]

In addition, an important contribution to the defects of NT conceptuses stems from the failure of the NT conceptus to engage in normal interactions with its maternal uterine environment (**Fig. 2**). NT and fertilized embryos elicit distinct transcriptional responses in the endometrium.[60,61] A main route of endometrial sensing of an embryo is through immune recognition of foreign paternal antigens expressed on the surface of embryo-derived cells. Indeed an antigenic dissimilarity between mother and fetus causes a size increase of the placenta, not dissimilar to that observed in NT pregnancies.[62,63] Trophoblast is specifically adapted to its role at the feto-maternal interface by expressing a unique repertoire of non-classical surface antigens that may serve to evade maternal immune rejection.[64] Importantly, an immunosuppressive function has also been attributed to some endogenous retrovirus-derived products, in addition to their role in trophoblast differentiation.[39,65] Since trophoblast antigen expression and endogenous retrovirus activity are controlled by DNA methylation, it is well feasible that an inadequate epigenetic reprogramming of trophoblast cells causes the abnormal embryo-maternal communication leading to early post-implantation failure as well as the placentomegaly syndrome of NT conceptuses.[46,66,67]

Perspective

Trophoblast cells are instrumental in mediating implantation, blood supply and nutrition of the embryo and thereby ensure developmental progression and

fetal survival, as well as health in adult life as a result of developmental programming.[68] Unravelling their unique transcriptional and epigenetic requirements,[69] in particular with regard to novel modification patterns such as non-CG DNA methylation as well as the recently identified 5-hydroxymethylcytosine base modification,[70,71] will provide important insights into early developmental processes, reprogramming and evolutionary aspects that underlie the seemingly similar mechanisms of epigenetic gene regulation in the mammalian placenta and plant endosperm.

Acknowledgements

The work in M.H.'s laboratory has been supported by the MRC, BBSRC and the Centre for Trophoblast Research, Cambridge.

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