

# OCT4 and the acquisition of oocyte developmental competence during folliculogenesis

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**ABSTRACT** The role that the transcription factor OCT4 plays during oocyte growth is yet unknown. In this review, we summarise the data on its potential role in the acquisition of oocyte developmental competence in the mouse. These studies describe the presence in MII oocytes and 2-cell embryos of an OCT4 transcriptional network that might be part of the molecular signature of maternal origin on which the inner cell mass and the embryonic stem cell-associated pluripotency is assembled and shaped. The Oct4-gene regulatory network thus provides a connection between eggs, early preimplantation embryos and embryonic stem cells.

**KEY WORDS:** OCT4, oocyte, developmental competence, preimplantation development, pluripotency

## Introduction

The key role played by the transcription factor OCT4 in the maintenance of cell pluripotency is well documented for different cell types, such as primordial germ cells (PGCs), spermatogonia, the blastocyst inner cell mass (ICM) and the epiblast. But also in cell types obtained experimentally, such as embryonal carcinoma cells, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). On the contrary, its presence in the ovary, although reported, remains yet unexplained. Here, we review the data on the presence of OCT4 in the mouse oocyte. Although still scattered, the information obtained thus far indicates a potential role for OCT4 in the acquisition of the oocyte developmental competence and in the establishment of the pluripotency of the ICM.

## OCT4 and pluripotency

During preimplantation development, *de novo* expression of the OCT4 protein is first observed soon after embryonic genome activation, at the 4-8 cell stage, and plays a key role in the establishment of the trophectoderm (TE) and ICM lineages, since down-regulation

of its expression is necessary for TE differentiation (Adjaye *et al.*, 2005; Zernicka-Goetz, 2011). Although heterogeneous levels of expression have been recorded in the different blastomeres throughout preimplantation, its expression level is not predictive of cell lineage patterning (Dietrich *et al.*, 2007). Instead, the analysis of OCT4 kinetic behaviour (i.e., the biological activity of transcription factors in live cells detected by the fluorescence decay after photoactivation assay) demonstrated that blastomeres with lower OCT4 kinetics are more likely to give rise to the pluripotent cells of the ICM (Plachta *et al.*, 2011). Down-regulation of OCT4 in the TE cells is accompanied by the down-regulation in the ICM of CDX2, another key factor in the establishment of the two first cell lineages in the preimplantation embryo (Bruce and Zernicka-Goetz, 2010).

Following implantation, OCT4 is confined to the epiblast and later in development is detected in primordial germ cells (PGCs) (Matsui *et al.*, 1992; Resnik *et al.*, 1992; Goto *et al.*, 1999), in the adult seminiferous epithelium where its presence is confined to type

*Abbreviations used in this paper:* ESC, embryonic stem cell; ICM, inner cell mass; iPSC, induced pluripotent stem cell; NSN, non surrounded nucleolus PGC, primordial germ cell; SN, surrounded nucleolus, TN, transcriptional network.

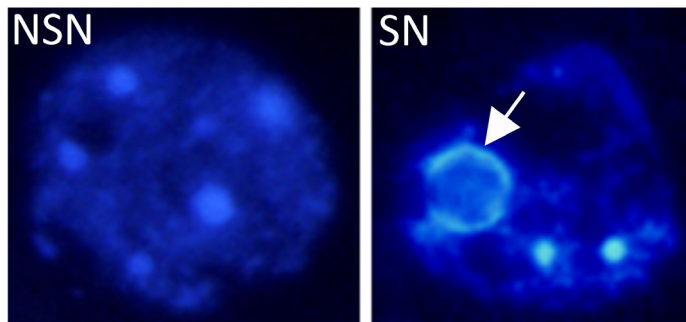
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A spermatogonia (for a review see Dym *et al.*, 2009), in the primordial and in growing oocytes (Pesce *et al.*, 1998; Adjaye *et al.*, 1999; Zuccotti *et al.*, 2008; 2009).

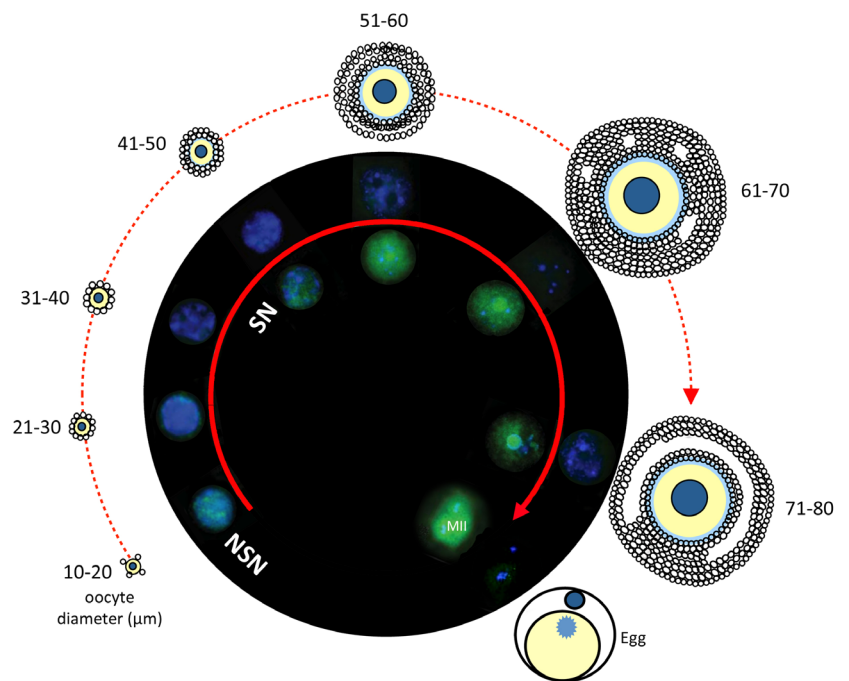
### OCT4 expression during oocyte growth

Most of our knowledge on the profile of expression of the *Oct4* gene and its protein in the oocyte during folliculogenesis has been obtained adopting a model study in which ovarian mouse oocytes are classified into two main groups depending on their chromatin configuration, as observed when cells are stained with the supravital fluorochrome Hoechst 33342. Following staining, an oocyte is classified as surrounded nucleolus (SN), if it possesses a ring of Hoechst-positive heterochromatin around its nucleolus, or as non surrounded nucleolus (NSN) oocyte, if it lacks of this ring and it shows a more dispersed chromatin (Fig. 1). In 4-6 week-old females, primordial/primary oocytes with a diameter of 10-20  $\mu\text{m}$  and the following growing phases up to a size of 40  $\mu\text{m}$ , own an NSN-type of chromatin organisation. Then, at the time of follicle recruitment (41-50  $\mu\text{m}$ ) about 5% of oocytes acquire the SN-type of chromatin configuration; a number that increases with growth, reaching a frequency of about 50% in fully-grown antral oocytes (Zuccotti *et al.*, 1995). An important feature of this model study is that when fully-grown antral SN oocytes are isolated from the ovary, cultured *in vitro* to the MII stage and inseminated, they complete preimplantation (Zuccotti *et al.*, 1998; 2002) and full-term (Inoue *et al.*, 2008) development; on the contrary, fully-grown NSN antral oocytes arrest development at the 2-cell stage. The presence of these two types of oocytes has been observed in most of the mammalian species studied: in rats (Mandl and Zuckerman, 1952), bovine (Lodde *et al.*, 2008), monkeys (Lefe`vre *et al.*, 1989), pigs (Crozet, 1983) and humans (Parfenov *et al.*, 1989). Only goat (Sui *et al.*, 2005) and equine (Hinrichs and Williams, 1997) oocytes seem to represent exceptions, as their germinal vesicles do not show the SN type of chromatin configuration (for a review see Tan *et al.*, 2009).

In the adult mouse ovary, *Oct4* transcripts are present throughout folliculogenesis without significant differences between SN and



**Fig. 1. Chromatin organisation in the nucleus of a non-surrounded nucleolus (NSN) and surrounded nucleolus (SN) oocyte after Hoechst 33342 staining.** The arrow indicates the ring of chromatin surrounding the nucleolus in the SN oocyte.



**Fig. 2. OCT4 expression in the nucleus of non-surrounded nucleolus (NSN) and surrounded nucleolus (SN) oocytes during folliculogenesis.** The *OCT4* protein (green fluorescence) is first detected in the nucleus of NSN primordial/primary oocytes (10-20  $\mu\text{m}$ ), then it is down-regulated to reappear again later but only in the nucleus of SN oocytes (41-50  $\mu\text{m}$ ). This profile of expression is maintained throughout oocyte growth and in the derived  $\text{MII}^{\text{NSN}}$  and  $\text{MII}^{\text{SN}}$  oocytes. The size of the nucleus of smaller oocytes has been enlarged for illustrative purposes. Nuclei are counterstained with Hoechst 33342 (blue fluorescence).

NSN oocytes, although the number of transcripts increases from primordial/primary oocytes (10-20  $\mu\text{m}$ ) to antral oocytes of 61-70  $\mu\text{m}$  and then it decreases in fully-grown and MII oocytes. Instead, the expression pattern of the *OCT4* protein during oocyte growth shows a marked difference in the two types of oocytes. *OCT4* is expressed in primordial/primary oocytes (10-20  $\mu\text{m}$ ), and then it is down-regulated in oocytes of 21-40  $\mu\text{m}$  and reappears again, but only in SN oocytes, when follicles are recruited to begin their growth (Pesce *et al.*, 1998; Zuccotti *et al.*, 2009). The profile of expression of this transcription factor remains confined to the SN-type of chromatin configuration also during the following maturation phases up to the fully-grown stage and to the derived developmentally competent  $\text{MII}^{\text{SN}}$  oocyte, whereas it is down-regulated in developmentally incompetent  $\text{MII}^{\text{NSN}}$  oocytes (Zuccotti *et al.*, 2009) (Fig. 2).

As already demonstrated for ESCs (Boyer *et al.*, 2005; Loh *et al.*, 2006; Babaie *et al.*, 2007), the down-regulation of *OCT4* in  $\text{MII}^{\text{NSN}}$  oocytes affects, directly or indirectly, the profile of expression of numerous genes, including specific known *OCT4*-regulated genes. In ESCs the *OCT4* transcription factor binds directly to the *Nanog* locus regulating the expression of a number of pluripotency genes therein, such as *Nanog*, *Stella* (also known as *Dppa3*), *Apobec1*, *Gdf3* and *Foxj2* (Levasseur *et al.*, 2008). Analogously, from the time of follicle recruitment and during the following oocyte growth, up-regulation of *OCT4* is paralleled by the up-regulation of the *STELLA* protein in SN oocytes, whereas its down-regulation corresponds to *STELLA* down-regulation in ovarian NSN and in their derived

MII<sup>NSN</sup> oocytes (Zuccotti *et al.*, 2009). Furthermore, as observed in ESCs, the expression of *Foxj2* in developmentally incompetent MII<sup>NSN</sup> oocytes is up-regulated in the absence of OCT4; whereas *Foxj2* is down-regulated in the presence of OCT4 in developmentally competent MII<sup>SN</sup> oocytes (Zuccotti *et al.*, 2009).

Both STELLA and *Foxj2* play an important role in preimplantation development. STELLA, the best known, is a maternal-effect factor required at the 1-cell stage to protect against demethylation of the maternal genome and of some paternal imprinted genes (Nakamura *et al.*, 2007); its lack of expression leads to a developmental arrest mainly at the 2-cell stage (Payer *et al.*, 2003). Furthermore, *Foxj2* up-regulation leads to a developmental block at the 2-cell stage (Martin-de-Lara *et al.*, 2008).

Although a direct function of OCT4 on the Nanog locus in oocytes as not been yet proved, the observed behaviour analogies of OCT4 in ESCs and oocytes indicate the centrality of this interaction in the acquisition of the oocyte developmental competence and suggest, in this respect, the need for further investigations.

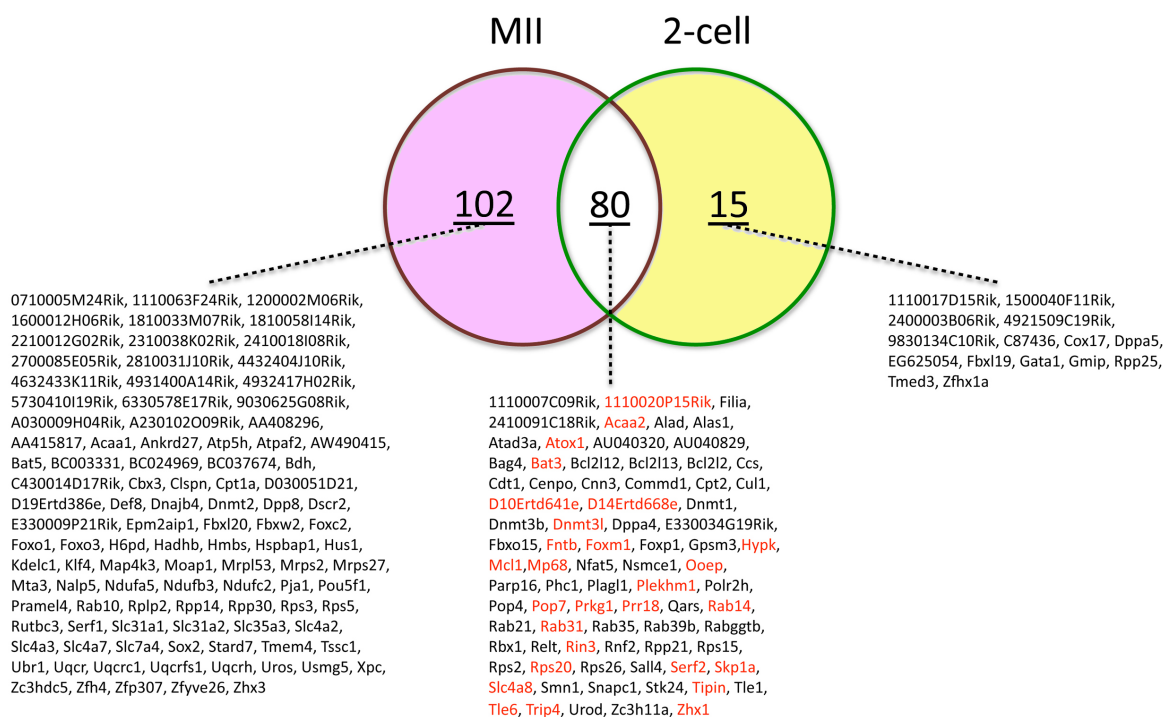
### Effects of the down-regulation of OCT4 on the oocyte transcriptome

Whilst the expression of other maternal-effect genes (i.e., *Npm2*, *Zar1*, *Smarca4* and *Prei3*) does not appear to be affected, as they are equally expressed in MII<sup>SN</sup> and MII<sup>NSN</sup> oocytes (Zuccotti *et al.*, 2008), the down-regulation of OCT4 in MII<sup>NSN</sup> oocytes affects a large number of other genes. Microarray-based comparison of the whole transcriptome profile of developmentally incompetent MII<sup>NSN</sup> vs. competent MII<sup>SN</sup> oocytes brought to light a group of 380 regulated genes, of which 303 up-regulated and 77 down-regulated in MII<sup>NSN</sup> oocytes. Twenty-five of the 380 regulated genes are known

to be regulated by OCT4, 18 of which (up-regulated) are assigned to apoptosis or mitochondrial dysfunction (Zuccotti *et al.*, 2008), indicating that OCT4 down-regulation activates biological pathways that are detrimental to the cell. Furthermore, in keeping with this approach, comparison between MII<sup>NSN</sup> vs. MII<sup>ctrl</sup> ovulated oocytes and their derived 2-cell<sup>NSN</sup> vs. 2-cell<sup>ctrl</sup>, identified an expanded Oct4 transcriptional network made of 197 genes, comprising 102 genes expressed exclusively in MII oocytes, 15 genes solely in 2-cell embryos and 80 genes in both MII oocytes and 2-cell embryos (Fig. 3) (Zuccotti *et al.*, 2011). Gene ontology enrichment analysis of the function of these 197 genes assigned them to several major biological processes, including pluripotency, chromatin organisation, apoptosis, subcortical maternal complex, transcription factors-cancer, translation-cancer, oxidative phosphorylation, porphyrin metabolism, anion exchange, TGF- $\beta$  signalling, copper distribution, regulation of transcription, protein phosphorylation, cell cycle, protein assembly and signal transduction (Fig. 4).

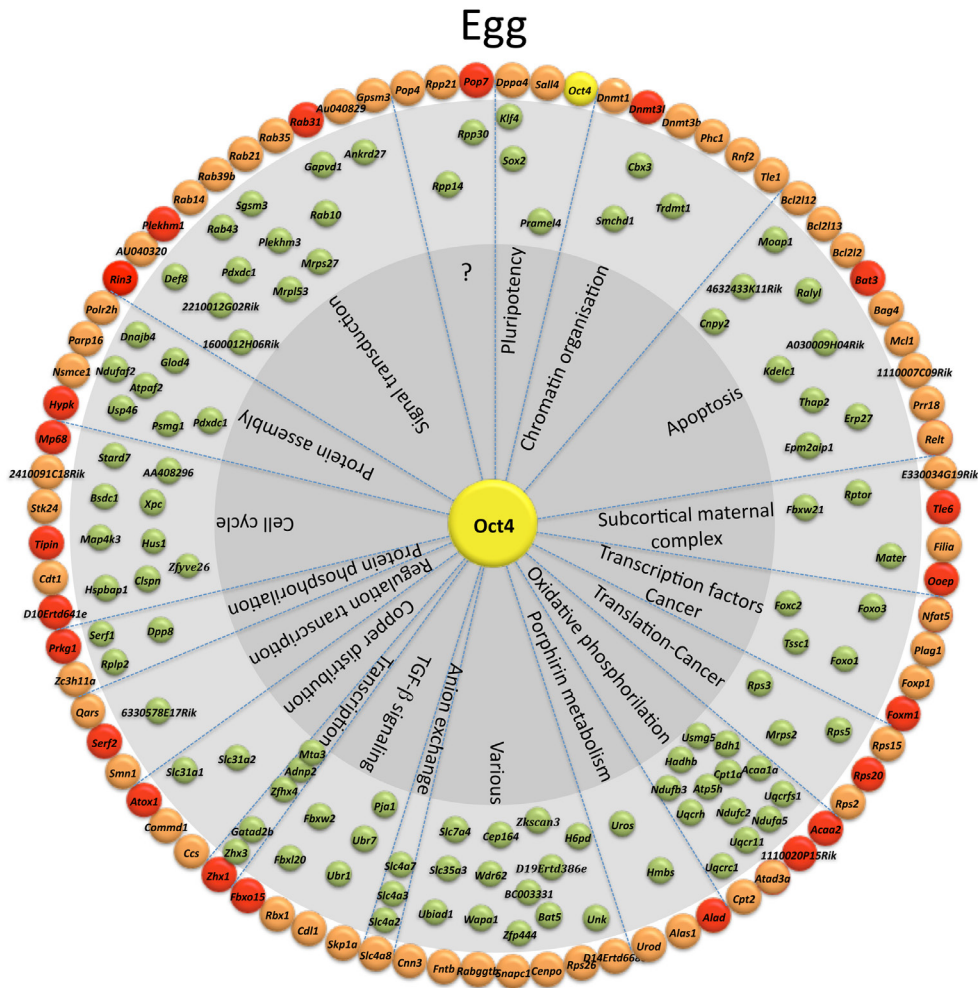
The group of 80 genes that operates in MII oocytes and includes known OCT4-regulated genes (from now on named Oct4 transcriptional network, Oct4-TN), survives the massive transcriptional erasure that occurs following fertilisation (Li *et al.*, 2010) and is expressed in 2-cell embryos. Most genes of the Oct4-TN are expressed in cancer cells and 37 are known partners of the Oct4 transcriptome in ESCs (Boyer *et al.*, 2005; Loh *et al.*, 2006; Babaie *et al.*, 2007) (Fig. 5). Interestingly, the majority of these genes are down-regulated in MII<sup>ctrl</sup> oocytes, whereas after fertilisation, the same genes result up-regulated in 2-cell<sup>ctrl</sup> embryos, an expression behaviour that is confirmed by the immunoanalysis of the proteins of two of these genes (DNMT3L and RSP20; Zuccotti *et al.*, 2011).

Among the biological processes that emerge in the Oct4-TN in MII oocytes, two are worth a particular mention for the role that they

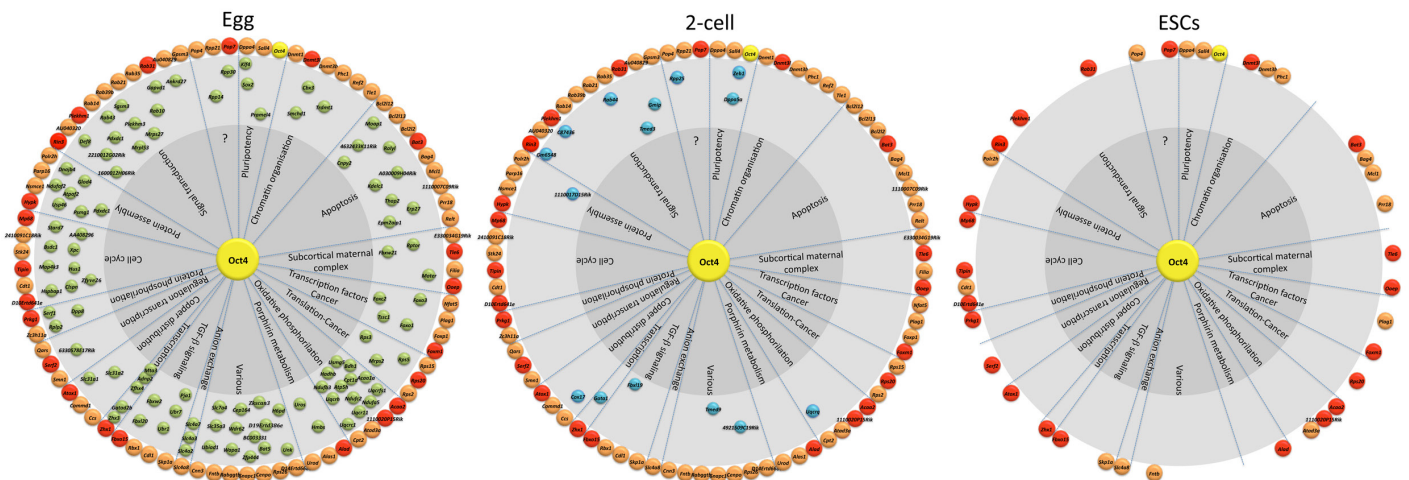


**Fig. 3.** Venn diagram showing the Oct4-transcriptional network genes that are expressed in MII oocytes or in 2-cell embryos and those that are present at both developmental stages. In red, OCT4-regulated genes.

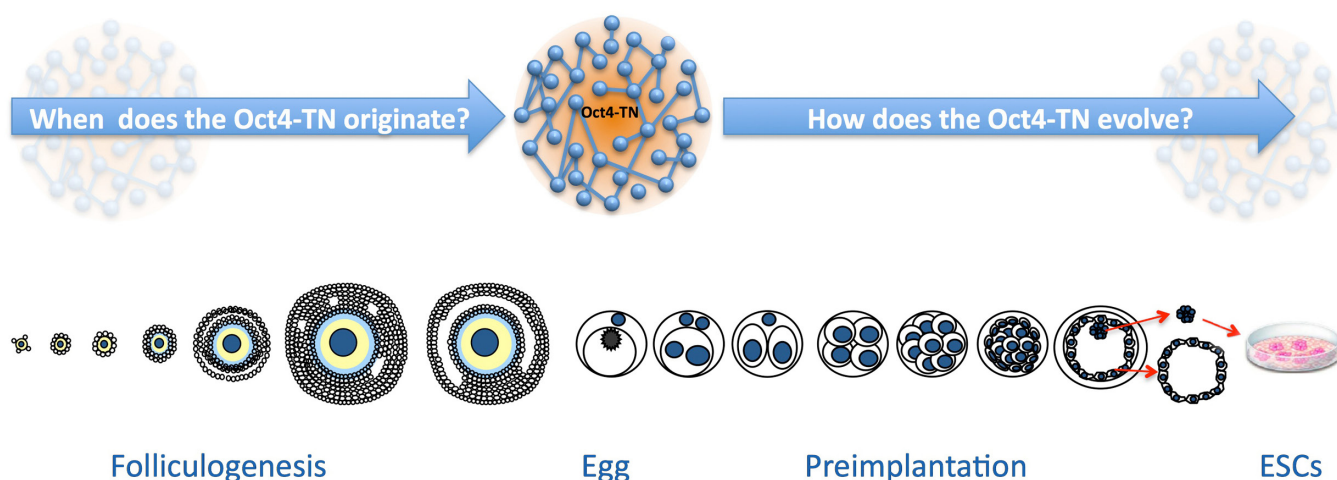




**Fig. 4 (above).** Distribution of the MII oocyte Oct4-transcriptional network genes in nineteen main biological processes. Green, gene transcripts detected only in MII oocytes; orange and red, genes of the Oct4-TN expressed in both eggs and 2-cell embryos; red, known OCT4-regulated genes.



**Fig. 5.** Oct4-transcriptional network (Oct4-TN) expression in eggs, 2-cell embryos and embryonic stem cells. Green, gene transcripts detected only in MII oocytes; orange and red, genes of the Oct4-TN expressed in both eggs and 2-cell embryos; red, known OCT4-regulated genes; blue, genes expressed only in 2-cell embryos.



**Fig. 6.** Future studies of the expression profile of the Oct4-transcriptional network (Oct4-TN) during folliculogenesis, aimed at understanding when it originates during folliculogenesis, and at describing the precise changes occurring during the transition from zygote to blastocyst and in the embryonic stem cells (ESCs).

play in developmental processes. The proteins of the maternal-effect genes *Mater*, *Tle6*, *Ooep* and *Filia* belong to the subcortical maternal complex (Fig. 4) (Li *et al.*, 2008), they are located in the subcortex of MII oocytes and required for zygotes to progress beyond the first embryonic cell divisions of preimplantation mouse development. During cleavage, these proteins are excluded from regions of blastomere-blastomere contact and segregate to the outer cells of the morula and blastocyst embryo during the TE/ICM differentiation. Another group of 'pluripotency'-associated genes includes *Dppa4*, *Sall4*, *Klf4* and *Sox2*, the latter two being well-known OCT4 companions in the maintenance of self-renewal and pluripotency in ESCs and their over-expression together with that of *Oct4* and *c-Myc* induces dedifferentiation of terminally differentiated somatic cells (e.g., fibroblasts) and the formation of iPSCs (Yamanaka, 2007).

### Further perspectives and experiments

Even though the results of these studies do not provide a definitive answer as to the precise function played by OCT4 in folliculogenesis, they reveal a number of evidences of a correlation between OCT4 and the oocyte developmental competence and of a relationship between this transcription factor and a number of genes that are present also in the OCT4 gene regulatory network operative in ESCs. These data indicate that Oct4-TN might be part of the molecular signature of maternal origin on which the ESCs molecular identity is assembled and shaped, thus providing a connection between eggs, early preimplantation embryos and ESCs.

Future experiments ought now to describe the transcriptional and translational behaviour of the Oct4-TN genes during oocyte growth and preimplantation development, up to the implanting blastocyst, when differentiation of the TE and ICM cell lines occurs (Fig. 6). Also, inactivation of the *Oct4* gene expression (e.g., by RNAi or morpholino injection into the oocyte) at the time of follicle recruitment, would give a more precise picture of the molecular function played by OCT4 within this developmental context.

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