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Cell cycle and pluripotency: Convergence on octamer-binding transcription factor 4 (Review)

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Abstract. Embryonic stem cells (ESCs) have unlimited expansion potential and the ability to differentiate into all somatic cell types for regenerative medicine and disease model studies. Octamer-binding transcription factor 4 (OCT4), encoded by the POU domain, class 5, transcription factor 1 gene, is a transcription factor vital for maintaining ESC pluripotency and somatic reprogramming. Many studies have established that the cell cycle of ESCs is featured with an abbreviated G1 phase and a prolonged S phase. Changes in cell cycle dynamics are intimately associated with the state of ESC pluripotency, and manipulating cell-cycle regulators could enable a controlled differentiation of ESCs. The present review focused primarily on the emerging roles of OCT4 in coordinating the cell cycle progression, the maintenance of pluripotency and the glycolytic metabolism in ESCs.

Contents

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1. Introduction

Embryonic stem cells (ESCs) are characterized by unlimited proliferation (self-renewal) and the ability to differentiate into three primary germ layers, namely the endoderm, mesoderm and ectoderm (pluripotency) (1-4). It has been established that complicated regulatory networks are present in ESCs that critically maintain the state of self-renewal and pluripotency for later development (5,6). Several transcription factors (TFs), including octamer-binding transcription factor 4 (OCT4), SRY-box 2 (SOX2) and homeobox protein NANOG (NANOG) are known to sit at the top of the regulatory hierarchy, regulating the expression of various downstream target genes (7,8). Among them, OCT4 serves an indispensable role in maintaining the pluripotency of ESCs (9,10) and in reprogramming the terminally-differentiated somatic cells back into the ESC-like cells (11-13). Furthermore, OCT4 can mediate the differentiation of murine ESCs induced by retinoic acid or Wnt/β-catenin in a manner that is independent of and distinct from other core TFs (14), indicating that OCT4 may have unique and non-substitutable roles in controlling the self-renewal, pluripotency and differentiation of ESCs.

Cell cycle progression is required for ESCs to proliferate and avoid staying in a quiescent state. Multiple studies have demonstrated that cell cycle-associated proteins can regulate various core TFs or differentiation markers (15). In a reciprocal manner, several TFs, such as NANOG and c-MYC proto-oncogene protein, can control the expression levels of multiple cell cycle-associated target genes (16,17). This review will be focused on reciprocal interplays between OCT4 and cell cycle checkpoints and their connections with the ESC pluripotency.

2. Cell cycle and pluripotency in ESCs

Cell cycle comprises four different phases; the S phase for DNA replication, the M phase for cell mitosis, and two gap phases between S phase and M phase (G1 phase for synthesis of proteins and lipids, and G2 phase for checking DNA integrity). Ample evidence has revealed that the duration of cell cycle in murine somatic cells is relatively long (>16 h), which is dominated by the G1 phase (18); in contrast, the cell

cycle of murine ESCs progresses faster (~8-10 h) (19), which is characterized by a truncated G1 phase and a prolonged S phase (20). Although the duration of cell cycle in human ESCs is significantly lengthened (~32-38 h) (21), the time spent at G1 phase is minimal (3 h in human ESCs vs. 10 h in human somatic cells) (15,22), indicating that the cell cycle dynamics may crucially impact on the differentiation potential of pluripotent stem cells. Indeed, ~1-5% of the total proteins differ their expression levels between ESCs and induced pluripotent (iPS) cells, and the majority of them are cell cycle proteins (23).

There is mounting evidence demonstrating that lengthening the G1 phase in ESCs contributes to inducing differentiation (24-27), and distinct G1 phase profiles will lead to different lineage fates. Human ESCs in early G1 phase can only differentiate into endoderm, whereas in late G1 phase they were limited to neuroectodermal differentiation (28). In fact, all-trans retinoic acid, a common differentiation inducer, can regulate the gene expression of Cyclin D1 (29,30) and result in G1 phase accumulation (31-33). It is therefore reasonable to propose that during the G1 phase, ESCs sense and integrate various extracellular and intracellular signals to make the decisions on the timing and the fate of differentiation. A shortened G1 phase may minimize the exposure of ESCs to various signals, thereby preserving their pluripotency. In addition, it was demonstrated in a recent study that G2 cell cycle arrest is also required for endodermal development (34); furthermore, specific disruption of S and G2 phases will affect the pluripotent state of human ESCs in a G1 phase-independent way (35-37). Gamma-ray-induced DNA damage induces G2/M blockage and the differentiation of ESCs (38,39). It is important that ESCs have a long enough G2 phase to check and restore the fidelity of the genome as a result of G1/S checkpoint deficiency.

3. OCT4 and G1/S transition

The expression of Cyclin-dependent kinase 4/6 (CDK4/6) and Cyclin D is increased in early G1 phase in somatic cells. Although the lack of Cyclin D expression was reported in murine ESCs (40), the mRNA levels of CDK4 and Cyclin D2 were increased in human ESCs (22,41). Further studies demonstrated that Cyclin D expression is enhanced in late G1 and G1/S phases in human ESCs. Notably, knocking down Cyclin D induces endodermal differentiation, whereas its overexpression promoted neuroectodermal differentiation by inhibiting mothers against decapentaplegic (SMAD) 2/3 nuclear translocation (28). In addition, Cyclin D can also recruit transcriptional co-regulators to development-assocaited gene loci and modify the epigenetics of target genes (42). There is evidence demonstrating that a proper level of Cyclin D is necessary for maintaining the pluripotent state of ESCs, while overexpression of them may induce reprogramming of epidermal cells into stem-like cells with higher expression levels of OCT4 and NANOG (43). In contrast, in adult stem cells or cancer cells, OCT4 can directly bind to the promoter region of Cyclin D1, thereby regulating its transcription and controlling G1/S transition (44-46). Meanwhile, OCT4 can bind with the conserved promoter of microRNA (miR)-302 (47), increasing the level of p16(Ink4a)/p19(Ink4d) and inhibiting the interaction between CDK4/6 and Cyclin D (48). Furthermore, OCT4 can also interact with SMAD2/3 to control the pluripotent state of ESCs (49,50). Taken together, these studies suggested that OCT4 is involved in the transcriptional regulation of Cyclin D as well as other target genes (Fig. 1).

CDK2-Cyclin E is constitutively expressed and involved in the progression of G1/S transition (26). In human ESCs, inhibition of CDK2 will lead to G1 phase arrest, which is accompanied with apoptosis or differentiation. Inhibition of CDK2 can induce sustained genomic damage and elicit DNA damage response, thus contributing to apoptosis of impaired ESCs (51,52). As demonstrated in further studies, OCT4 expression can be suppressed by downregulating CDK2 (53,54), while CDK2 can enhance reprogramming efficiency by phosphorylating SOX2 at Ser-39 and Ser-253 sites (55). Although the regulation of CDK2-Cyclin A/E by OCT4 in ESCs has not been reported, OCT4 can promote tumor proliferation by activating Cyclin E (56). Thus, it remains possible that OCT4 may regulate the expression of CDK2-Cyclin A/E in ESCs.

Retinoblastoma (RB) protein is a downstream target of CDK4/6-Cyclin D, which can inhibit the transcription activity of E2F transcription factor 1 (E2F) in its hypophosphorylated state. After being hyperphosphorylated by CDK2-Cyclin E, RB can release E2F for the ultimate regulation of a number of targets involved in G1 phase progression and S phase entry (Fig. 1). Therefore, it came as no surprise that the activity of RB-E2F can influence the ESC self-renewal and pluripotency (57,58). In fact, activated RB can directly bind to the promoter regions of OCT4 and SOX2, leading to their transcriptional suppression and a declined reprogramming efficiency (59); in contrast, the inactive RB allows for generation of iPS cells in the absence of exogenous SOX2 expression (60). Furthermore, RB can also regulate OCT4 level by suppressing the expression of forkhead box protein M1, which is a transcription factor promoting OCT4 expression (61,62). In addition, E2f will switch from an active state in stem cells to a suppressed state in differentiated cells through forming a complex with RB (63). Conversely, in murine ESCs, OCT4 maintains the hypo-phosphorylated state of RB by inhibiting the activity of protein phosphatase 1 (64), which is well-known for its role in triggering mitotic exit (65). Additionally, OCT4 can also directly bind to the promoter region of E2f3a and increase its expression level in murine ESCs, which contributes to relieving the cell growth retardation caused by OCT4 knockdown (66). As inhibition of E2F2 can impair self-renewal and cell cycle progression in human ESCs, the pluripotency is preserved in E2F2 silencing cells (67). Therefore, the effects of RB on the pluripotency of ESCs are unlikely mediated by E2F. The other roles of RB in ESCs will be discussed later.

4. OCT4 and G2/M transition

In somatic cells, CDK1-Cyclin A/B is a critical cell cycle regulator that can promote G2/M transition. As has been demonstrated in multiple studies, CDK1-Cyclins serve critical roles in the self-renewal and development of ESCs. The expression level of Cyclin A, the first cloned Cyclin protein, is higher in ESCs in G2 phase than that in fibroblast cells (68), and resetting its expression level in early-passage iPS cells can improve the pluripotency and reduce the tumorigenicity (23). In addition, the Cyclin B1 level is also upregulated in ESCs

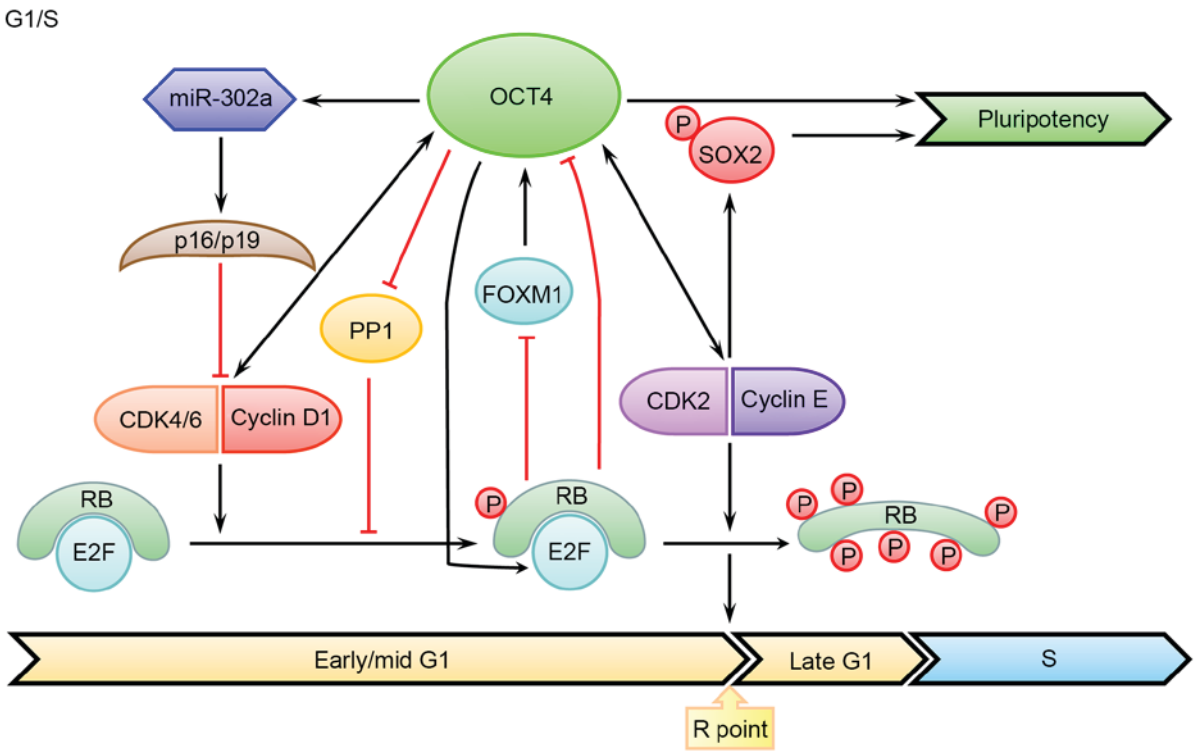

Figure 1. An overview of the roles of OCT4 in coordinating the G1/S transition and the maintenance of pluripotency. OCT4 promotes the phosphorylation of hypo-phosphorylated RB (a prerequisite for the R-point transition) by downregulating PP1 and upregulating CDK4/6-Cyclin D in early and mid G1 phase. At this point, phosphorylated RB still binds to E2Fs and blocks their transcription-activating domains, leading to suppressed expression of several cell-cycle promoting genes, including OCT4. OCT4 can further promote RB hyperphosphorylation by upregulating CDK2-Cyclin E complex, which leads to the E2F release, the R-point transition, and the entry into the S phase. CDK2 can also phosphorylate SOX2 to enhance reprogramming efficiency. Black arrows indicate positive regulation, while red bar-headed lines indicate negative regulation. PP1, protein phosphatase 1; CDK, cyclin-dependent kinase; FOXM1, forkhead box protein M1; RB, retinoblastoma; E2F, E2F transcription factor 1; OCT4, octamer-binding transcription factor 4; p, phosphorylated.

in G2 phase compared with that in somatic cells. Increased expression of Cyclin B1 in G2 phase can delay the dissolution of pluripotent state in human ESCs, while knockdown of Cyclin B1 induces markedly declined expression of pluripotent markers in human ESCs (36). The same is true for CDK1. In human ESCs, down-regulating CDK1 leads to loss of pluripotency, increased differentiation markers, accumulation of double-strand breaks, as well as the inability to arrest at G2 phase and commit to apoptosis (69,70). CDK1 can enhance the binding of OCT4 to the promoter and suppress the transcription of homeobox protein CDX2, a classic differentiation marker (71). Furthermore, several markers of G2/M are expressed during the meso- and endodermal differentiation (e.g., WEE1 G2 checkpoint kinase blocks entry into mitosis by phosphorylating CDK1 at Y15), rather than the ectodermal differentiation (34). In contrast, OCT4 can inhibit the activation of CDK1 by cell division cycle 25 phosphorylation, which is independent of its transcriptional activity (Fig. 2). Thus, ESCs have to express more CDK1 to overcome the inhibitory effect of OCT4. Inhibition of CDK1 by OCT4 will lead to a prolonged duration of G2 phase, which allows for subsequent checking of genome integrity and reducing chromosomal mis-segregation (72). Indeed, inhibition of CDK1 can activate the response to DNA damage and promote nuclear translocation and activation of p53, thereby maintaining the survival of ESCs (73). The potential connection between OCT4 and Cyclin A/B has not been elucidated in any study yet, but there is evidence that SOX2, a core TF frequently associated with OCT4, can promote the expression of Cyclin A/B in cancer cells (74-76). The direct regulation of CDK1-Cyclin by OCT4 warrants further investigation.

Growth arrest and DNA-damage-inducible protein 45 (GADD45), which includes several isoforms, is crucial for protecting genome stability in G2/M transition by suppressing cell cycle and repairing DNA. GADD45ag morpholino knockdown in *Xenopus* can induce differentiation of neural embryonic cells by inducing various cell cycle related inhibitors, such as p53, p21 and Cyclin G1. Additionally, GADD45ag morphants exhibit increased expression of *Xenopus* OCT4 homologs, indicating that GADD45ag is required for early embryonic cells to exit pluripotency and enter differentiation (77). In addition, GADD45a can bind to the OCT4 promoter and promote its demethylation in *Xenopus* oocytes, which is accompanied with DNA repair (78,79). Furthermore, studies in human cells indicated that GADD45 G is a downstream target of OCT4, which is significantly increased in the OCT4 knockdown system (80,81).

As discussed above, RB is a tumor-suppressor gene controlling the activity of transcription factor of E2F family, which serves an indispensable role in G1/S transition. Increased activity of RB can trigger cell cycle arrest, differentiation or death of ESCs (82). However, the inactivation of RB family in ESCs can also induce G2/M arrest and cell death (57), which may be attributed to the loss of its function in maintaining the genetic stability (83-85). These findings indicated that the expression level of RB needs to be tightly controlled at a

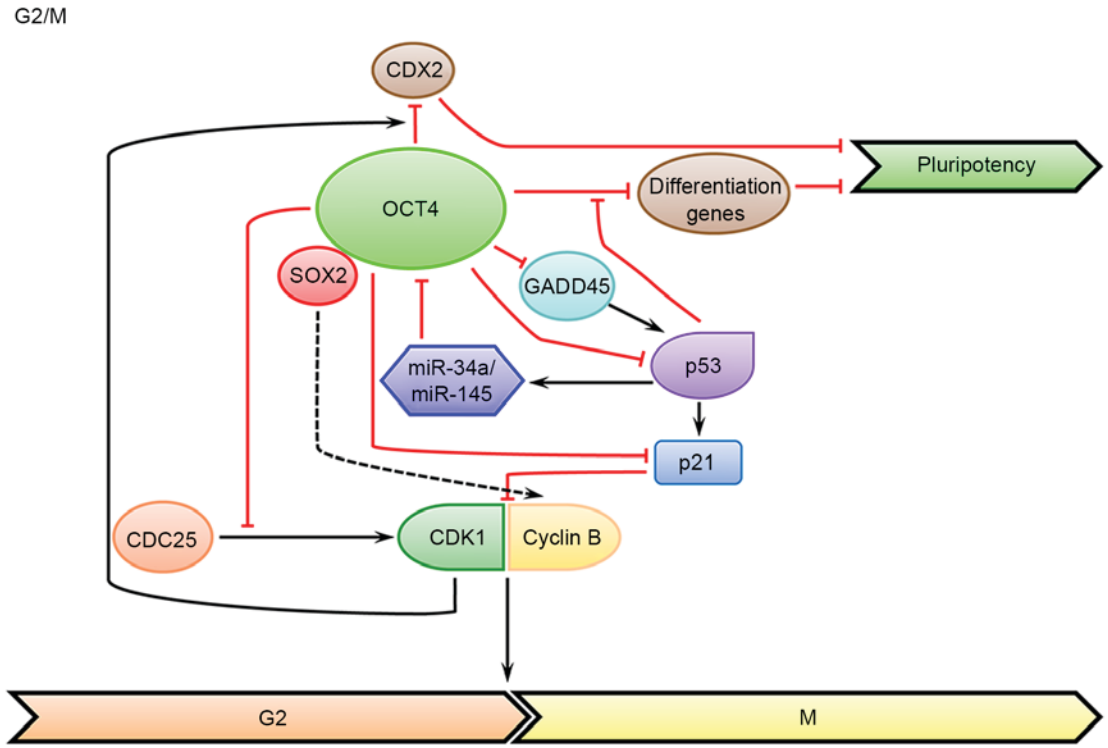

Figure 2. An overview of the roles of OCT4 in coordinating the G2/M transition and the maintenance of pluripotency. At the G2/M phase, via a non-transcriptional mechanism, OCT4 can inhibit the activation of CDK1 and lead to a prolonged G2 phase, allowing for subsequent checking of genome integrity and reducing chromosomal mis-segregation. Reciprocally, CDK1 can enhance the binding of OCT4 to the CDX2 promoter and suppress its transcription, contributing to the maintenance of ESC pluripotency. Black arrows indicate positive regulation, while red bar-headed lines indicate negative regulation. CDX2, homeobox protein CDX2; CDC25, cell cycle division 25; miR, microRNA; CDK1, cyclin-dependent kinase 1; GADD45, DNA-damage-inducible protein 45; SOX2, SRY-box 2; OCT4, octamer-binding transcription factor 4.

proper level, so that the pluripotency and self-renewal of ESCs can be maintained. Furthermore, overexpression of RB in S phase can lead to G2 phase arrest (86). Additionally, RB can directly bind to cohesin and condensin II, which can regulate centromere functions and control mitosis (87-91).

5. OCT4 and p53-p21 checkpoints

The p53-p21 signaling pathway is a major checkpoint in cell cycle of G1/S and G2/M transition. The expression level of p53 is kept low in ESCs, which is predominantly present in the cytoplasm. The extremely low level of p53 in the nucleus is also inactivated. p53 will translocate to cell nucleus and initiate the transcription of its target genes in the event of DNA damage (92). In addition, p53 can promote the translocation of active Bcl-2-associated X protein from the Golgi to mitochondria to initiate apoptosis under DNA damage stresses (93). It is demonstrated that p53 deficiency will lead to genomic instability in ESCs (94). In contrast, the activated p53 in ESCs will result in differentiation (31,95,96) or apoptosis (73,97). However, it has also been demonstrated in other studies that p53 has anti-differentiation effects in ESCs (98), indicating that p53 exerts its functions in a context-dependent manner, and that proper intracellular levels and subcellular localization of p53 are critical for its roles in maintaining the pluripotent state in ESCs.

In addition, p53 can regulate the expression of various key TFs in ESCs. For example, knockdown of p53 can lead to downregulated NANOG expression (99). As a common differentiation inducer of ESCs, p53 expression is activated after exposure to retinoic acid, which drives the expression of miR-34a and miR-145 and reduces the OCT4 expression (31). In addition, the differentiation-activated p53 can recruit UTX and lysine-specific demethylase 6B (JMJD3), the H3K27me3-specific demethylases, bind to the promoter regions of developmental transcription factors that are repressed by OCT4, and increase the expression of various differentiation genes (100). p53 is also the downstream target of OCT4 (Fig. 2). Studies have revealed that silencing OCT4 will lead to p53 activation and induce differentiation (101-103). For instance, silencing OCT4 significantly reduces the expression of SIRT1, a deacetylase known to inhibit p53 activity and the differentiation of ESCs, leading to increased acetylation of p53 at lysine 120 and 164 that is required for its stabilization and functionality (104). In addition, OCT4 can bind to the promoter region of CD49f (integrin subunit α6), which can also decrease the level of p53 (105).

p21, a downstream target of p53, can inhibit the activation of CDKs and result in cell cycle arrest (Fig. 2); in addition, it can also be regulated in a p53-independent way. It has been revealed in studies that p21 is involved in DNA repair, transcriptional regulation, differentiation and apoptosis. In ESCs, the expression level of p21 is compromised due to epigenetic modification (106), and the lack of p21 function is required for maintaining the pluripotent state (107). Ionizing radiation-induced DNA damage can lead to elevated p21 mRNA level and cell cycle arrest at G2 phase (108). Upregulation of p21 in human ESCs will induce G1 phase arrest and

subsequent differentiation into multiple lineages (109). This result is consistent with the finding that p21 has multiple fuctions in both G1/S and G2/M checkpoints (110,111). p21 can also mediate apoptosis in murine ESCs that are exposed to dihydrolipoic acid (112). In addition, increased p21 expression leads to decreased reprogramming efficiency in somatic cells (113). Conversely, OCT4 can inhibit the activity of p21 by directly binding to its promoter region or by indirectly up-regulating DNA (cytosine-5)-methyltransferase 1, a DNA methyltransferase, which can inhibit lineage differentiation (114-116).

6. OCT4 and ESC metabolism

A large amount of energy is generated in ESCs to meet the requirements for biosynthesis and cell cycle progression. The energy metabolism mode of primed ESCs is similar to that of other adult stem cells or cancer cells with a high glycolytic flux rather than oxidative phosphorylation (OXPHOS), which is known as the 'Warburg effect' (117-121). This phenomenon can be partly attributed to the immature structure and function of mitochondria and a hypoxic niche (5% of physiological level) (122,123). Though glycolysis produces less ATPs than OXPHOS, it has faster rate of ATP generation, which makes it competent to support active cell proliferation. Additionally, pyruvate, the product of glycolysis, together with other intermediate products of tricarboxylic acid (TCA) cycle, can be used for biosynthesis (such as DNA, protein and lipid) in ESCs as well as in cancer cells for shortening the G1 phase (123-125). A high glycolytic flux metabolism in hypoxia may reduce the damages to DNA caused by reactive oxide species (ROS), which may impair the pluripotency ESCs and induce their differentiation (126,127).

Initial evidence indicated OCT4 may be involved in regulating metabolism as its knockdown resulted in increases in TCA cycle activity and decreases in glycolytic flux (117). Further studies demonstrated that OCT4 can directly regulate the transcription of hexokinase 2 (HK2) and pyruvate kinase (PK) M2, the two key glycolytic enzymes that determine the rate of glycolysis. Overexpression of HK2 and PKM2 contributes to sustaining the high glycolysis level and preserving the pluripotency of ESCs (128). Notably, PKM2 can directly bind to OCT4 and enhance OCT4-mediated transcription (129,130).

7. Conclusion

It has been known for a while that ESCs are characterized by an abbreviated G1 phase and a prolonged S phase. However, the underlying mechanisms remain largely elusive. Emerging evidence has implicated a direct role of the master pluripotency factor OCT4 in controlling the transcription of several key cell cycle regulators. In general, OCT4 appears to directly or indirectly activate the transcription of cell cycle machineries that promote G1/S transition and avoid differentiation (Fig. 1). Meanwhile, by suppressing multiple cell cycle genes, OCT4 controls proper duration of G2 phase to ensure the genomic integrity via both the transcription-dependent and -independent mechanisms (Fig. 2). Reciprocally, the cell cycle regulators especially CDK1 can directly interact with OCT4 and promote its suppressive binding to the differentiation genes and thereby maintaining the ESC pluripotency.

Another important feature of ESCs is their high glycolytic metabolism under hypoxic conditions that may minimize the oxidative damage of ROS to genetic material. Recent studies revealed that OCT4 can promote glycolysis by transcriptionally upregulating the expression of several key glycolytic enzymes, directly linking ESC metabolism to their self-renewal and pluripotency. Given the convergence of ESC pluripotency and cell cycle control on OCT4, it would be of interest to investigate in future studies how OCT4 and other master pluripotency factors coordinate ESC metabolism with their cell cycle progression.

The rapid cell cycle progression of ESCs requires high-fidelity DNA replication and repair mechanisms. The investigation into the potential connection between ESC cell cycle control and DNA replication/repair is just at its infancy, and it remains to be seen if the master pluripotency factors such as OCT4 may also serve a role in these events.

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