Opinion

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Gating pluripotency via nuclear pores

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In recent years, growing evidence has pointed to the interesting idea that pluripotency might be regulated by a nuclear-pore-coordinated network that controls the level of pluripotency factors in the nucleus. A thorough understanding of this process might improve our comprehension of cell pluripotency and differentiation during embryogenesis, as well as aiding the development of novel models for studying human diseases.

Introduction

Nuclear-pore complexes (NPCs) are multi-protein channels that are embedded in the nuclear envelope and are comprised of approximately 30 different nucleoporins (Nups). NPCs serve as the primary conduit for communication between the nucleus and cytoplasm. Nucleocytoplasmic trafficking via NPCs is a complex yet precise mechanism that is mediated by many transport factors, such as importins, exportins, the GTP-binding nuclear protein Ran, and Nups (Box 1). In addition to their primary function in nucleocytoplasmic trafficking, nuclear pores are involved in a number of important cellular processes, including gene regulation and chromatin organization [1]. Recently, an emerging role of nuclear pores in regulating pluripotency and differentiation has been revealed [2–7].

Regulating nuclear transport of pluripotency factors via post-translational modifications

Pluripotency factors such as POU class 5 homeobox 1 (POU5F1, also known as Oct4), SRY(sex determining region Y)-box 2 (Sox2), and Nanog homeobox (Nanog) are transcription factors that are required for the maintenance of pluripotency and suppression of lineage-specific differentiation in pluripotent stem cells (PSCs), including embryonic stem cells (ESCs). In order to perform their functions, these factors need to access the nucleus, which is gated by nuclear pores. Recent studies have shown that post-translational modifications of pluripotency factors influence their nuclear trafficking through nuclear pores and subsequently regulate cell-fate determination.

Oct4

Lin *et al.* reported that the phosphorylation of Oct4 at T235 by an Akt protein kinase promoted self-renewal and survival of embryonal carcinoma cells (ECCs) — the malignant counterpart of ESCs [2]. Akt-mediated phosphorylation prevented Oct4 from being degraded and increased the stability of intracellular Oct4. Stabilized Oct4 exhibited predominant nuclear localization (Figure 1). However, when cells were treated with MG132, a proteasome inhibitor, the Oct4-T235A mutant, which cannot be phosphorylated by Akt, accumulated more in the cytoplasm as compared to wild-type Oct4 or the Oct4-T235D phosphorylation mimic. These observations indicate that unphosphorylated Oct4 is exported from the nucleus and degraded in the cytoplasm. Importantly, treatment with a specific Akt inhibitor, Akti-1/2, together with MG132 markedly accelerated the cytoplasmic accumulation of Oct4, a phenomenon that could be partially reversed by the nuclear export inhibitor leptomycin B (LMB) [2]. Therefore, Akt-mediated phosphorylation stabilizes Oct4 in the nucleus and prevents it from being exported from the nucleus via nuclear pores, a mechanism that presumably involves the export factor CRM1 (also known as exportin-1). Although most of the previous evidence suggests that the nuclear export of Oct4 is an active process that is regulated by CRM1, a recent study proposed an alternative model, claiming that most Oct4 is exported from the nucleus by passive diffusion [8]. Despite the possible controversy, it remains to be elucidated how different mechanisms coordinately regulate nuclear export of Oct4. In addition, it has been suggested that Oct4 requires Akt-mediated phosphorylation to maintain the association with other pluripotency factors, such as Sox2 and Kruppel-like factor 4 (KLF4) [2]. By regulating the binding affinity of Oct4 to Sox2 at gene promoters, Akt-mediated phosphorylation might directly increase the transcription of other pluripotency genes, such as Nanog [2]. Thus, Akt-mediated phosphorylation causes both nuclear accumulation of Oct4 and increased Oct4 transcriptional activity by promoting its partnering with Sox2, and together these processes contribute to the self-renewal and survival of ECCs [2].

The phosphorylation of Oct4 at different sites might also determine its nucleocytoplasmic redistribution or

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Box 1. Nucleocytoplasmic trafficking mechanism

Nucleocytoplasmic trafficking via nuclear-pore complexes (NPCs) includes energy-independent passive diffusion and energy-dependent active transport. Small molecules undergo passive diffusion to enter the nucleus without regulation and use of energy. However, macromolecules, such as most transcription factors, histones, mRNA, or non-coding RNAs, are actively transported, and these processes are mediated by transport factors, such as importins, exportins, the GTP-binding nuclear protein Ran, and nucleoporins. Importins are the most important participants in nuclear importing. These proteins are able to recognize the specific amino acid sequences — nuclear localization signals (NLSs) — on cargos. Importins, which bind cargos in the cytoplasm, interact with NPCs to get through the channel. As long as the cargos enter the nucleus, importins disassociate from the cargos and return to the cytoplasm. Importin-α and importin-β are the best-known importins and have been shown to import many proteins, such as POU class 5 homeobox 1 (POU5F1, also known as Oct4) and SRY(sex determining region Y)-box 2 (Sox2). Conversely, exportins bind to the nuclear export signals (NESs) of cargos and exit from the nucleus through the pores to the cytoplasm, where the exportin–cargo complexes disassemble. The export factor CRM1, also known as exportin-1, exports cargos with leucine-rich NESs; exportin-5 specifically mediates the exit of microRNA. Ran proteins are responsible for the supply of energy. Ran hydrolyzes GTP to GDP and produces energy for nuclear transport. Nucleocytoplasmic trafficking precisely controls the localization of macromolecules, which in turn might regulate processes related to cell pluripotency and differentiation.

degradation. Ferro *et al.* showed that Oct4 was phosphorylated at serines 105 and 107 and became mainly cytoplasmic after the differentiation of dental pulp stem cells (DPSCs) into osteoblastic, hepatic, myocytic, and neural lineages. Conversely, Oct4 was localized not only in the cytoplasm but also in the nucleus in undifferentiated DPSCs [3]. Furthermore, phosphorylation-motif analysis showed that serine 105 of Oct4 was a putative phosphorylation site for casein kinase II (CK-II), which has been previously proven to have a central role in facilitating phosphorylation of nuclear proteins and mediating their nucleocytoplasmic shuttling via a CRM1-dependent mechanism (Figure 1). More recently, the same group demonstrated that Oct4 was phosphorylated at serine 111 by the Mitogen-activated protein kinase kinase/ Extracellular signal-regulated kinases 1 (also known as MEK/ERK1) signaling pathway. Instead of increasing the nuclear localization and stabilizing the protein, this site-specific phosphorylation of Oct4 triggered its CRM1-mediated nuclear export and ubiquitin-proteasomal degradation [9] (Figure 1). Although the essential role of Oct4 in governing pluripotency is well established, a recent study has uncovered differential roles for Oct4 in maintaining or reconstructing pluripotency through Oct4 nucleocytoplasmic shuttling. Data demonstrated that transient retention of Oct4 in the nucleus was sufficient to maintain an undifferentiated state in ESCs, whereas the long-term intranuclear localization of Oct4 was critical for cell reprogramming-associated chromatin remodeling and epigenetic modifications [8]. This finding revealed an underappreciated role of Oct4 nucleocytoplasmic shuttling in cell-fate determination. However, the underlying mechanism remains to be elucidated.

Sox2

Another pluripotency factor, Sox2, has also been proposed to be governed by nuclear-pore-mediated regulation, which might affect cell-fate determination. For example, protein acetylation had been identified to have a direct effect on nuclear transport of Sox2 [10]. Sox2 had been shown to

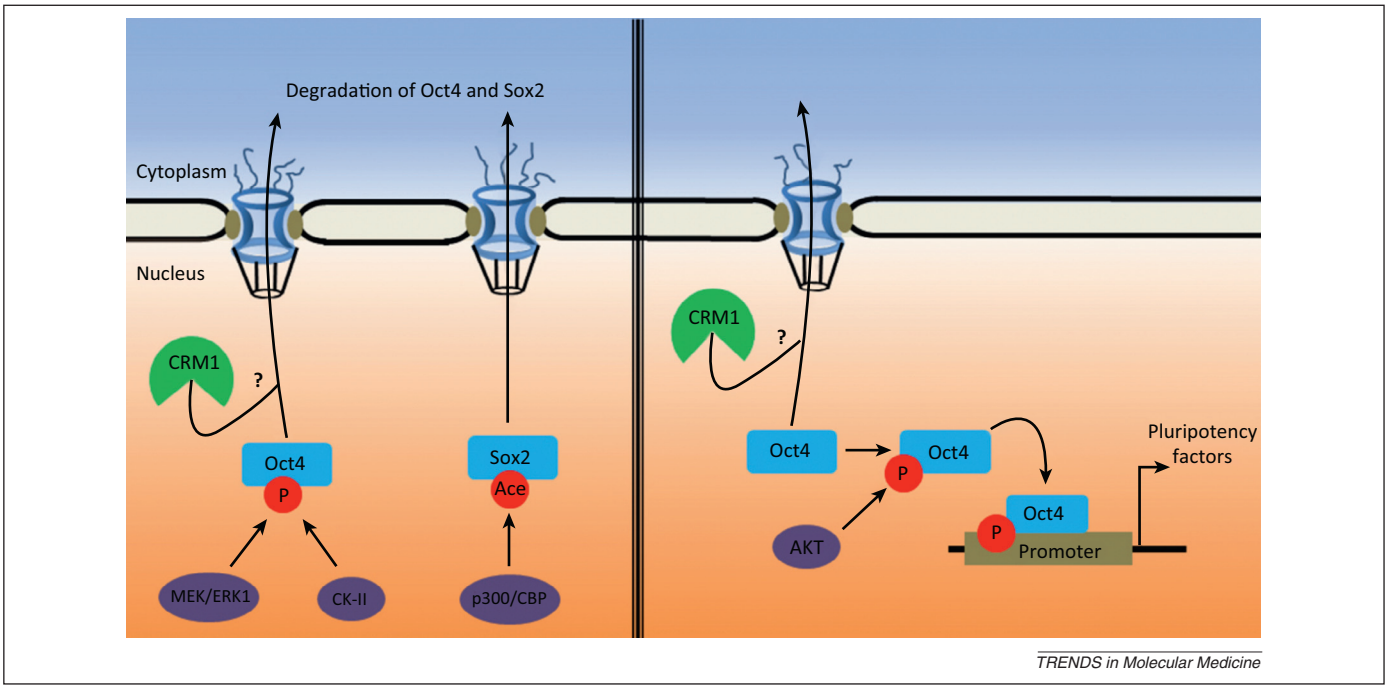

Figure 1. Regulation of nuclear localization and function of POU class 5 homeobox 1 (POU5F1, also known as Oct4) and SRY(sex determining region Y)-box 2 (Sox2) via post-translational modifications. Phosphorylation mediated by Mitogen-activated protein kinase kinase/extracellular signal-regulated kinases 1 (MEK/ERK1) or casein kinase-II (CK-II) leads to the nuclear export and degradation of Oct4, thereby triggering cell differentiation. The transcriptional coactivators p300/CBP-mediated acetylation results in the nuclear export and subsequent degradation of Sox2 in the cytoplasm. Finally, Akt-dependent phosphorylation of Oct4 prevents its nuclear export, resulting in the transcriptional induction of pluripotency genes.

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