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—Mini Review—

The Ubiquitin-proteasome System in the Maternal-to-zygotic Transition

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Abstract: During the maternal-to-zygotic transition (MZT), maternal proteins in oocytes are degraded by the ubiquitin-proteasome system (UPS), which is first event after fertilization, and new proteins are then synthesized from the zygotic genome. Although degradation of accumulated maternal protein is essential for normal early embryonic development, the specific mechanisms underlying the UPS at the MZT are not well understood. We recently provided evidence that proteasomal degradation of maternal proteins is important for the onset of zygotic gene activation (ZGA), and that the zygote-specific proteasome assembly chaperone (ZPAC) plays an important role in the degradation of maternal proteins during mouse MZT. Here, we review why the degradation of maternal proteins via UPS is essential for embryonic reprogramming of the oocyte into a totipotent zygote that is makes somatic development possible.

Key words: Maternal-to-zygotic transition, Ubiquitin-proteasome system, ZPAC

Introduction

After fertilization, erasure of the oogenic program and reprogramming by the establishment of embryonic programs for the creation for a totipotent zygote are coordinately regulated (Fig. 1) [1, 2]. This process is called the maternal-to-zygotic transition (MZT), and is accompanied by the degradation of maternal mRNAs and proteins, and the transcription of zygotic genes, which are essential components for the progress of embryogenesis [1, 3–5].

Two major pathways for degradation of intracellular proteins exist in eukaryotic cells, one of which is autophagy-mediated lysosomal degradation. Recently, the importance of autophagy for preimplantation development was highlighted in studies using mice [6]. It was reported that oocyte-specific *Atg5*-knockout mice exhibited early embryonic arrest at the 4-cell or 8-cell stage. The other proteolytic pathway is the ubiquitin-proteasome mediated degradation (Fig. 2). This proteolytic system is selective, compared to the autophagy-mediated lysosomal degradation, due to ubiquitin ligases specifically recognizing substrate proteins and attaching polyubiquitin chains to them as a degradation signal for the proteasome [7, 8]. These two major pathways are essential for the maintenance of cellular homeostasis in eukaryotic cells [9–11].

Involvement of the UPS in the degradation of stored maternal proteins after fertilization has been reported [12, 13], and in general, degradation by the UPS is carefully regulated. However, the mechanisms underlying the structure and functions of the UPS in the MZT are not well understood. Recently, we provided evidence showing the importance of proteasomal degradation after fertilization for the onset of zygotic gene activation (ZGA), and also found a zygote-specific proteasome assembly chaperone (ZPAC), which is specifically expressed in the mouse gonads and zygote [4, 5]. In the early mouse embryo, expression of ZPAC is transiently augmented at the MZT and plays an important role in the removal of maternal proteins by enhancing the biogenesis of the 20S proteasome. Here, we conduct a review of recent reports that ubiquitin-mediated proteasomal degradation of maternal protein after fertilization is essential for embryonic reprogramming the oocyte into a totipotent zygote.

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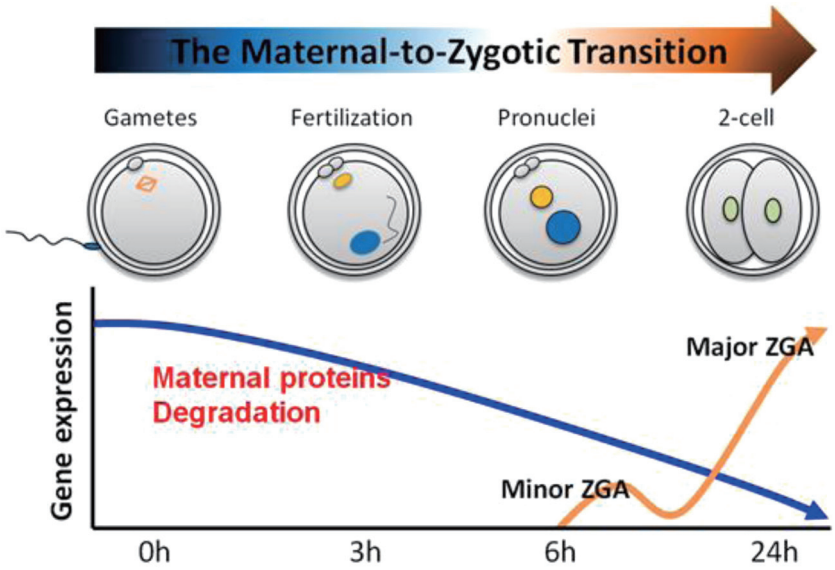

Fig. 1. The maternal-to-zygotic transition in mice. MZT is initiated when sperm and an ovulated oocyte meet in the ampulla of the oviduct and fuse to effect fertilization. Each haploid gamete forms a pronucleus and after syngamy develops into a 1-cell zygote that divides to form the 2-cell embryo. After fertilization, maternal proteins accumulated in the oocyte during mouse oogenesis are gradually degraded in the early embryonic stages. Transcription of the embryonic genome is initiated at the 1-cell stage (minor ZGA) and robustly activated at the 2-cell stage (major ZGA).

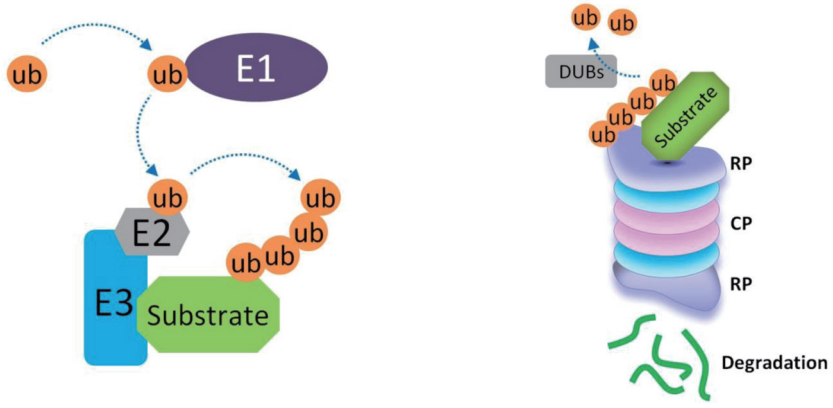

Fig. 2. The ubiquitin-proteasome system. The ubiquitin (Ub) pathway consists of three kinds of enzymes: E1 (Ub-activation enzyme), E2 (Ub-conjugation enzyme), E3 (Ub ligase). Ubiquitin is activated by E1 and is transferred to E2, and E3 then attaches Ub to a specific substrate protein. Ub is covalently attached to lysine residues of the substrate. Polyubiquitinated substrates are recognized and degraded by the 26S proteasome in an ATP-dependent manner. Deubiquitination enzymes (DUBs) on the regulatory particle (RP) remove polyubiquitin from proteasome substrates before substrates are translocated into the 20S proteasome core particle (CP) and regenerate free Ub from unanchored polyubiquitin chains.

The Ubiquitin-proteasome System in Mammalian Embryonic Development

The selective degradation of many short-lived proteins in eukaryotic cells is carried out by the ubiquitin-mediated proteasomal degradation system [7, 8]. This system plays important roles in the cell-cycle, stress response, immune system, transcription and translation regulation, DNA repair, quality control, and signal transduction [9–11]. Recently, expression or localization of ubiquitin, proteasome and ubiquitin-associated proteins in early embryonic development was reported [5, 12, 14, 15]. UBE2I (UBC9), SUMO-1 (UBL1) ligase is localized in the nucleus at the 2-cell stage [12]. The 20S core particle preferentially localizes to the nuclei of the full-grown oocytes and 1- to 16-cell embryos. A large number of ubiquitin-associated, ubiquitin-like proteins and deubiquitinating enzymes (DUBs), and 20S and 19S proteasome subunits are highly expressed in the MZT [14]. From mass spectrometry analysis of GV, MII oocytes and zygotes, we know that proteins involved in not only the ubiquitin pathway and ubiquitin association, but also proteasome members, are highly enriched in the zygote compared to GV and MII stage oocytes [15]. Also, E3 ubiquitin ligases are up-regulated in the zygote stage [15]. Polyubiquitinated maternal proteins are highly accumulated in germinal vesicle (GV) stage and metaphase II (MII) stage oocytes and they are degraded after fertilization [5]. This raises the possibility that accumulated polyubiquitinated maternal proteins in the oocyte are degraded by the proteasome before the 2-cell stage. Indeed, knockout of the *Psmc3* and *Psmc4* genes is lethal for mouse embryos before implantation, and these embryos display defective blastocyst development [16]. Also early embryonic development to the 2-cell stage is arrested by temporal treatment with proteasome inhibitor at the 1-cell stage, suggesting that ubiquitin-mediated proteasomal degradation of maternal proteins after fertilization is essential for normal early embryonic development [5].

The Importance of the Degradation of Maternal-effect Proteins

Previous reports have indicated that ubiquitin-mediated proteasomal degradation of maternal proteins is essential for normal embryonic development after fertilization. However, little is known about the functions of the ubiquitin-mediated system and proteasomal degradation of maternal proteins in early embryonic development. To date, there have been reports about maternal-effect genes such as *Nucleophosmin 2* (*Npm2*) [17], *Zfp3612* [18], *Zygote arrest 1* (*Zar1*) [19], *Heat shock factor 1* (*Hsf1*) [20], *Mater* [21], *Brahma-related gene 1* (*Brg1*) [22], *Basonuclin* [23], *Argonaute 2* (*Ago2*) [24], and *Bromodomain and WD repeat-containing protein* (*BRWD1*) [25], which are important for oogenesis and are degraded after fertilization. Interestingly, early embryonic development is arrested at the 1- or 2-cell stage by their knockout (KO). This invites the question, why is early embryonic development arrested at the 1- or 2-cell stage in maternal-effect gene KO mice, but not in earlier stages, like oogenesis? The importance of maternal protein degradation by the UPS for the onset of ZGA has been reported [4], implying that ubiquitin-mediated proteasomal degradation of maternal proteins is an essential prerequisite for successful early embryonic reprogramming.

Zygote-specific Proteasome Assembly

The proteasome is a highly conserved protein degradation machine made up of two complexes: the catalytic 20S proteasome (also called the core particle, CP) and the 19S regulatory particle (RP), both of which have a set of multiple distinct subunits [7, 26]. The 20S proteasome is composed of 28 subunits arranged in a cylindrical particle as four heteroheptameric rings (α_{1-7} β_{1-7} β_{1-7} α_{1-7}) [8, 27], the correct assembly of which requires a set of dedicated chaperones named the proteasome assembly chaperone (PAC) 1–4 (Psmg 1–4), and the ubiquitin-mediated proteolysis 1 (Ump1, also called POMP or Proteassemblin) [28–34]. The oocyte is the one of the largest single cells. For successful early embryonic reprogramming, accurate assembly of the proteasome complex is needed for sudden and accurate degradation of large amounts of maternal proteins in the oocytes after fertilization. Recently, we identified a molecule named ZPAC that is specifically expressed in mouse gonads, and the expression of ZPAC transiently increases in the mouse MZT [5]. ZPAC forms a complex with Ump1 and associates with precursor forms of 20S proteasomes (Fig. 3). The ZPAC gene is also under the control of an autoregulatory feedback mechanism for the compensation of reduced proteasome activity similar to Ump1 and 20S proteasome subunit gene expression. Knockdown of ZPAC in early embryos causes a significant reduction of proteasome activity and decreases in Ump1 and mature proteasomes, leading to the accumulation of the proteins that need to be degraded in the MZT and early developmental arrest. Therefore, a unique proteasome assembly pathway mediated by ZPAC is important for progression of the mouse MZT.

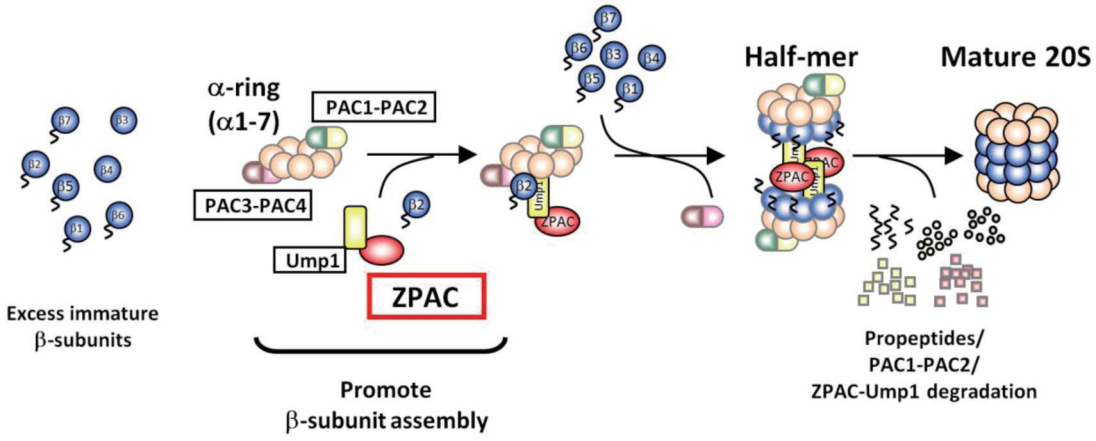

Fig. 3. A schematic model of ZPAC-mediated zygotic specific proteasome assembly in early mouse embryos. In the zygote, ZPAC is transiently expressed in the MZT and interacts with Ump1 increasing the stability of Ump1, which then promotes assembly of immature *β*-subunits that already exist in excess amounts in the zygote.

Proteasomal Degradation in Oocyte Maturation and the Cell Cycle

The major morphological changes occurring during oocyte maturation, such as germinal vesicle breakdown (GVBD), and chromosome condensation and segregation are regulated by the canonical M-phase promoting factor (MPF), which is a complex of cyclin-dependent kinase 1 (Cdk1) and cyclin B1 [35, 36]. First polar body extrusion is triggered by the inactivation of Cdk1, following the degradation of its regulatory subunit, cyclin B1, by the anaphase-promoting complex (APC), a multi-subunit E3 ubiquitin ligase, and ubiquitin-mediated proteolysis. In fact, nearly all the cell cycle during oocyte maturation and after fertilization is regulated by the UPS, which also includes the activators or inhibitors of APC itself. Ubiquitin-mediated proteolysis of cytoplasmic polyadenylation element-binding protein 1 (CPEB1) during meiosis is crucial for oocyte maturation. CPEB1 regulates the polyadenylation and is involved in the transcription of several cell cycle proteins such as cyclin A and cyclin B. CPEB1 plays a role as an activator or repressor depending on the its phosphorylation state [37], and its degradation occurs during the first meiotic division [38]. Its degradation requires Cdk1-mediated phosphorylation of CPEB1 followed by polyubiquitination. $SCF^{\beta\text{-TrCP}}$ E3 ligase complex, which binds the TSG motif phosphorylation by Plk1, is involved in the ubiquitination of CPEB1 in *Xenopus* oocytes [39].

The UPS for Initiation of ZGA

ZGA is a critical event and is regulated by maternal factors that govern not only transition from maternal-to-zygotic control, but also embryogenesis [3, 40]. A great number of studies have shown that maternal factors are equally critical for regulating development through epigenetic instructions and initiating transition from the maternal-to-zygotic transcription reprogramming [41]. Upon fertilization, the maternal and paternal nuclei undergo drastic chromatin changes, in which the sperm nucleus is stripped off its protamines, which are rapidly replaced by maternally provide histones [42]. Epigenetic reprogramming is also marked by loss of DNA methylation of the male pronucleus and deposition of replication-independent histone variants such as H3.3 [43]. At the same time, the maternal program breaks down and ZGA occurs. This switch off of MZT is thought to be regulated by maternal epigenetic factors and oocyte-derived factors [44–46]. Most fertilized eggs have their development arrested by inactivation of proteasome [4], suggesting that the UPS pivotally affects epigenetic reprogramming, such as histone modification after fertilization. Interestingly, a recent study focused on the role of Polycomb in mouse oocytes and their early development [47]. Its authors showed that E3 ubiquitin-protein ligase Ring1 and Rnf2, components of Polycomb-repressive complex 1 (PRC1), have redundant transcriptional functions during oogenesis that are essential for proper ZGA, replication and cell cycle progression in early embryos, as well as development beyond the 2-cell stage. PRC1 has histone-modifying activities and mediates mono ubiquitination of

H2A at lysine 119 (H2AK119ub1). Loss-of-function mutants of PRC1 complex members have led to the discovery of distinct as well as redundant functional roles for these proteins.

Application of the UPS to Somatic Cell Nuclear Transfer (SCNT)

The somatic cell nuclear transfer (SCNT) cloning technique has been applied successfully in a range of mammalian species giving rise to offspring [48], and is one of the tools used in reprogramming research. Unfortunately, the success rate of SCNT cloning is extremely low, and the mechanisms involved in reprogramming are unknown. Recently, the improvement of the SCNT success rate in mouse cloning, by the use of a low concentration of histone deacetylase inhibitor, trichostatin A (TSA) and proteasome inhibitor MG132, has been reported [49, 50]. TSA is an inhibitor of class I and II histone deacetylases (HDACs), which enhance the pool of acetylated histones [51] and DNA demethylation [52]. Of the HDACs, HDAC6 belongs to class IIb and is primarily a cytoplasmic protein which associates with non-histone substrates, such HSP90 and α-tubulin [53]. HDAC6 can bind to both mono- and poly-ubiquitinated proteins and promotes its own ubiquitination [54]. Suppression of HDAC6 function causes accumulation of acetylated α-tubulin and HSP90. Acetylation of HSP90 leads to loss of chaperone function and exposes its client proteins, such as Akt, Bcr-Abl, c-Raf and ErbB2, to polyubiquitination and proteasomal degradation. HDAC6 is also a regulator of the aggresome, a cellular structure that constitutes the major site of degradation for both non-ubiquitinated and ubiquitinated misfolded protein aggregates [55]. The BUZ domain of HDAC6 has high affinity for the ubiquitin molecule and is involved in the transport of polyubiquitinated proteins. HDAC6 functions as a bridge between the dynein and the ubiquitination processes, directing the polyubiquitinated proteins to the aggresome.

MG132 is one of the proteasome inhibitors and acts primarily on the chymotrypsin-like site in the *β*-subunit of the 20S core particle, and also inhibits the caspase-like site at high concentrations. In the case of rats, MG132 treatment seems to be required for successful cloning because ovulated rat oocytes are spontaneously activated, indicating that the suppression of spontaneous activation by inhibition of proteasome, such as inhibition of cyclin B1, and maternal proteins' degradation are the keys to successful cloning [50]. In porcine, the expression of zygotic genes such as *DPPA2*, *DPPA3*, *DPPA5* and *NDP52l1* and *POU5F1* is increased in SCNT embryos treated with low concentrations of MG132 [56], and treatment of immature oocytes with MG132 in the later stages of maturation improves gene expression in *in vitro* matured oocytes and SCNT embryos [57]. *POU5F1*, also known Oct4, and Nanog are specifically regulated by ubiquitin in undifferentiated pluripotent cells [58]. The half-lives of Oct4 and Nanog proteins in pluripotent embryonic stem cells (ESCs) are of the order of only a few hours, suggesting that the abundance of these key regulators of totipotency and pluripotency are strictly controlled by UPS-mediated degradation.

Conclusion

Since the discovery of ubiquitin and proteasome, a number of molecular mechanisms have been elucidated. We have learned much and are also now finding new biological phenomena related to the UPS. The importance of maternal degradation after fertilization has long been a topic of research, and many issues connected with it remain to be elucidated. In this review, we have simply summarized the importance of UPS and the zygote-specific assembly mechanism of the 20S proteasome in the MZT. Understanding of the involvement UPS in the degradation of maternal proteins and the onset of ZGA in the MZT would help to elucidate the molecular mechanisms governing the remodeling of the oocyte into a totipotent zygote, and may also have implications for regulation of pluripotency.

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