равно как и на важную роль иммуннопротеасом в удалении окисленных белков.

ЗАКЛЮЧЕНИЕ

ПСК обладают уникальными транскриптомными, эпигеномными и протеомными характеристиками, которые обеспечиваются работой высокоточной регуляторной сети. Кроме того, эти клетки характеризуются усиленной активностью защитных клеточных систем, включая УПС. УПС регулирует протеостаз клетки, и, тем самым, играет одну из определяющих ролей в поддержании плюрипотентности и в дифференцировке ПСК посредством координации уровней транскрипционных факторов плюрипотентности и участников регуляторных сетей с помощью убиквитинирования ферментами E1, E2 и E3 и деубиквитинирования DUB-ферментами, а также за счет модуляции экспрессии, активности и субстратной специфичности протеасомных комплексов. Совместная работа ферментов E1, E2 и E3 с одной стороны, и DUB, с другой, обеспечивает определенный баланс между протеолизом и стабилизацией факторов плюрипотентности и других ключевых факторов и, тем самым, определяет судьбу ПСК – поддержание плюрипотентного состояния или выход из него в процесс дифференцировки.

Известно, что ЭСК намного более чувствительны к манипуляциям с сетью протеостаза (например, к ингибированию протеасом) чем дифференцированные клетки (Vilchez et al., 2012a). Это можно объяснить, в частности, накоплением поврежденных белков вследствие инактивации протеасом и, следовательно, запуском гибели ЭСК. Кроме того, самоподдержание ЭСК также требует высокой строгости и точности протеостаза, в то время как его дисфункция может запускать проапоптотические сигналы до того, как начнут накапливаться поврежденные белки.

С каждым годом благодаря появлению новых высокотехнологичных подходов и высокопроизводительных скрининговых исследований растет понимание роли УПС в поддержании плюрипотентности ПСК и в их дифференцировке, однако, остается все еще много нерешенных вопросов. Как, например, убиквитинирование и деубиквитинирование динамически регулирует различные состояния плюрипотентности, такие как наивное, формативное и праймированное (Гордеев и др., 2021). Какие механизмы обеспечивают модуляцию работы различных форм протеасомных комплексов в различных состояниях плюрипотентности и в разных направлениях дифференцировки? Дальнейшее изучение протеостаза и его регуляции поможет ответить на эти и другие вопросы, достичь лучшего понимания биологии ПСК, а также привести к разработке новых подходов к модуляции клеточной спецификации и дифференцировки.

ФИНАНСИРОВАНИЕ РАБОТЫ

Работа выполнена при финансовой поддержке Российского научного фонда (№ 22-14-00390).

СОБЛЮДЕНИЕ ЭТИЧЕСКИХ СТАНДАРТОВ

Авторы не проводили эксперименты с участием животных или человека.

КОНФЛИКТ ИНТЕРЕСОВ

Авторы заявляют об отсутствии конфликтов интересов.

ВКЛАД АВТОРОВ

У.И. Поденкова, И.В. Зубарев: написание основной части работы, подбор литературы (внесли равный вклад в подготовку статьи). У.И. Поденкова и А.С. Цимоха: подготовка иллюстраций. А.С. Цимоха: подбор литературы, написание заключения; А.Н. Томилин и А.С. Цимоха: редактирование и правки текста.

СПИСОК ЛИТЕРАТУРЫ

Гордеев М.Н., Бахмет Е.И., Томилин А.Н. 2021. Динамика плюрипотентности в эмбриогенезе и в культуре. Онтогенез. Т. 52. № 6. С. 429. (*Gordeev M., Bakhmet E., Tomilin A.* 2021. Pluripotency dynamics during embryogenesis and in cell culture. Russ. J. Dev. Biol. V. 52. № 6. P. 379.) https://doi.org/10.1134/S1062360421060059

Селенина А.В., Цимоха А.С., Томилин А.Н. 2017. Протеасомы в регуляции белкового гомеостаза плюрипотентных стволовых клеток. Acta Naturae. Т. 9. № 3. С. 42. (*Selenina A.V., Tsimokha A.S., Tomilin A.N. 2017.* Proteasomes in protein homeostasis of pluripotent stem cells. Acta Naturae. V. 9. № 3. P. 42.)

Abu-Dawud R., Graffmann N., Ferber S., Wruck W., Adjaye J. 2018. Pluripotent stem cells: induction and self-renewal. Philos. Trans. R. Soc. Lond. B Biol. Sci. V. 373. P. 20170213. https://doi.org/10.1098/rstb.2017.0213

Al Mamun M.M., Khan M.R., Zhu Y., Zhang Y., Zhou S., Xu R., Bukhari I., Thorne R.F., Li J., Zhang X.D. 2022. Stub1 maintains proteostasis of master transcription factors in embryonic stem cells. Cell Rep. V. 39. P. 110919. https://doi.org/10.1016/j.celrep.2022.110919

Alekseenko Z., Dias J.M., Adler A.F., Kozhevnikova M., van Lunteren J.A., Nolbrant S., Jeggari A., Vasylovska S., Yoshitake T., Kehr J. 2022. Robust derivation of transplantable dopamine neurons from human pluripotent stem cells by timed retinoic acid delivery. Nature Commun. V.13. P. 1. https://doi.org/10.1038/s41467-022-30777-8

Babaie Y., Herwig R., Greber B., Brink T.C., Wruck W., Groth D., Lehrach H., Burdon T., Adjaye J. 2007. Analysis of Oct4-dependent transcriptional networks regulating self-renewal and pluripotency in human embryonic stem cells. Stem Cells. V. 25. P. 500. https://doi.org/10.1634/stemcells.2006-0426

Baharvand H., Hajheidari M., Ashtiani S.K., Salekdeh G.H. 2006. Proteomic signature of human embryonic stem cells.

Proteomics. V. 6. P. 3544.
https://doi.org/10.1002/pmic.200500844

Bai M., Zhao X., Sahara K., Ohte Y., Hirano Y., Kaneko T., Yashiroda H., Murata S. 2014. Assembly mechanisms of specialized core particles of the proteasome. Biomolecules. V. 4. P. 662.
https://doi.org/10.3390/biom4030662

Beckwith R., Estrin E., Worden E.J., Martin A. 2013. Reconstitution of the 26S proteasome reveals functional asymmetries in its AAA+ unfoldase. Nat. Struct. Mol. Biol. V. 20. P. 1164.
https://doi.org/10.1038/nsmb.2659

Behbahan I.S., Duan Y., Lam A., Khoobyari S., Ma X., Ahuja T.P., Zern M.A. 2011. New approaches in the differentiation of human embryonic stem cells and induced pluripotent stem cells toward hepatocytes. Stem Cell Rev. Rep. V. 7. P. 748.
https://doi.org/10.1007/s12015-010-9216-4

Bernstein B.E., Mikkelsen T.S., Xie X., Kamal M., Huebert D.J., Cuff J., Fry B., Meissner A., Wernig M., Plath K. 2006. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell. V. 125. P. 315.
https://doi.org/10.1016/j.cell.2006.02.041

Biancotti J.C., Narwani K., Buehler N., Mandefro B., Golan-Lev T., Yanuka O., Clark A., Hill D., Benvenisty N., Lavon N. 2010. Human embryonic stem cells as models for aneuploid chromosomal syndromes. Stem Cells. V. 28. P. 1530.
https://doi.org/10.1002/stem.483

Blondelle J., Shapiro P., Domenighetti A.A., Lange S. 2017. Cullin E3 ligase activity is required for myoblast differentiation. J. Mol. Biol. V. 429. P. 1045.
https://doi.org/10.1016/j.jmb.2017.02.012

Buckley S.M., Aranda-Orgilles B., Strikoudis A., Apostolou E., Loizou E., Moran-Crusio K., Farnsworth C.L., Koller A.A., Dasgupta R., Silva J.C., Stadtfeld M., Hochedlinger K., Chen E.I., Aifantis I. 2012. Regulation of pluripotency and cellular reprogramming by the ubiquitin-proteasome system. Cell Stem Cell. V. 11. P. 783.
https://doi.org/10.1016/j.stem.2012.09.011

Budenholzer L., Cheng C.L., Li Y., Hochstrasser M. 2017. Proteasome Structure and Assembly. J. Mol. Biol. V. 429. P. 3500.
https://doi.org/10.1016/j.jmb.2017.05.027

Bustos F., Segarra-Fas A., Chaugule V.K., Brandenburg L., Branigan E., Toth R., Macartney T., Knebel A., Hay R.T., Walden H. 2018. RNF12 X-linked intellectual disability mutations disrupt E3 ligase activity and neural differentiation. Cell Rep. V. 23. P. 1599.
https://doi.org/10.1016/j.celrep.2018.04.022

Cao F., Lin S., Xie X., Ray P., Patel M., Zhang X., Drukker M., Dylla S.J., Connolly A.J., Chen X. 2006. In vivo visualization of embryonic stem cell survival, proliferation, and migration after cardiac delivery. Circulation. V. 113. P. 1005.
https://doi.org/10.1161/CIRCULATIONAHA.105.588954

Cascio P., Hilton C., Kisselev A.F., Rock K.L., Goldberg A.L. 2001. 26S proteasomes and immunoproteasomes produce mainly N-extended versions of an antigenic peptide. EMBO J. V. 20. P. 2357.
https://doi.org/10.1093/emboj/20.10.2357

Choi J., Baek K.H. 2018. Cellular functions of stem cell factors mediated by the ubiquitin-proteasome system. Cell. Mol. Life Sci. V. 75. P. 1947.
https://doi.org/10.1007/s00018-018-2770-7

Ciechanover A., Kwon Y.T. 2015. Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies. Exp. Mol. Med. V. 47. P. e147.
https://doi.org/10.1038/emm.2014.117

Cui Z., Hwang S.M., Gomes A.V. 2014. Identification of the immunoproteasome as a novel regulator of skeletal muscle differentiation. Mol. Cell. Biol. V. 34. P. 96.
https://doi.org/10.1128/MCB.00622-13

Dahlmann B. 2005. Proteasomes. Essays Biochem. V. 41. P. 31.
https://doi.org/10.1042/EB0410031

de Napoles M., Mermoud J.E., Wakao R., Tang Y.A., Endoh M., Appanah R., Nesterova T.B., Silva J., Otte A.P., Vidal M. 2004. Polycomb group proteins Ring1A/B link ubiquitylation of histone H2A to heritable gene silencing and X inactivation. Dev. Cell. V. 7. P. 663.
https://doi.org/10.1016/j.devcel.2004.10.005

Diefenbacher M.E., Chakraborty A., Blake S.M., Mitter R., Popov N., Eilers M., Behrens A. 2015. Usp28 counteracts Fbw7 in intestinal homeostasis and cancer. Cancer Res. V. 75. P. 1181.
https://doi.org/10.1158/0008-5472.CAN-14-1726

Dieudonne F.-X., Sévère N., Biosse-Duplan M., Weng J.-J., Su Y., Marie P.J. 2013. Promotion of osteoblast differentiation in mesenchymal cells through Cbl-mediated control of STAT5 activity. Stem Cells. V. 31. P. 1340.
https://doi.org/10.1002/stem.1380

Drews O., Taegtmeyer H. 2014. Targeting the ubiquitin-proteasome system in heart disease: the basis for new therapeutic strategies. Antioxid. Redox. Signal. V. 21. P. 2322.
https://doi.org/10.1089/ars.2013.5823

Du Z., He F., Yu Z., Bowerman B., Bao Z. 2015. E3 ubiquitin ligases promote progression of differentiation during C. elegans embryogenesis. Dev. Biol. V. 398. P. 267.
https://doi.org/10.1016/j.ydbio.2014.12.009

Dutta D., Sharma V., Mutsuddi M., Mukherjee A. 2021. Regulation of Notch signaling by E3 ubiquitin ligases. FEBS J. V. 289. P. 937.
https://doi.org/10.1111/febs.15792

Endoh M., Endo T.A., Endoh T., Fujimura Y.-I., Ohara O., Toyoda T., Otte A.P., Okano M., Brockdorff N., Vidal M. 2008. Polycomb group proteins Ring1A/B are functionally linked to the core transcriptional regulatory circuitry to maintain ES cell identity. Development. V. 135. P. 1513.
https://doi.org/10.1242/dev.014340

Fabre B., Lambour T., Garrigues L., Amalric F., Vigneron N., Menneteau T., Stella A., Monsarrat B., Van den Eynde B., Burlet-Schiltz O. 2015. Deciphering preferential interactions within supramolecular protein complexes: the proteasome case. Mol. Syst. Biol. V. 11. P. 771.
https://doi.org/10.15252/msb.20145497

Fang L., Zhang L., Wei W., Jin X., Wang P., Tong Y., Li J., Du J.X., Wong J. 2014. A methylation-phosphorylation switch determines Sox2 stability and function in ESC maintenance or differentiation. Mol. Cell. V. 55. P. 537.
https://doi.org/10.1016/j.molcel.2014.06.018

Finley D., Tanaka K., Mann C., Feldmann H., Hochstrasser M., Vierstra R., Johnston S., Hampton R., Haber J., McCusker J., Silver P., Frontali L., Thorsness P., Varshavsky A., Byers B. et al. 1998. Unified nomenclature for subunits of the Saccharomyces cerevisiae proteasome regulatory particle. Trends Biochem. Sci. V. 23. P. 244.
https://doi.org/10.1016/s0968-0004(98)01222-5

Fort P., Kajava A.V., Delsuc F., Coux O. 2015. Evolution of proteasome regulators in eukaryotes. Genome Biol. Evol. V. 7. P. 1363.
https://doi.org/10.1093/gbe/evv068

Fu X. 2014. The immunogenicity of cells derived from induced pluripotent stem cells. Cell. Mol. Immunol. V. 11. P. 14.
https://doi.org/10.1038/cmi.2013.60

Fuchs G., Shema E., Vesterman R., Kotler E., Wolchinsky Z., Wilder S., Golomb L., Pribluda A., Zhang F., Haj-Yahya M., Feldmesser E., Brik A., Yu X., Hanna J., Aberdam D., Domany E., Oren M. 2012. RNF20 and USP44 regulate stem cell differentiation by modulating H2B monoubiquitylation. Mol. Cell. V. 46. P. 662.
https://doi.org/10.1016/j.molcel.2012.05.023

Fujikawa T., Oh S.-H., Pi L., Hatch H.M., Shupe T., Petersen B.E. 2005. Teratoma formation leads to failure of treatment for type I diabetes using embryonic stem cell-derived insulin-producing cells. Am. J. Pathol. V. 166. P. 1781.
https://doi.org/10.1016/S0002-9440(10)62488-1

Gao C., Xiao G., Hu J. 2014. Regulation of Wnt/β-catenin signaling by posttranslational modifications. Cell Biosci. V. 4. P. 13.
https://doi.org/10.1186/2045-3701-4-13

Gao J., Buckley S.M., Cimmino L., Guillamot M., Strikoudis A., Cang Y., Goff S.P., Aifantis I. 2015. The CUL4-DDB1 ubiquitin ligase complex controls adult and embryonic stem cell differentiation and homeostasis. Elife. V. 4. P. e07539.
https://doi.org/10.7554/eLife.07539

Glickman M.H., Rubin D.M., Coux O., Wefes I., Pfeifer G., Cjeka Z., Baumeister W., Fried V.A., Finley D. 1998. A subcomplex of the proteasome regulatory particle required for ubiquitin-conjugate degradation and related to the COP9-signalosome and eIF3. Cell. V. 94. P. 615.
https://doi.org/10.1016/s0092-8674(00)81603-7

Groll M., Bajorek M., Kohler A., Moroder L., Rubin D.M., Huber R., Glickman M.H., Finley D. 2000. A gated channel into the proteasome core particle. Nat. Struct. Biol. V. 7. P. 1062.
https://doi.org/10.1038/80992

Groll M., Bochtler M., Brandstetter H., Clausen T., Huber R. 2005. Molecular machines for protein degradation. Chembiochem. V. 6. P. 222.
https://doi.org/10.1002/cbic.200400313

Groll M., Ditzel L., Lowe J., Stock D., Bochtler M., Bartunik H.D., Huber R. 1997. Structure of 20S proteasome from yeast at 2.4 A resolution. Nature. V. 386. P. 463.
https://doi.org/10.1038/386463a0

Hatakeyama S. 2012. Ubiquitin-mediated regulation of JAK-STAT signaling in embryonic stem cells. JAKSTAT. V. 1. P. 168.
https://doi.org/10.4161/jkst.21560

Hayashi K., de Sousa Lopes S.M.C., Tang F., Surani M.A. 2008. Dynamic equilibrium and heterogeneity of mouse pluripotent stem cells with distinct functional and epigenetic states. Cell Stem Cell. V. 3. P. 391.
https://doi.org/10.1016/j.stem.2008.07.027

He M., Zhou Z., Shah A.A., Zou H., Tao J., Chen Q., Wan Y. 2016. The emerging role of deubiquitinating enzymes in genomic integrity, diseases, and therapeutics. Cell Biosci. V. 6. P. 62.
https://doi.org/10.1186/s13578-016-0127-1

Hernebring M., Brolen G., Aguilaniu H., Semb H., Nystrom T. 2006. Elimination of damaged proteins during differentiation of embryonic stem cells. Proc. Natl. Acad. Sci. USA. V. 103. P. 7700.
https://doi.org/10.1073/pnas.0510944103

Hernebring M., Fredriksson A., Liljevald M., Cvijovic M., Norrman K., Wiseman J., Semb H., Nystrom T. 2013. Removal of damaged proteins during ES cell fate specification requires the proteasome activator PA28. Sci. Rep. V. 3. P. 1381.
https://doi.org/10.1038/srep01381

Hershko A., Ciechanover A. 1992. The ubiquitin system for protein degradation. Annu. Rev. Biochem. V. 61. P. 761.
https://doi.org/10.1146/annurev.bi.61.070192.003553

Hershko A., Ciechanover A. 1998. The ubiquitin system. Annu. Rev. Biochem. V. 67. P. 425.
https://doi.org/10.1146/annurev.biochem.67.1.425

Inoue D., Aihara H., Sato T., Mizusaki H., Doiguchi M., Higashi M., Imamura Y., Yoneda M., Miyanishi T., Fujii S. 2015. Dzip3 regulates developmental genes in mouse embryonic stem cells by reorganizing 3D chromatin conformation. Sci. Rep. V. 5. P. 16567.
https://doi.org/10.1038/srep16567

Jiang T.X., Zhao M., Qiu X.B. 2018. Substrate receptors of proteasomes. Biol. Rev. Camb. Philos. Soc. V. 93. P. 1765.
https://doi.org/10.1111/brv.12419

Jing X., Infante J., Nachtman R.G., Jurecic R. 2008. E3 ligase FLRF (Rnf41) regulates differentiation of hematopoietic progenitors by governing steady-state levels of cytokine and retinoic acid receptors. Exp. Hematol. V. 36. P. 1110.
https://doi.org/10.1016/j.exphem.2008.04.001

Kammerl I.E., Dann A., Mossina A., Brech D., Lukas C., Vosyka O., Nathan P., Conlon T.M., Wagner D.E., Overkleeft H.S. 2016. Impairment of immunoproteasome function by cigarette smoke and in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. V. 193. P. 1230.
https://doi.org/10.1164/rccm.201506-1122OC

Kim S.-H., Kim M.O., Cho Y.-Y., Yao K., Kim D.J., Jeong C.-H., Yu D.H., Bae K.B., Cho E.J., Jung S.K. 2014. ERK1 phosphorylates Nanog to regulate protein stability and stem cell self-renewal. Stem Cell Res. V. 13. P. 1.
https://doi.org/10.1016/j.scr.2014.04.001

Konstantinova I.M., Tsimokha A.S., Mittenberg A.G. 2008. Role of proteasomes in cellular regulation. Int. Rev. Cell. Mol. Biol. V. 267. P. 59.
https://doi.org/10.1016/S1937-6448(08)00602-3

Li S., Xiao F., Zhang J., Sun X., Wang H., Zeng Y., Hu J., Tang F., Gu J., Zhao Y., Jin Y., Liao B. 2018. Disruption of OCT4 ubiquitination increases OCT4 protein stability and ASH2L-B-mediated H3K4 methylation promoting pluripotency acquisition. Stem Cell Reports. V. 11. P. 973.
https://doi.org/10.1016/j.stemcr.2018.09.001

Liao B., Zhong X., Xu H., Xiao F., Fang Z., Gu J., Chen Y., Zhao Y., Jin Y. 2013. Itch, an E3 ligase of Oct4, is required for embryonic stem cell self-renewal and pluripotency induction. J. Cell. Physiol. V. 228. P. 1443.
https://doi.org/10.1002/jcp.24297

Liu X., Yao Y., Ding H., Han C., Chen Y., Zhang Y., Wang C., Zhang X., Zhang Y., Zhai Y. 2016. USP21 deubiquitylates Nanog to regulate protein stability and stem cell pluripotency. Signal Transduct. Target. Ther. V. 1. P. 16024.
https://doi.org/10.1038/sigtrans.2016.24

Liu Y.-J., Nakamura T., Nakano T. 2012. Essential role of DPPA3 for chromatin condensation in mouse oocytogenesis. Biol. Reprod. V. 86. P. 40.
https://doi.org/10.1095/biolreprod.111.095018

Liu Y., Xu H.W., Wang L., Li S.Y., Zhao C.J., Hao J., Li Q.Y., Zhao T.T., Wu W., Wang Y. 2018. Human embryonic stem cell-derived retinal pigment epithelium transplants as a potential treatment for wet age-related macular degeneration. Cell Discov. V. 4. P. 50.
https://doi.org/10.1038/s41421-018-0053-y

Mattout A., Meshorer E. 2010. Chromatin plasticity and genome organization in pluripotent embryonic stem cells. Curr. Opin. Cell Biol. V. 22. P. 334.
https://doi.org/10.1016/j.ceb.2010.02.001

Meiners S., Keller I.E., Semren N., Caniard A. 2014. Regulation of the proteasome: evaluating the lung proteasome as a new therapeutic target. Antioxid. Redox. Signal. V. 21. P. 2364.
https://doi.org/10.1089/ars.2013.5798

Meiners S., Ludwig A., Stangl V., Stangl K. 2008. Proteasome inhibitors: poisons and remedies. Med. Res. Rev. V. 28. P. 309.
https://doi.org/10.1002/med.20111

Meshorer E., Misteli T. 2006. Chromatin in pluripotent embryonic stem cells and differentiation. Nat. Rev. Mol. Cell Biol. V. 7. P. 540.
https://doi.org/10.1038/nrm1938

Miyazono K. 2000. TGF-β signaling by Smad proteins. Cytokine Growth Factor Rev. V. 11. P. 15.
https://doi.org/10.1016/s1359-6101(99)00025-8

Morozov A.V., Karpov V.L. 2018. Biological consequences of structural and functional proteasome diversity. Heliyon. V. 4. P. e00894.
https://doi.org/10.1016/j.heliyon.2018.e00894

Murata S., Takahama Y., Tanaka K. 2008. Thymoproteasome: probable role in generating positively selecting peptides. Curr. Opin. Immunol. V. 20. P. 192.
https://doi.org/10.1016/j.coi.2008.03.002

Nakagawa T., Kajitani T., Togo S., Masuko N., Ohdan H., Hishikawa Y., Koji T., Matsuyama T., Ikura T., Muramatsu M. 2008. Deubiquitylation of histone H2A activates transcriptional initiation via trans-histone cross-talk with H3K4 di- and trimethylation. Genes Dev. V. 22. P. 37.
https://doi.org/10.1101/gad.1609708

Nakamura T., Arai Y., Umehara H., Masuhara M., Kimura T., Taniguchi H., Sekimoto T., Ikawa M., Yoneda Y., Okabe M. 2007. PGC7/Stella protects against DNA demethylation in early embryogenesis. Nat. Cell Biol. V. 9. P. 64.
https://doi.org/10.1038/ncb1519

Nakamura T., Liu Y.-J., Nakashima H., Umehara H., Inoue K., Matoba S., Tachibana M., Ogura A., Shinkai Y., Nakano T. 2012. PGC7 binds histone H3K9me2 to protect against conversion of 5mC to 5hmC in early embryos. Nature. V. 486. P. 415.
https://doi.org/10.1038/nature11093

Nandi D., Tahiliani P., Kumar A., Chandu D. 2006. The ubiquitin-proteasome system. J. Biosci. V. 31. P. 137.
https://doi.org/10.1007/BF02705243

Ng H.-H., Surani M.A. 2011. The transcriptional and signalling networks of pluripotency. Nat. Cell Biol. V. 13. P. 490.
https://doi.org/10.1038/ncb0511-490

Nguyen D.T.T., Richter D., Michel G., Mitschka S., Kolanus W., Cuevas E., Wulczyn F.G. 2017. The ubiquitin ligase LIN41/TRIM71 targets p53 to antagonize cell death and differentiation pathways during stem cell differentiation. Cell Death Differ. V. 24. P. 1063.
https://doi.org/10.1038/cdd.2017.54

Noormohammadi A., Calculli G., Gutierrez-Garcia R., Khodakarami A., Koyuncu S., Vilchez D. 2018. Mechanisms of protein homeostasis (proteostasis) maintain stem cell identity in mammalian pluripotent stem cells. Cell. Mol. Life Sci. V. 75. P. 275.
https://doi.org/10.1007/s00018-017-2602-1

Okita Y., Matsumoto A., Yumimoto K., Isoshita R., Nakayama K.I. 2012. Increased efficiency in the generation of induced pluripotent stem cells by F bxw7 ablation. Genes Cells. V. 17. P. 768.
https://doi.org/10.1111/j.1365-2443.2012.01626.x

Okita Y., Nakayama K.I. 2012. UPS delivers pluripotency. Cell Stem Cell. V. 11. P. 728.
https://doi.org/10.1016/j.stem.2012.11.009

Okumura F., Matsunaga Y., Katayama Y., Nakayama K.I., Hatakeyama S. 2010. TRIM8 modulates STAT3 activity through negative regulation of PIAS3. J. Cell Sci. V. 123. P. 2238.
https://doi.org/10.1242/jcs.068981

Osmulski P.A., Hochstrasser M., Gaczynska M. 2009. A tetrahedral transition state at the active sites of the 20S proteasome is coupled to opening of the alpha-ring channel. Structure. V. 17. P. 1137.
https://doi.org/10.1016/j.str.2009.06.011

Pak C., Danko T., Zhang Y., Aoto J., Anderson G., Maxeiner S., Yi F., Wernig M., Südhof T.C. 2015. Human neuropsychiatric disease modeling using conditional deletion reveals synaptic transmission defects caused by heterozygous mutations in NRXN1. Cell Stem Cell. V. 17. P. 316.
https://doi.org/10.1016/j.stem.2015.07.017

Pan J., Deng Q., Jiang C., Wang X., Niu T., Li H., Chen T., Jin J., Pan W., Cai X., Yang X., Lu M., Xiao J., Wang P. 2015. USP37 directly deubiquitinates and stabilizes c-Myc in lung cancer. Oncogene. V. 34. P. 3957.
https://doi.org/10.1038/onc.2014.327

Pickering A.M., Davies K.J. 2012. Degradation of damaged proteins: the main function of the 20S proteasome. Prog. Mol. Biol. Transl. Sci. V. 109. P. 227.
https://doi.org/10.1016/B978-0-12-397863-9.00006-7

Qian M.X., Pang Y., Liu C.H., Haratake K., Du B.Y., Ji D.Y., Wang G.F., Zhu Q.Q., Song W., Yu Y., Zhang X.X., Huang H.T., Miao S., Chen L.B., Zhang Z.H., Liang Y.N. et al. 2013. Acetylation-mediated proteasomal degradation of core histones during DNA repair and spermatogenesis. Cell. V. 153. P. 1012.
https://doi.org/10.1016/j.cell.2013.04.032

Rezania A., Bruin J.E., Arora P., Rubin A., Batushansky I., Asadi A., O'dwyer S., Quiskamp N., Mojibian M., Albrecht T. 2014. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat. Biotechnol. V. 32. P. 1121.
https://doi.org/10.1038/nbt.3033

Sang H., Wang D., Zhao S., Zhang J., Zhang Y., Xu J., Chen X., Nie Y., Zhang K., Zhang S. 2019. Dppa3 is critical for Lin28a-regulated ES cells naïve–primed state conversion. J. Mol. Cell Biol. V. 11. P. 474.
https://doi.org/10.1093/jmcb/mjy069

Saretzki G., Armstrong L., Leake A., Lako M., von Zglinicki T. 2004. Stress defense in murine embryonic stem cells is su-

perior to that of various differentiated murine cells. Stem Cells. V. 22. P. 962.
https://doi.org/10.1634/stemcells.22-6-962

Saric T., Chang S.-C., Hattori A., York I.A., Markant S., Rock K.L., Tsujimoto M., Goldberg A.L. 2002. An IFN-γ–induced aminopeptidase in the ER, ERAP1, trims precursors to MHC class I–presented peptides. Nat. Immunol. V. 3. P. 1169.
https://doi.org/10.1038/ni859

Sato N., Sanjuan I.M., Heke M., Uchida M., Naef F., Brivanlou A.H. 2003. Molecular signature of human embryonic stem cells and its comparison with the mouse. Dev. Biol. V. 260. P. 404.
https://doi.org/10.1016/s0012-1606(03)00256-2

Schuldiner M., Eiges R., Eden A., Yanuka O., Itskovitz-Eldor J., Goldstein R.S., Benvenisty N. 2001. Induced neuronal differentiation of human embryonic stem cells. Brain Res. V. 913. P. 201.
https://doi.org/10.1016/s0006-8993(01)02776-7

Schwartz S.D., Regillo C.D., Lam B.L., Eliott D., Rosenfeld P.J., Gregori N.Z., Hubschman J.-P., Davis J.L., Heilwell G., Spirn M. 2015. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet. V. 385. P. 509.
https://doi.org/10.1016/S0140-6736(14)61376-3

Seemuller E., Lupas A., Stock D., Lowe J., Huber R., Baumeister W. 1995. Proteasome from Thermoplasma acidophilum: a threonine protease. Science. V. 268. P. 579.
https://doi.org/10.1126/science.7725107

Sinenko S.A., Starkova T.Y., Kuzmin A.A., Tomilin A.N. 2021. Physiological signaling functions of reactive oxygen species in stem cells: From flies to man. Front. Cell Dev. Biol. V. 9. P. 714370.
https://doi.org/10.3389/fcell.2021.714370

Smalle J., Vierstra R.D. 2004. The ubiquitin 26S proteasome proteolytic pathway. Annu. Rev. Plant Biol. V. 55. P. 555.
https://doi.org/10.1146/annurev.arplant.55.031903.141801

Stadtmueller B.M., Hill C.P. 2011. Proteasome activators. Mol. Cell. V. 41. P. 8.
https://doi.org/10.1016/j.molcel.2010.12.020

Sun X.X., He X., Yin L., Komada M., Sears R.C., Dai M.S. 2015. The nucleolar ubiquitin-specific protease USP36 deubiquitinates and stabilizes c-Myc. Proc. Natl. Acad. Sci. USA. V. 112. P. 3734.
https://doi.org/10.1073/pnas.1411713112

Suresh B., Lee J., Kim K.S., Ramakrishna S. 2016. The importance of ubiquitination and deubiquitination in cellular reprogramming. Stem Cells Int. V. 2016. P. 6705927.
https://doi.org/10.1155/2016/6705927

Takahashi K., Yamanaka S. 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. V. 126. P. 663.
https://doi.org/10.1016/j.cell.2006.07.024

Thomson J.A., Itskovitz-Eldor J., Shapiro S.S., Waknitz M.A., Swiergiel J.J., Marshall V.S., Jones J.M. 1998. Embryonic stem cell lines derived from human blastocysts. Science. V. 282. P. 1145.
https://doi.org/10.1126/science.282.5391.1145

Uechi H., Hamazaki J., Murata S. 2014. Characterization of the testis-specific proteasome subunit alpha4s in mammals. J. Biol. Chem. V. 289. P. 12365.
https://doi.org/10.1074/jbc.M114.558866

Urbach A., Benvenisty N. 2009. Studying early lethality of 45, XO (Turner's syndrome) embryos using human embryonic stem cells. PLoS One. V. 4. P. e4175.
https://doi.org/10.1371/journal.pone.0004175

Uyama M., Sato M.M., Kawanami M., Tamura M. 2012. Regulation of osteoblastic differentiation by the proteasome inhibitor bortezomib. Genes Cells. V. 17. P. 548.
https://doi.org/10.1111/j.1365-2443.2012.01611.x

van der Stoop P., Boutsma E.A., Hulsman D., Noback S., Heimerikx M., Kerkhoven R.M., Voncken J.W., Wessels L.F., van Lohuizen M. 2008. Ubiquitin E3 ligase Ring1b/Rnf2 of polycomb repressive complex 1 contributes to stable maintenance of mouse embryonic stem cells. PLoS One. V. 3. P. e2235.
https://doi.org/10.1371/journal.pone.0002235

Verma R., Aravind L., Oania R., McDonald W.H., Yates J.R., 3rd, Koonin E.V., Deshaies R.J. 2002. Role of Rpn11 metalloprotease in deubiquitination and degradation by the 26S proteasome. Science. V. 298. P. 611.
https://doi.org/10.1126/science.1075898

Vilchez D., Boyer L., Lutz M., Merkwirth C., Morantte I., Tse C., Spencer B., Page L., Masliah E., Berggren W.T., Gage F.H., Dillin A. 2013. FOXO4 is necessary for neural differentiation of human embryonic stem cells. Aging Cell. V. 12. P. 518.
https://doi.org/10.1111/acel.12067

Vilchez D., Boyer L., Morantte I., Lutz M., Merkwirth C., Joyce D., Spencer B., Page L., Masliah E., Berggren W.T., Gage F.H., Dillin A. 2012a. Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. Nature. V. 489. P. 304.
https://doi.org/10.1038/nature11468

Vilchez D., Morantte I., Liu Z., Douglas P.M., Merkwirth C., Rodrigues A.P., Manning G., Dillin A. 2012b. RPN-6 determines C. elegans longevity under proteotoxic stress conditions. Nature. V. 489. P. 263.
https://doi.org/10.1038/nature11315

Voutsadakis I.A. 2012. The ubiquitin–proteasome system and signal transduction pathways regulating epithelial mesenchymal transition of cancer. J. Biomed. Sci. V. 19. P. 67.
https://doi.org/10.1186/1423-0127-19-67

Wang D., Bu F., Zhang W. 2019. The role of ubiquitination in regulating embryonic stem cell maintenance and cancer development. Int. J. Mol. Sci. V. 20. P. 2667.
https://doi.org/10.3390/ijms20112667

Wang X., Meul T., Meiners S. 2020. Exploring the proteasome system: a novel concept of proteasome inhibition and regulation. Pharmacol. Ther. V. 211. P. 107526.
https://doi.org/10.1016/j.pharmthera.2020.107526

Watanabe M., Takahashi H., Saeki Y., Ozaki T., Itoh S., Suzuki M., Mizushima W., Tanaka K., Hatakeyama S. 2015. The E3 ubiquitin ligase TRIM23 regulates adipocyte differentiation via stabilization of the adipogenic activator PPARγ. Elife. V. 4. P. e05615.
https://doi.org/10.7554/eLife.05615

Weitzman M.D., Lilley C.E., Chaurushiya M.S. 2010. Genomes in conflict: maintaining genome integrity during virus infection. Annu. Rev. Microbiol. V. 64. P. 61.
https://doi.org/10.1146/annurev.micro.112408.134016

Werner A., Manford A.G., Rape M. 2017. Ubiquitin-dependent regulation of stem cell biology. Trends Cell Biol. V. 27. P. 568.
https://doi.org/10.1016/j.tcb.2017.04.002

Xiao N., Eto D., Elly C., Peng G., Crotty S., Liu Y.-C. 2014. The E3 ubiquitin ligase Itch is required for the differentiation of follicular helper T cells. Nat. Immunol. V. 15. P. 657.
https://doi.org/10.1038/ni.2912

Xu H., Wang W., Li C., Yu H., Yang A., Wang B., Jin Y. 2009. WWP2 promotes degradation of transcription factor OCT4 in human embryonic stem cells. Cell Res. V. 19. P. 561.
https://doi.org/10.1038/cr.2009.31

Yadav D., Lee J.Y., Puranik N., Chauhan P.S., Chavda V., Jin J.-O., Lee P.C. 2022. Modulating the ubiquitin–proteasome system: a therapeutic strategy for autoimmune diseases. Cells. V. 11. P. 1093.
https://doi.org/10.3390/cells11071093

Yao T., Cohen R.E. 2002. A cryptic protease couples deubiquitination and degradation by the proteasome. Nature. V. 419. P. 403.
https://doi.org/10.1038/nature01071

Young L.E., Fernandes K., McEvoy T.G., Butterwith S.C., Gutierrez C.G., Carolan C., Broadbent P.J., Robinson J.J., Wilmut I., Sinclair K.D. 2001. Epigenetic change in IGF2R is associated with fetal overgrowth after sheep embryo culture. Nat. Genet. V. 27. P. 153.
https://doi.org/10.1038/84769

Young R.A. 2011. Control of the embryonic stem cell state. Cell. V. 144. P. 940.
https://doi.org/10.1016/j.cell.2011.01.032

Zhang F., Hu Y., Huang P., Toleman C.A., Paterson A.J., Kudlow J.E. 2007. Proteasome function is regulated by cyclic AMP-dependent protein kinase through phosphorylation of Rpt6. J. Biol. Chem. V. 282. P. 22460.
https://doi.org/10.1074/jbc.M702439200

Zhang F., Laiho M. 2003. On and off: proteasome and TGF-beta signaling. Exp. Cell Res. V. 291. P. 275.
https://doi.org/10.1016/j.yexcr.2003.07.007

Zhang X., Linder S., Bazzaro M. 2020. Drug development targeting the ubiquitin–proteasome system (UPS) for the treatment of human cancers. Cancers. V. 12. P. 902.
https://doi.org/10.3390/cancers12040902

Zhang Y., Ding H., Wang X., Wang X., Wan S., Xu A., Gan R., Ye S.-D. 2021. MK2 promotes Tfcp2l1 degradation via β-TrCP ubiquitin ligase to regulate mouse embryonic stem cell self-renewal. Cell Rep. V. 37. P. 109949.
https://doi.org/10.1016/j.celrep.2021.109949

Zhao S., Zhang C., Xu J., Liu S., Yu L., Chen S., Wen H., Li Z., Liu N. 2022. Dppa3 facilitates self-renewal of embryonic stem cells by stabilization of pluripotent factors. Stem Cell Res. Ther. V. 13. P. 169.
https://doi.org/10.1186/s13287-022-02846-8

Zhou L., Mideros S.X., Bao L., Hanlon R., Arredondo F.D., Tripathy S., Krampis K., Jerauld A., Evans C., St Martin S.K. 2009. Infection and genotype remodel the entire soybean transcriptome. BMC Genomics. V. 10. P. 49.
https://doi.org/10.1186/1471-2164-10-49

Zhou W., Zhu P., Wang J., Pascual G., Ohgi K.A., Lozach J., Glass C.K., Rosenfeld M.G. 2008. Histone H2A monoubiquitination represses transcription by inhibiting RNA polymerase II transcriptional elongation. Mol. Cell. V. 29. P. 69.
https://doi.org/10.1016/j.molcel.2007.11.002

Ubiquitin–Proteasome System in Cell Pluripotency and Differentiation

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Pluripotent stem cells (PSCs), represented primarily by embryonic stem cells and induced pluripotent stem cells (iPSCs), have a unique ability to self-renew and differentiate into all types of somatic cells. Dissecting molecular mechanisms controlling these properties is important for an efficient and safe introduction of PSCs into clinics. Growing evidence indicates that the proteostasis plays a central role in PSCs fate decisions. This review focuses on the role of the ubiquitin-proteasome system, a key member of the proteostasis network, in the regulation of pluripotency and differentiation of PSCs.

Keywords: deubiquitinases, differentiation, embryonic stem cells, pluripotency, proteasome, ubiquitin ligases, ubiquitin–proteasome system

Liu Y.-J., Nakamura T., Nakano T. 2012. Essential role of DPPA3 for chromatin condensation in mouse oocytogenesis. Biol. Reprod. V. 86. P. 40.
https://doi.org/10.1095/biolreprod.111.095018

Liu Y., Xu H.W., Wang L., Li S.Y., Zhao C.J., Hao J., Li Q.Y., Zhao T.T., Wu W., Wang Y. 2018. Human embryonic stem cell-derived retinal pigment epithelium transplants as a potential treatment for wet age-related macular degeneration. Cell Discov. V. 4. P. 50.
https://doi.org/10.1038/s41421-018-0053-y

Mattout A., Meshorer E. 2010. Chromatin plasticity and genome organization in pluripotent embryonic stem cells. Curr. Opin. Cell Biol. V. 22. P. 334.
https://doi.org/10.1016/j.ceb.2010.02.001

Meiners S., Keller I.E., Semren N., Caniard A. 2014. Regulation of the proteasome: evaluating the lung proteasome as a new therapeutic target. Antioxid. Redox. Signal. V. 21. P. 2364.
https://doi.org/10.1089/ars.2013.5798

Meiners S., Ludwig A., Stangl V., Stangl K. 2008. Proteasome inhibitors: poisons and remedies. Med. Res. Rev. V. 28. P. 309.
https://doi.org/10.1002/med.20111

Meshorer E., Misteli T. 2006. Chromatin in pluripotent embryonic stem cells and differentiation. Nat. Rev. Mol. Cell Biol. V. 7. P. 540.
https://doi.org/10.1038/nrm1938

Miyazono K. 2000. TGF-β signaling by Smad proteins. Cytokine Growth Factor Rev. V. 11. P. 15.
https://doi.org/10.1016/s1359-6101(99)00025-8

Morozov A.V., Karpov V.L. 2018. Biological consequences of structural and functional proteasome diversity. Heliyon. V. 4. P. e00894.
https://doi.org/10.1016/j.heliyon.2018.e00894

Murata S., Takahama Y., Tanaka K. 2008. Thymoproteasome: probable role in generating positively selecting peptides. Curr. Opin. Immunol. V. 20. P. 192.
https://doi.org/10.1016/j.coi.2008.03.002

Nakagawa T., Kajitani T., Togo S., Masuko N., Ohdan H., Hishikawa Y., Koji T., Matsuyama T., Ikura T., Muramatsu M. 2008. Deubiquitylation of histone H2A activates transcriptional initiation via trans-histone cross-talk with H3K4 di- and trimethylation. Genes Dev. V. 22. P. 37.
https://doi.org/10.1101/gad.1609708

Nakamura T., Arai Y., Umehara H., Masuhara M., Kimura T., Taniguchi H., Sekimoto T., Ikawa M., Yoneda Y., Okabe M. 2007. PGC7/Stella protects against DNA demethylation in early embryogenesis. Nat. Cell Biol. V. 9. P. 64.
https://doi.org/10.1038/ncb1519

Nakamura T., Liu Y.-J., Nakashima H., Umehara H., Inoue K., Matoba S., Tachibana M., Ogura A., Shinkai Y., Nakano T. 2012. PGC7 binds histone H3K9me2 to protect against conversion of 5mC to 5hmC in early embryos. Nature. V. 486. P. 415.
https://doi.org/10.1038/nature11093

Nandi D., Tahiliani P., Kumar A., Chandu D. 2006. The ubiquitin-proteasome system. J. Biosci. V. 31. P. 137.
https://doi.org/10.1007/BF02705243

Ng H.-H., Surani M.A. 2011. The transcriptional and signalling networks of pluripotency. Nat. Cell Biol. V. 13. P. 490.
https://doi.org/10.1038/ncb0511-490

Nguyen D.T.T., Richter D., Michel G., Mitschka S., Kolanus W., Cuevas E., Wulczyn F.G. 2017. The ubiquitin ligase LIN41/TRIM71 targets p53 to antagonize cell death and differentiation pathways during stem cell differentiation. Cell Death Differ. V. 24. P. 1063.
https://doi.org/10.1038/cdd.2017.54

Noormohammadi A., Calculli G., Gutierrez-Garcia R., Khodakarami A., Koyuncu S., Vilchez D. 2018. Mechanisms of protein homeostasis (proteostasis) maintain stem cell identity in mammalian pluripotent stem cells. Cell. Mol. Life Sci. V. 75. P. 275.
https://doi.org/10.1007/s00018-017-2602-1

Okita Y., Matsumoto A., Yumimoto K., Isoshita R., Nakayama K.I. 2012. Increased efficiency in the generation of induced pluripotent stem cells by F bxw7 ablation. Genes Cells. V. 17. P. 768.
https://doi.org/10.1111/j.1365-2443.2012.01626.x

Okita Y., Nakayama K.I. 2012. UPS delivers pluripotency. Cell Stem Cell. V. 11. P. 728.
https://doi.org/10.1016/j.stem.2012.11.009

Okumura F., Matsunaga Y., Katayama Y., Nakayama K.I., Hatakeyama S. 2010. TRIM8 modulates STAT3 activity through negative regulation of PIAS3. J. Cell Sci. V. 123. P. 2238.
https://doi.org/10.1242/jcs.068981

Osmulski P.A., Hochstrasser M., Gaczynska M. 2009. A tetrahedral transition state at the active sites of the 20S proteasome is coupled to opening of the alpha-ring channel. Structure. V. 17. P. 1137.
https://doi.org/10.1016/j.str.2009.06.011

Pak C., Danko T., Zhang Y., Aoto J., Anderson G., Maxeiner S., Yi F., Wernig M., Südhof T.C. 2015. Human neuropsychiatric disease modeling using conditional deletion reveals synaptic transmission defects caused by heterozygous mutations in NRXN1. Cell Stem Cell. V. 17. P. 316.
https://doi.org/10.1016/j.stem.2015.07.017

Pan J., Deng Q., Jiang C., Wang X., Niu T., Li H., Chen T., Jin J., Pan W., Cai X., Yang X., Lu M., Xiao J., Wang P. 2015. USP37 directly deubiquitinates and stabilizes c-Myc in lung cancer. Oncogene. V. 34. P. 3957.
https://doi.org/10.1038/onc.2014.327

Pickering A.M., Davies K.J. 2012. Degradation of damaged proteins: the main function of the 20S proteasome. Prog. Mol. Biol. Transl. Sci. V. 109. P. 227.
https://doi.org/10.1016/B978-0-12-397863-9.00006-7

Qian M.X., Pang Y., Liu C.H., Haratake K., Du B.Y., Ji D.Y., Wang G.F., Zhu Q.Q., Song W., Yu Y., Zhang X.X., Huang H.T., Miao S., Chen L.B., Zhang Z.H., Liang Y.N. et al. 2013. Acetylation-mediated proteasomal degradation of core histones during DNA repair and spermatogenesis. Cell. V. 153. P. 1012.
https://doi.org/10.1016/j.cell.2013.04.032

Rezania A., Bruin J.E., Arora P., Rubin A., Batushansky I., Asadi A., O'dwyer S., Quiskamp N., Mojibian M., Albrecht T. 2014. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat. Biotechnol. V. 32. P. 1121.
https://doi.org/10.1038/nbt.3033

Sang H., Wang D., Zhao S., Zhang J., Zhang Y., Xu J., Chen X., Nie Y., Zhang K., Zhang S. 2019. Dppa3 is critical for Lin28a-regulated ES cells naïve–primed state conversion. J. Mol. Cell Biol. V. 11. P. 474.
https://doi.org/10.1093/jmcb/mjy069

Saretzki G., Armstrong L., Leake A., Lako M., von Zglinicki T. 2004. Stress defense in murine embryonic stem cells is su-

perior to that of various differentiated murine cells. Stem Cells. V. 22. P. 962.
https://doi.org/10.1634/stemcells.22-6-962

Saric T., Chang S.-C., Hattori A., York I.A., Markant S., Rock K.L., Tsujimoto M., Goldberg A.L. 2002. An IFN-γ–induced aminopeptidase in the ER, ERAP1, trims precursors to MHC class I–presented peptides. Nat. Immunol. V. 3. P. 1169.
https://doi.org/10.1038/ni859

Sato N., Sanjuan I.M., Heke M., Uchida M., Naef F., Brivanlou A.H. 2003. Molecular signature of human embryonic stem cells and its comparison with the mouse. Dev. Biol. V. 260. P. 404.
https://doi.org/10.1016/s0012-1606(03)00256-2

Schuldiner M., Eiges R., Eden A., Yanuka O., Itskovitz-Eldor J., Goldstein R.S., Benvenisty N. 2001. Induced neuronal differentiation of human embryonic stem cells. Brain Res. V. 913. P. 201.
https://doi.org/10.1016/s0006-8993(01)02776-7

Schwartz S.D., Regillo C.D., Lam B.L., Eliott D., Rosenfeld P.J., Gregori N.Z., Hubschman J.-P., Davis J.L., Heilwell G., Spirn M. 2015. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet. V. 385. P. 509.
https://doi.org/10.1016/S0140-6736(14)61376-3

Seemuller E., Lupas A., Stock D., Lowe J., Huber R., Baumeister W. 1995. Proteasome from Thermoplasma acidophilum: a threonine protease. Science. V. 268. P. 579.
https://doi.org/10.1126/science.7725107

Sinenko S.A., Starkova T.Y., Kuzmin A.A., Tomilin A.N. 2021. Physiological signaling functions of reactive oxygen species in stem cells: From flies to man. Front. Cell Dev. Biol. V. 9. P. 714370.
https://doi.org/10.3389/fcell.2021.714370

Smalle J., Vierstra R.D. 2004. The ubiquitin 26S proteasome proteolytic pathway. Annu. Rev. Plant Biol. V. 55. P. 555.
https://doi.org/10.1146/annurev.arplant.55.031903.141801

Stadtmueller B.M., Hill C.P. 2011. Proteasome activators. Mol. Cell. V. 41. P. 8.
https://doi.org/10.1016/j.molcel.2010.12.020

Sun X.X., He X., Yin L., Komada M., Sears R.C., Dai M.S. 2015. The nucleolar ubiquitin-specific protease USP36 deubiquitinates and stabilizes c-Myc. Proc. Natl. Acad. Sci. USA. V. 112. P. 3734.
https://doi.org/10.1073/pnas.1411713112

Suresh B., Lee J., Kim K.S., Ramakrishna S. 2016. The importance of ubiquitination and deubiquitination in cellular reprogramming. Stem Cells Int. V. 2016. P. 6705927.
https://doi.org/10.1155/2016/6705927

Takahashi K., Yamanaka S. 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. V. 126. P. 663.
https://doi.org/10.1016/j.cell.2006.07.024

Thomson J.A., Itskovitz-Eldor J., Shapiro S.S., Waknitz M.A., Swiergiel J.J., Marshall V.S., Jones J.M. 1998. Embryonic stem cell lines derived from human blastocysts. Science. V. 282. P. 1145.
https://doi.org/10.1126/science.282.5391.1145

Uechi H., Hamazaki J., Murata S. 2014. Characterization of the testis-specific proteasome subunit alpha4s in mammals. J. Biol. Chem. V. 289. P. 12365.
https://doi.org/10.1074/jbc.M114.558866

Urbach A., Benvenisty N. 2009. Studying early lethality of 45, XO (Turner's syndrome) embryos using human embryonic stem cells. PLoS One. V. 4. P. e4175.
https://doi.org/10.1371/journal.pone.0004175

Uyama M., Sato M.M., Kawanami M., Tamura M. 2012. Regulation of osteoblastic differentiation by the proteasome inhibitor bortezomib. Genes Cells. V. 17. P. 548.
https://doi.org/10.1111/j.1365-2443.2012.01611.x

van der Stoop P., Boutsma E.A., Hulsman D., Noback S., Heimerikx M., Kerkhoven R.M., Voncken J.W., Wessels L.F., van Lohuizen M. 2008. Ubiquitin E3 ligase Ring1b/Rnf2 of polycomb repressive complex 1 contributes to stable maintenance of mouse embryonic stem cells. PLoS One. V. 3. P. e2235.
https://doi.org/10.1371/journal.pone.0002235

Verma R., Aravind L., Oania R., McDonald W.H., Yates J.R., 3rd, Koonin E.V., Deshaies R.J. 2002. Role of Rpn11 metalloprotease in deubiquitination and degradation by the 26S proteasome. Science. V. 298. P. 611.
https://doi.org/10.1126/science.1075898

Vilchez D., Boyer L., Lutz M., Merkwirth C., Morantte I., Tse C., Spencer B., Page L., Masliah E., Berggren W.T., Gage F.H., Dillin A. 2013. FOXO4 is necessary for neural differentiation of human embryonic stem cells. Aging Cell. V. 12. P. 518.
https://doi.org/10.1111/acel.12067

Vilchez D., Boyer L., Morantte I., Lutz M., Merkwirth C., Joyce D., Spencer B., Page L., Masliah E., Berggren W.T., Gage F.H., Dillin A. 2012a. Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. Nature. V. 489. P. 304.
https://doi.org/10.1038/nature11468

Vilchez D., Morantte I., Liu Z., Douglas P.M., Merkwirth C., Rodrigues A.P., Manning G., Dillin A. 2012b. RPN-6 determines C. elegans longevity under proteotoxic stress conditions. Nature. V. 489. P. 263.
https://doi.org/10.1038/nature11315

Voutsadakis I.A. 2012. The ubiquitin–proteasome system and signal transduction pathways regulating epithelial mesenchymal transition of cancer. J. Biomed. Sci. V. 19. P. 67.
https://doi.org/10.1186/1423-0127-19-67

Wang D., Bu F., Zhang W. 2019. The role of ubiquitination in regulating embryonic stem cell maintenance and cancer development. Int. J. Mol. Sci. V. 20. P. 2667.
https://doi.org/10.3390/ijms20112667

Wang X., Meul T., Meiners S. 2020. Exploring the proteasome system: a novel concept of proteasome inhibition and regulation. Pharmacol. Ther. V. 211. P. 107526.
https://doi.org/10.1016/j.pharmthera.2020.107526

Watanabe M., Takahashi H., Saeki Y., Ozaki T., Itoh S., Suzuki M., Mizushima W., Tanaka K., Hatakeyama S. 2015. The E3 ubiquitin ligase TRIM23 regulates adipocyte differentiation via stabilization of the adipogenic activator PPARγ. Elife. V. 4. P. e05615.
https://doi.org/10.7554/eLife.05615

Weitzman M.D., Lilley C.E., Chaurushiya M.S. 2010. Genomes in conflict: maintaining genome integrity during virus infection. Annu. Rev. Microbiol. V. 64. P. 61.
https://doi.org/10.1146/annurev.micro.112408.134016

Werner A., Manford A.G., Rape M. 2017. Ubiquitin-dependent regulation of stem cell biology. Trends Cell Biol. V. 27. P. 568.
https://doi.org/10.1016/j.tcb.2017.04.002

Xiao N., Eto D., Elly C., Peng G., Crotty S., Liu Y.-C. 2014. The E3 ubiquitin ligase Itch is required for the differentiation of follicular helper T cells. Nat. Immunol. V. 15. P. 657.
https://doi.org/10.1038/ni.2912

Xu H., Wang W., Li C., Yu H., Yang A., Wang B., Jin Y. 2009. WWP2 promotes degradation of transcription factor OCT4 in human embryonic stem cells. Cell Res. V. 19. P. 561.
https://doi.org/10.1038/cr.2009.31

Yadav D., Lee J.Y., Puranik N., Chauhan P.S., Chavda V., Jin J.-O., Lee P.C. 2022. Modulating the ubiquitin–proteasome system: a therapeutic strategy for autoimmune diseases. Cells. V. 11. P. 1093.
https://doi.org/10.3390/cells11071093

Yao T., Cohen R.E. 2002. A cryptic protease couples deubiquitination and degradation by the proteasome. Nature. V. 419. P. 403.
https://doi.org/10.1038/nature01071

Young L.E., Fernandes K., McEvoy T.G., Butterwith S.C., Gutierrez C.G., Carolan C., Broadbent P.J., Robinson J.J., Wilmut I., Sinclair K.D. 2001. Epigenetic change in IGF2R is associated with fetal overgrowth after sheep embryo culture. Nat. Genet. V. 27. P. 153.
https://doi.org/10.1038/84769

Young R.A. 2011. Control of the embryonic stem cell state. Cell. V. 144. P. 940.
https://doi.org/10.1016/j.cell.2011.01.032

Zhang F., Hu Y., Huang P., Toleman C.A., Paterson A.J., Kudlow J.E. 2007. Proteasome function is regulated by cyclic AMP-dependent protein kinase through phosphorylation of Rpt6. J. Biol. Chem. V. 282. P. 22460.
https://doi.org/10.1074/jbc.M702439200

Zhang F., Laiho M. 2003. On and off: proteasome and TGF-beta signaling. Exp. Cell Res. V. 291. P. 275.
https://doi.org/10.1016/j.yexcr.2003.07.007

Zhang X., Linder S., Bazzaro M. 2020. Drug development targeting the ubiquitin–proteasome system (UPS) for the treatment of human cancers. Cancers. V. 12. P. 902.
https://doi.org/10.3390/cancers12040902

Zhang Y., Ding H., Wang X., Wang X., Wan S., Xu A., Gan R., Ye S.-D. 2021. MK2 promotes Tfcp2l1 degradation via β-TrCP ubiquitin ligase to regulate mouse embryonic stem cell self-renewal. Cell Rep. V. 37. P. 109949.
https://doi.org/10.1016/j.celrep.2021.109949

Zhao S., Zhang C., Xu J., Liu S., Yu L., Chen S., Wen H., Li Z., Liu N. 2022. Dppa3 facilitates self-renewal of embryonic stem cells by stabilization of pluripotent factors. Stem Cell Res. Ther. V. 13. P. 169.
https://doi.org/10.1186/s13287-022-02846-8

Zhou L., Mideros S.X., Bao L., Hanlon R., Arredondo F.D., Tripathy S., Krampis K., Jerauld A., Evans C., St Martin S.K. 2009. Infection and genotype remodel the entire soybean transcriptome. BMC Genomics. V. 10. P. 49.
https://doi.org/10.1186/1471-2164-10-49

Zhou W., Zhu P., Wang J., Pascual G., Ohgi K.A., Lozach J., Glass C.K., Rosenfeld M.G. 2008. Histone H2A monoubiquitination represses transcription by inhibiting RNA polymerase II transcriptional elongation. Mol. Cell. V. 29. P. 69.
https://doi.org/10.1016/j.molcel.2007.11.002

Ubiquitin–Proteasome System in Cell Pluripotency and Differentiation

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Pluripotent stem cells (PSCs), represented primarily by embryonic stem cells and induced pluripotent stem cells (iPSCs), have a unique ability to self-renew and differentiate into all types of somatic cells. Dissecting molecular mechanisms controlling these properties is important for an efficient and safe introduction of PSCs into clinics. Growing evidence indicates that the proteostasis plays a central role in PSCs fate decisions. This review focuses on the role of the ubiquitin-proteasome system, a key member of the proteostasis network, in the regulation of pluripotency and differentiation of PSCs.

Keywords: deubiquitinases, differentiation, embryonic stem cells, pluripotency, proteasome, ubiquitin ligases, ubiquitin–proteasome system