a hallmark in those processes, is partway consequence of the ubiquitin-proteasome system malfunction. Therefore, there is a great clinical expectation that the prevention of aggregates upon proteasome activation might improve clinical manifestations in those pathologies.

The mechanism underlying the extension of life span through proteasome activation has not been explored, although it might shed light on the particular mechanisms involved in the aging process and proteostasis.

Notably, epidemiologic data collected by combining studies of neurodegeneration and cancer[26,27] revealed an inverse association between both processes throughout life. Based on genetic and proteomic studies of cancer and neurodegeneration, both studies above concluded that the ubiquitin-proteasome system is one of the central metabolic pathways, as the 20S proteasome catalytic core presents decreased activity in neurodegeneration and, in turn, is increased in tumor cells. Indeed, the half-lives of tumor suppressor proteins, many DNA repair proteins and anti-apoptotic proteins, which are key regulators of tumor cell fate and neuron loss, are regulated by the ubiquitin-proteasome system. Tumor cells present increased expression of many components of the ubiquitin-proteasome system that is related to the increased proteasome activity observed in those cells[28,29]. On the other hand, proteasome activity is decreased in cancer stem cells (CSCs), probably due to the low metabolic activity of CSCs[30]. As already described, low proteasome activity predisposes tumor-initiating cells to form spheres in osteosarcoma, increasing tumorigenesis. Therefore, one would expect that the increased proteasome activity in CSCs would prevent tumorigenesis[31]. In conclusion, researchers have not yet clearly identified the role of the ubiquitin-proteasome system in either tumor development or its progression.

Future perspectives

Although proteasome activation is an important tool for examining degenerative processes that rely on the loss of proteostasis, one should be aware of the possible long-term toxic effects underlying proteasomal activation. As the ubiquitin-proteasome system is a complex system that regulates the half-life of proteins, other components of the system might be more reliable targets for intervention for future studies. Among those components, E3 proteins are undoubtedly important targets. These proteins are highly specific in the recognition of their targets to promote poly-ubiquitylation of the substrate. Therefore, a better comprehension of their mechanisms of action and the regulation of their expression could direct target proteins for degradation. As in the case of drugs that increase the translation of proteasome subunits, a more comprehensive approach to examining the mechanisms of E3 ligase expression might be beneficial to induce the degradation of key proteins without promoting widespread protein degradation. Furthermore, direct proteasome activation is a powerful tool for preventing protein aggregation.

References

1. Fenteany G, Standaert RF, Reichard GA, et al. A Beta-Lactone Related to Lactacystin Induces Neurite Outgrowth in a Neuroblastoma Cell-Line and Inhibits Cell-Cycle Progression in an Osteosarcoma Cell-Line. Proc Natl Acad Sci USA. 1994; 91(8): 3358–3362.
2. Fenteany G, Standaert RF, Lane WS, et al. Inhibition of proteasome activities and subunit-specific amino-terminal threonine modification by lactacystin. Science. 1995; 268(5211): 726-731.
3. Chondrogianni N, Tzavelas C, Pemberton AJ, et al. Overexpression of proteasome beta5 assembled subunit increases the amount of proteasome and confers ameliorated response to oxidative stress and higher survival rates. J Biol Chem. 2005; 280(12): 11840-11850
4. Chondrogianni N, Voutetakis K, Kapetanou M, et al. Proteasome activation: An innovative promising approach for delaying aging and retarding age-related diseases. Ageing Res Rev. 2015; 23(Pt A): 37–55.
5. Huang L, Chen CH. Proteasome regulators: activators and inhibitors. Cur Med Chem. 2009; 16(8): 931–939.
6. Dal Vechio FH, Cerqueira F, Augusto O, et al. Peptides that activate the 20S proteasome by gate opening increased oxidized protein removal and reduced protein aggregation. Free Rad Biol Med. 2014; 67: 304–313.
7. Papaevgeniou N, Sakellari M, Jha S, et al. 18α-Glycyrrhetinic Acid Proteasome Activator Decelerates Aging and Alzheimer's Disease Progression in Caenorhabditis elegans and Neuronal Cultures. Antiox Redox Signal. 2016; 25(16): 855-869.
8. Krahn JH, Kaschani F, Kaiser M. Turning-ON Proteasomes. Cell Chem Biol. 2017; 24(6): 653-655.
9. Varshavsky A. The Ubiquitin System, Autophagy, and Regulated Protein Degradation. Ann Rev Biochem. 2017; 86: 123-128.
10. Baugh JM, Viktorova EG, Pilipenko EV. Proteasomes can degrade a significant proportion of cellular proteins independent of ubiquitination. J Mol Biol. 2009; 386(3): 814-827.
11. Ben Nissan G, Sharon M. Regulating the 20S proteasome ubiquitin-independent degradation pathway. Biomolecules. 2014; 4(3): 862-884.
12. Erales J, Coffino P. Ubiquitin-independent proteasomal degradation. Biochim Biophys Acta. 2014; 1843(1): 216-221.
13. Demasi M, Netto LE, Silva GM, et al. Redox regulation of the proteasome via S-glutathionylation. Redox Biology. 2013; 2: 44–51.
14. Davies KJA. Degradation of oxidized proteins by the 20S proteasome. Biochimie. 2001; 83(3-4): 301–310.
15. Kwak MK, Cho JM, Huang B, et al. Role of increased expression of the proteasome in the protective effects of sulforaphane against hydrogen peroxide-mediated cytotoxicity in murine neuroblastoma cells. Free Rad Biol Med. 2007; 43: 809–817.
16. Chondrogianni N, Gonos ES. Proteasome activation as a novel antiaging strategy. IUBMB Life. 2008; 60(10): 651–655.
17. Dahlmann B, Rutschmann M, Kuehn L, et al. Activation of the multicatalytic proteinase from rat skeletal muscle by fatty acids or sodium dodecyl sulphate. Biochem J. 1985; 228(1): 171–177.
18. Katsiki M, Chondrogianni N, Chinou I, et al. The olive constituent oleuropein exhibits proteasome stimulatory properties in vitro and confers life span extension of human embryonic fibroblasts. Rejuv Res. 2007; 10(2): 157–172.

19. Rodriguez KA, Osmulski PA, Pierce A, et al. A cytosolic protein factor from the naked mole-rat activates proteasomes of other species and protects these from inhibition. Biochem Biophys Acta. 2014; 1842(11): 2060–2072.

20. Lopes-Ferreira M, Silva C, Pimenta D, et al. Anti-inflammatory and anti-allergic cyclic peptides. www.patenscope.wipo.int/ Pub No. WO2008009085. 2008.

21. Goldberg AL, Smith DM. Activators of proteasomal degradation and uses threof. www.patenscope.wipo.int/ Pub No. WO2012/075393 A2. 2012.

22. Trader DJ, Simanski S, Dickson P, et al. Establishment of a suite of assays that support the discovery of proteasome stimulators. Biochim Biophys Acta. 2017; 1861(4): 892-899.

23. Lee BH, Lee MJ, Park S, et al. Enhancement of proteasome activity by a small-molecule inhibitor of USP14. Nature. 2010; 467(7312): 179-184.

24. Ferreira JC, Boer BN, Grinberg M, et al. Protein quality control disruption by PKCβII in heart failure; rescue by the selective PKCβII inhibitor, βIIV5-3. PLoS One. 2012; 7(3): e33175.

25. Hedge AN, van Leeuwen FW. Ubiquitin and the brain: roles of proteolysis in the normal and abnormal nervous system. Frontiers Mol Neurosc. 2017; 10: 220-222.

26. Tabarés-Seisdedos R, Rubenstein JL. Inverse cancer comorbidity: a serendipitous opportunity to gain insight into CNS disorders. Nat Rev Neurosci. 2013; 14(4): 293-304.

27. Driver JA. Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence. Biogerontology. 2014; 15(6): 547–557.

28. Arlt A, Bauer I, Schafmayer C, et al. Increased proteasome subunit protein expression and proteasome activity in colon cancer relate to an enhanced activation of nuclear factor E2-related factor 2 (Nrf2). Oncogene. 2009; 28(45): 3983–3996.

29. Furuyama T, Tanaka S, Shimada S, et al. Proteasome activity is required for the initiation of precancerous pancreatic lesions. Sci Rep. 2016; 6(1): 27044-27055.

30. Voutsadakis IA. Proteasome expression and activity in cancer and cancer stem cells. Tumor Biol. 2017; 39(3): 1-17.

31. Tamari K, Hayashi K, Ishii H, et al. Identification of chemoradiation-resistant osteosarcoma stem cells using an imaging system for proteasome activity. International J Oncol. 2014; 45(6): 2349–2354.