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The case for therapeutic proteostasis modulators

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Abstract

A functional ubiquitin proteasome pathway (UPP) is vital for all eukaryotic cellular systems and therefore any alteration in this critical component of proteostasis machinery has rpotential pathological consequences. A proteostasis imbalance can be induced by environmental pollutants, age or genetic factors. Though the exact underlying mechanisms are unclear, a decrease in proteasome activity weakens the homeostatic cellular capacity to remove proteins that are either misfolded or need to be replenished, which favors the development of neurodegenerative, cardiac and other conformational diseases. In contrast, induction of proteasome activity is an attribute of many diseases including muscle wasting, sepsis, cachexia and uraemia. In the case of misfolded protein disorders, higher degradation of a single protein leads to the pathophysiological consequences due to the absence of functional protein. Therefore, selective proteostasis inhibition is a potential treatment strategy for misfolded protein disorders, while broad-spectrum proteasome inhibitor drugs are designed to target tumor metastasis. In contrast, for muscle wasting and neurodegeneration, the use of proteostasis-activating or modulating compounds could be more effective.

Keywords

degradation; proteasome; proteostasis; therapeutics; ubiquitin

1. Introduction

The proteostasis imbalance and its possible involvement in the development of diseases has been studied extensively but there is a clear gap in our understanding of the precise molecular mechanisms involved in this process. Environmental pollutants, age and/or genetic factors deter proteasomal activity and autophagy response by diverse mechanisms resulting in accumulation of ubiquitinated protein that induces inflammatory signaling, oxidative stress and apoptosis (Figure 1). Though the exact underlying mechanisms are unclear, decrease in proteasome activity or defective autophagy induced by variety of pathogenetic and environmental factors weakens the cellular capacity to remove misfolded or normal proteins and favors the development of neurodegenerative, cardiac and conformational diseases. In contrast, induction of proteasome activity is an attribute of diseases such as muscle wasting, sepsis, cachexia and uraemia. In addition, different individuals may have varied constitutive ability to combat proteostatic challenge. This is

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supported by the fact that proteasomes in various cells and tissues are not a multitude of identical 20S proteasomes but a mixture of proteasome subpopulations (standard and immuno-proteasomes) and intermediates of each subpopulation [1,2] that have different substrate specificities. In the case of misfolded protein disorders, higher degradation of single protein leads to the pathophysiological consequences due to the absence of functional protein. Therefore, selective proteostasis inhibition is a potential treatment strategy for misfolded protein disorders, while broad-spectrum proteasome inhibitor drugs like PS-341 (Bortezomib/Velcade) are designed to target tumor metastasis. In contrast, for muscle wasting and neurodegeneration, the use of proteostasis-activating or modulating compounds could be more effective.

2. Proteostasis-imbalance in chronic diseases

Recent studies indicate that the unfolded protein response (UPR) plays an important homeostatic function in combating proteostasis-imbalance by regulating inflammatory and anti-oxidant responses [3,4]. The UPR activates in response to cellular stress such as injury, infection, reactive oxygen species (ROS) and environmental pollutants that impair protein folding in the lumen of the endoplasmic reticulum (ER). Activation of the UPR compensates for abnormalities in protein folding by transcriptional activation and increased expression of proteostasis machinery that includes protein chaperones, folding, translation and degradation [3–5]. It is of interest that many basic cellular processes (e.g., cell cycle regulation, apoptosis, energy metabolism, inflammation, ion transport and acute phase reactants) that depend on an adequate supply of fully functional membrane and secreted proteins are also regulated by the UPR [3,6].

As discussed above, proteostasis-imbalance can be induced by environmental pollutants, age or genetic factors. Although the role of aberrant proteasomal, autophagic and/or protease activities in pathogenesis of various chronic inflammatory diseases is well documented, the exact function of the immunoproteasome is not clear [7]. A recent review [7] discusses in detail, how age-related increases in the concentration of immunoproteasome subunits in brain and muscle tissues may reflect a state of constant inflammation or cell stress. Thus, increased concentration of immunoproteasomes in muscle of patients suffering from myofibrillar myopathy and inclusion body myositis [8], as well as in neurons of a mouse model of Huntington's disease [9], can be regarded as a consequence of, rather than the cause of, these diseases. Alternatively, this increased concentration can have a protective function, since induction of immunoproteasome subunits by NO via cGMP/cAMP-mediated mechanisms was recently shown to occur in endothelial cells. The NO-induced synthesis of immunoproteasomes protected the cells against transferrin iron-induced oxidative stress by regulating the level of transferrin receptor [10]. Since NO regulates processes such as vasodilatation, neurotransmittance, the immune response and apoptosis, an imbalance in this mediator has many pathological consequences. A NO-dependent change in the ratio of standard to immunoproteasomes is thought to contribute to these consequences [11–14]. Similarly, treatment of SH-SY5Y neural cells with non-toxic doses (1 – 10 μM) of H_2O_2 induced not only the formation of oxidized proteins but also synthesis of immunoproteasome subunits (detected by western blotting and real-time RT-PCR), indicating the sensitivity of the proteasome system to react and cope with cell stress. Such an adaptation of the proteasome system was lost in senescent human fibroblasts, which displayed a decreased concentration of standard proteasome subunits but retention of the immunoproteasome subunits β1i, β2i and β5i. In contrast to confluent young fibroblasts, the concentration of immunoproteasome subunits could not be augmented by treatment with gamma interferon [15] confirming the critical affect of aging on proteasomal activity. In addition, a recent study clearly demonstrates that immunoproteasomes increase the MHC class I antigen supply for antigen presentation to maintain protein homeostasis [1]. The

study also clarifies the role of immunoproteasomes in modulating protein aggregation in mammalian cells.

3. Targeting proteostasis

It is clear that primary aim while modulating the ubiquitinproteasome activity is to selectively target the proteolytic pathway. Interestingly, a recent study shows that inhibition of proteasomal activity induces the *de novo* synthesis of proteasomes [16] that warrants further investigation. This has potential application in disease states that are the outcome of reduced or aberrant proteasomal activity, as in aging. In support of this, treatment of endothelial cells with low, non-toxic doses of the proteasome inhibitor MG132 was found to activate an antioxidant defense program that included upregulation of eNOS, glutathione peroxidase-3, glutathione S-transferase and others, resulting in an improvement in endothelial functions [17,18]. This is not only promising in the search for treatments for patients suffering from atherosclerosis and coronary heart diseases, but also provides a strategy to prevent the pathogenesis of these diseases and other neurodegenerative conditions [19]. This is substantiated by recent studies where vascular endothelial dysfunction and neuronal death after embolic stroke were found to be restricted and terminable in animal models treated with proteasome inhibitors (PS-341 [20,21] or MLN519 [22]). PS-341 (Bortezomib/Velcade, pyrazylcarbonyl-Phe-Leu-boronate) is a FDA-approved drug for multiple myeloma [23–25] while MLN519 ((1*R*-[1*S*,4*R*,5*S*])-1-(1hydroxy-2-methylpropyl-6-oxa-2-azabi-cyclo [3.2.1] heptane-3,7-dione)) is a synthetic analog of lactacystin developed by Millennium Pharmaceuticals that is under evaluation in a Phase I clinical trial [26]. An exact knowledge of the susceptibility of the different forms of proteasomes to these and other therapeutic inhibitors will help development of optimal treatments and therapies for a wide range of diseases. Finally, aside from proteasome inhibitors or activators, proteasomes themselves could be useful as diagnostic and even prognostic markers, since the level of circulating proteasomes reflects the state of health of patients suffering from cancer and autoimmune diseases [27].

4. Expert opinion

Environmental exposure, injury, infection and age-related changes in protein processing, proteasomal activity and autophagy responses, result in accumulation of ubiquitinated protein that induces chronic inflammatory signaling, oxidative stress and apoptosis (Figure 1). Identification of critical components of protein processing that are involved in protein ubiquitination, aggregation and degradation or trafficking will lead to development of novel therapeutics for diseases caused by proteostasis-imbalance.

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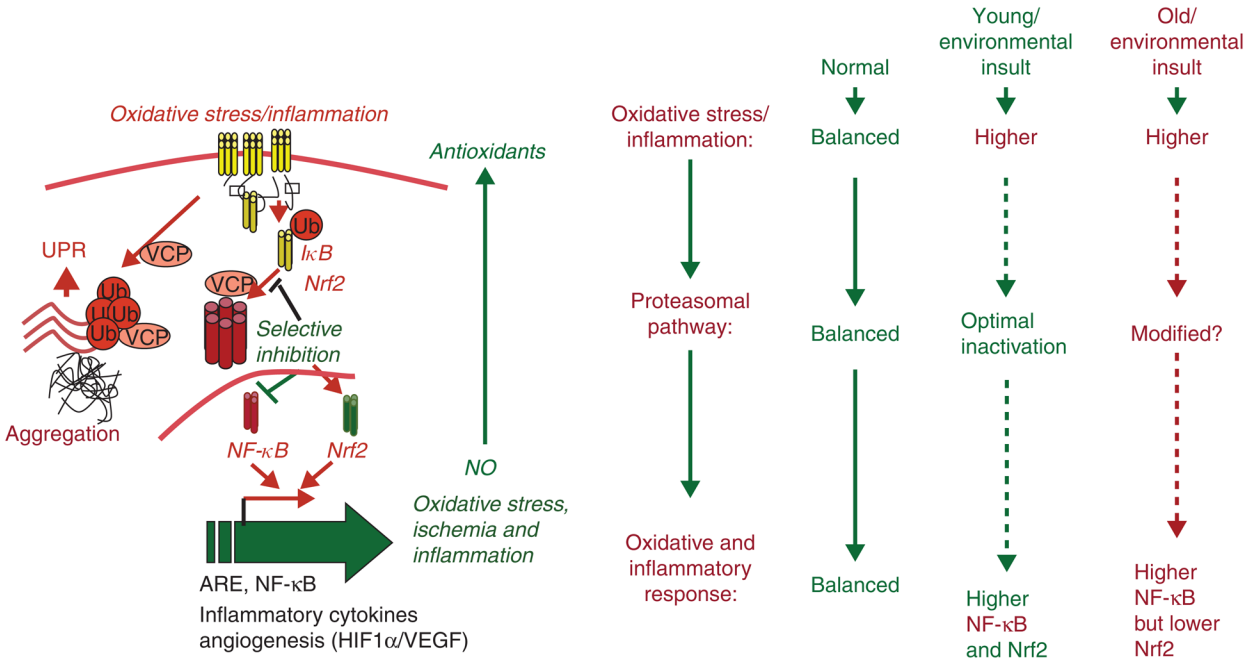

Figure 1. Schematic on the role of ubiquitin proteasome pathway (UPP) imbalance in chronic diseases

Under normal conditions, optimal activation of UPP balances Nrf2 and IκB (endogenous inhibitor of NF-κB) levels so that there is no induction of antioxidant and inflammatory pathways. While in a normal healthy young person, exposure to infection, cigarette smoke or injury induces oxidative stress that results in optimal activation of proteasomal pathway via Nrf2 resulting in increased NF-κB-mediated stress response that is balanced by induction of protective Nrf2 response. Notably, the UPP modification (inherent and/or environmental insult or age-related change) induces degradation of both IκB and Nrf2. The lack of compensatory antioxidant gene activation and chronic NF-κB activation, thus resulting in persistent oxidative stress and chronic inflammation. The inability to regulate protein degradation machinery and aberrant-autophagy results in fatal disease.

ARE: Antioxidant response element; HIF: Hypoxia-inducible factor; Nrf2: Nuclear factor erythroid 2-related factor 2; Ub: Ubiquitin; UPR: Ubiquitin proteasome response; VCP: Valosin containing protein; VEGF: Vascular endothelial growth factor.