What shall we do with the damaged proteins in lung disease? Ask the proteasome!

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Abstract

The proteasome constitutes the main protein waste disposal and recycling system of the cell. Together with the endoplasmatic reticulum (ER) stress and the autophagosome pathway, it also takes centre stage in cellular protein quality control. In lung research, the proteasome is – first of all - a promising therapeutic target to intervene with malignant growth of lung cancer cells. Therapeutic targeting of the proteasome has also been extended to pulmonary fibrosis and asthma, using animal models. Moreover, the proteasome is involved in lung pathogenesis: In cystic fibrosis, rapid proteasomal degradation of mutant cystic fibrosis transmembrane regulator contributes to loss of function of lung epithelial cells. In chronic obstructive pulmonary disease (COPD), pulmonary proteasome expression and activity is downregulated and inversely correlates with lung function. In addition, as the proteasome degrades signaling mediators that have been oxidatively modified in COPD, it contributes to further compromise cellular function. The consequences of proteasomal dysfunction are loss of protein quality control, accumulation of misfolded proteins, and exacerbation of cellular stress, which are also hallmarks of protein quality diseases and premature aging. This suggests that proteasome dysfunction can be regarded as a new pathomechanism for chronic lung diseases, awaiting further therapeutic exploration in the future.

Chronic lung diseases (CLD), including chronic obstructive pulmonary disease (COPD), lung cancer, asthma, or pulmonary fibrosis are the second leading cause of death in the world. Of concern, death rates due to chronic lung disease continue to increase, while death rates due to other leading causes of death such as heart disease, cancer, or stroke are declining (American Lung Association, 2008). Currently, only limited therapeutic strategies exist to treat CLD, most of which are symptomatic instead of causal. Historically, therapeutic interventions have been designed around the attenuation of specific signaling pathways, such as G protein-coupled receptor activation, interference with TGF-beta signaling, or tyrosine kinase inhibition. Only few novel therapeutic strategies attempt to intervene with general cellular pathways. Among them, inhibitors of the proteasome interfere with the central protein degradation machinery of the cell.

In clinical research, the proteasome has been shown to present a promising therapeutic target against malignant growth of cancer cells. In 2003, the first clinically applicable proteasome inhibitor Bortezomib was FDA-approved for the therapy of relapsed and refractory multiple myeloma [1]. In addition, impaired proteasome function has been associated with protein misfolding diseases such as neurodegenerative disorders, cardiac and endothelial dysfunction, and cataract formation [2-4]. It is, however, still controversial whether proteasome dysfunction is the chicken or the egg for disease pathogenesis as pointed out aptly by Aaron Ciechanover [3]. As proteasome research seems to be largely neglected in the lung field except for lung cancer research, we would like to stimulate proteasome research in the lung with this review.

1. Function of the Ubiquitin-Proteasome System

Every protein that is synthesized needs to be disposed at some point of its life. This is mainly achieved by the proteasome. About 90% of the cellular proteins are degraded by the ubiquitin-proteasome pathway into small peptides [5]. Proteins can be degraded by the proteasome at different rates with half-lives ranging from minutes to weeks. Proper proteasome function is thus essential for numerous cellular processes such as protein turnover and quality control, cell growth and cell signaling, immune response and antigen presentation [6-8]. The exceptional biological significance of this protein degradation pathway was publicly acknowledged in 2004, when Aaron Ciechanover, Avram Hershko, and Irvine Rose were awarded the Nobel Prize in Chemistry for their first description of the ubiquitin-proteasome system.

For degradation, proteins are first marked with chains of several ubiquitin molecules [9]. Ubiquitin binds covalently to a specific lysine residue of the substrate via an enzymatic cascade that involves the ubiquitin-activating enzyme E1, an E2 ubiquitin-conjugating enzyme, and a specific ubiquitin ligase (E3). Subsequently, further ubiquitin moieties are transferred to the previously conjugated ubiquitin molecule. While addition of only single ubiquitin residues to a protein has a sorting function, tagging of a protein with at least 4 ubiquitin moieties serves as a degradation signal for the 26S proteasome [10].

The 26S proteasome consists of a catalytic core and two regulatory complexes (Figure 1). The 19S regulatory particle with its more than 20 subunits forms a lid- and base-like structure. While the "lid" serves regulatory functions such as binding of polyubiquitinated proteins and deubiquitination of substrates, the "base" mediates energy-dependent unfolding of substrates and "opens the door" to the catalytic core - the 20S proteasome. The 20S core has a barrel-like structure with twofold symmetry (Figure 1): the two outer rings are composed of seven different but related α subunits (α1–α7). The two inner rings contain seven different β subunits (β1–β7) [11]. Three of these beta subunits (β1, β2, and β5) contain catalytic active sites with different cleavage specificities. These catalytic subunits can be exchanged by three inducible subunits, LMP2, MECL-1, and LMP7, respectively [7]. These subunits are expressed in response to stimulation of cells with cytokines, namely interferon-γ and rapidly assemble into the so called immunoproteasome which has altered cleavage site preferences and thus generates a different set of protein degradation products [12].

1.1. Protein Quality Control

Proper protein function critically depends on the folding of the peptide chain into a complex three-dimensional structure. Protein misfolding arises as a consequence of stress-induced protein modification and denaturation, destabilizing missense mutations or lack of oligomeric assembly partners. In addition, about 30% of newly synthesized proteins are cotranslationally destroyed within minutes of their synthesis by the proteasome. These so called defective ribosomal products (DRiPs) probably fail to adopt their native conformation e.g. due to translational errors–[13]. A network of chaperones such as hsp40, 70, and 90, and co chaperones assist the folding of denatured proteins into their proper functional conformational states [14]. In case chaperones are unable to successfully restore protein folding, the protein is targeted for destruction via ubiquitin-dependent proteasomal degradation. This concept is known as the protein triage model of protein quality control [15]. The major enzyme for ubiquitination of misfolded proteins is the hsp70-dependent E3-Ligase CHIP (carboxy

terminus of hsp70-interacting protein) [16]. There is still some controversy whether degradation of misfolded and modified proteins is strictly dependent on ubiquitination or can take place in the absence of ubiquitination [17, 18]. The ubiquitin-proteasome system thus serves as the central quality control system to rapidly destroy misfolded proteins and translational junk. Proteasome-mediated protein quality control, however, appears to be restricted by the solubility of misfolded proteins. While soluble proteins and small soluble protein aggregates are degraded by the proteasome, insoluble aggregates that are sequestered into inclusion bodies or microtubule-associated aggresomes are disposed by autophagy via the lysosomal pathway [19]. Such sequestration of misfolded proteins protects against the proteotoxic effects of unfolded proteins that stick to normal proteins thereby interfering with cellular function [20]. Interestingly, ubiquitin-dependent proteasomal degradation and autophagy are closely linked as ubiquitinated protein aggregates are recognized by components of the autophagosome [21]. The close interplay of these two cellular disposal machineries is also supported by the observations that impairment of the proteasome is compensated by increased autophagy but that defective autophagy results in impaired degradation of proteasomal substrates [22].

The ER offers a specialized form of quality control for secretory proteins. ER resident chaperones support and supervise folding of secretory proteins. Misfolded ER proteins are tagged with a specific set of sugar moieties within the ER, recognized by specialized ubiquitin ligases that span or associate with the ER membrane, and are retro-translocated into the cytosol for subsequent degradation by the proteasome [23]. This process is termed ER associated degradation pathway (ERAD) and complements the unfolded protein response (UPR), a coordinated programme that adjusts the capacity of folding and disposal of the ER [24, 25]. Proteasome function and ER stress response are closely coupled: proteasomes are not only found in close association with the ER membrane but cotranslational degradation of ER proteins by the proteasome protects from ER overload [26]. Vice versa, inhibition of proteasome function induces a terminal UPR in secretory cells which is triggered by the accumulation of misfolded ER proteins due to ERAD dysfunction [27]. The close interplay of the ER stress and proteasome pathway is also reflected by the fact that expression of proteasomal genes and thus proteasome function is directly controlled by the ER-associated transcription factor Nrf1 (TCF11) via an ERAD-dependent feedback loop [28]. In case ERAD efficiency is compromised, autophagy may serve as a backup system for disposal of misfolded and aggregated proteins as shown for aggregation-prone mutants of alpha-1-

antitrypsin [29]. The interplay of the ER-, proteasome, and autophagy pathways as adaptive protein quality control systems of the cell is outlined in Figure 2.

1.2. Antigenpresentation

The finesse of proteasomal degradation of cellular proteins lies in the fact that the waste products are not simply "lost" but used as a communication system to define the cellular "self" towards the immune system. As most of the cellular proteins are at some point degraded by the proteasome either in form of translational junk proteins (DRiPs, see above) or at the end of their life as functional proteins this ensures a stochastic and mean representation of the total cell protein's content in form of short peptides [30]. Peptides are transported into the ER lumen, trimmed by ER-resident protein peptidases, mounted onto MHC class I molecules, and presented to CD8-positive T immune cells. Incorporation of immunoproteasomal subunits results in the preferential generation of peptides with improved binding for MHC I molecules [7]. T-cells that are reactive towards "self" peptides are eliminated during development of the immune system. In contrast, nonself-antigenic peptides are recognized by activated CD8-positive T-cells and trigger a cytotoxic T-cell mediated lysis (CTL) of those cells that are brand-marked with "foreign" antigenic MHC I peptides. MHC I dependent CTL-activation thus provides an efficient surveillance mechanism for the detection of any cell bearing abnormal genes or proteins as seen in response to viral infections, tumor antigens, and rejection of transplants [31-33]. There is also some evidence that posttranslational modifications of antigenic peptides, such as phosphopeptides, add to the complexity of MHC I mediated immune responses [34, 35]. Thus, MHC I mediated antigen presentation may be regarded as a sophisticated form of intercellular communication that not only betrays a foreign or abnormal protein content but may also report signaling dysfunction and stress.

2. Drug Targeting of the Proteasome

Inhibitors of the proteasome typically bind to the substrate binding pockets of the 20S proteasome and covalently modify the N-terminal threonine residues of the catalytically active beta subunits β1, 2, 5, and their inducible counterparts. Most synthetic inhibitors are short peptides with varying pharmacophore groups at their C-terminal end such as aldehyde, vinyl sulfone, or boronate groups. Other inhibitors are drugs derived from natural compounds, such as α1, β1-epoxyketones, syrbactins, and β-lactones [36]. Crystallographic data suggest that the various inhibitors not only differ in their specificity and reversibility of active site

modifications, but also in their fitting into the specific substrate pockets of the three active sites [37]. This raises the intriguing possibility of generating site specific inhibitors, as recently shown for the immunoproteasome subunit LMP7-specific proteasome inhibitor PR-957 or a specific β2-active site inhibitor [38, 39]. Only recently, a new – reversible and non-covalent - mode of binding was identified for hydroxyurea-based compounds, which specifically inhibit the β5 active site of the proteasome [40]. Accumulating evidence suggests that site-specific inhibition of single proteolytic sites of the proteasome affects specific sets of substrates within the cell. This may mediate the observed differential cellular effects in different cell types [41, 42]. The cell-type-specific effects of the clinically approved inhibitor Bortezomib on multiple myeloma compared with solid tumor cells have been attributed to the particular sensitivity of secretory cells to proteasome inhibitor-induced UPR induction and apoptosis [27]. A differential and dose-dependent degree of inhibition of the three active sites of the proteasome due may explain the wide-spread therapeutic applications of bortezomib in mice and men, not only as anti-tumor but also as anti-fibrotic, anti-inflammatory, and anti-hypertrophic drugs [43-46]. The challenge of the future will be to define the cellular responses to specific proteasome inhibitors depending on their degree of active–site specific inhibition to enable defined therapeutic applications of proteasome inhibitors beyond cancer treatment.

3. Proteasome in Chronic Lung Diseases (CLD)

In the following sections, we will highlight and review the available data on proteasome dysfunction in CLD. This will entail pathways and diseases, which have been shown to be affected by proteasome dysfunction. We will also summarize the available data on the use of proteasome inhibitors as a therapeutic drug for CLD.

3.1. Lung Cancer

The timely and controlled degradation of numerous cell cycle regulators, signaling mediators, and transcription factors by the proteasomal pathway is essential to ensure proper cell growth and function. Inhibitors of the proteasome block degradation of these signal regulators thereby inhibiting cell proliferation and inducing apoptosis [47]. Thus, proteasome inhibition was early considered as a promising cytotoxic approach to combat malignant growth of tumour cells. Several in vitro studies and clinical trials suggest that the FDA-approved inhibitor Bortezomib might also be useful as a mono- or combinatorial drug to inhibit proliferation of lung tumor cells, sensitize them to apoptosis, reduce the metastatic potential,

and to overcome drug resistance in small and non-small cell lung cancer cells as recently reviewed [48, 49]. Several second-generation proteasome inhibitors have been developed and are currently under clinical investigation as anti-cancer drugs for hematologic malignancies and solid tumors [50]. Of note, the new proteasome inhibitor NPI-0052 is currently tested in clinical phase I amongst others for therapeutic efficacy in Non-small Cell Lung Cancer (www.clinicaltrials.gov). Only recently, a different route to interfere with proteasomal protein degradation has been taken by inhibiting the activity of deubiquitinating enzymes, so called DUBs. These enzymes are essential for the cleavage and recycling of ubiquitin molecules from substrates preceding their degradation by the proteasome [51]. Blocking DUB activities results in accumulation of polyubiquitinated cellular substrates and has been shown to inhibit cancer growth [52].

Taken together, these data suggest that the proteasome is a highly promising anti-cancer target that can be therapeutically exploited by different means.

3.2. Asthma

Proteasome inhibitors also have potent anti-inflammatory effects due to the diminished activation of the inflammatory transcription factor NFκB [53]. At resting conditions, NFκB is kept silent by cytoplasmic complexing with its inhibitor IκB. Inflammatory signaling, e.g. by TNFα or TLR agonists, induces phosphorylation of IκB and its subsequent degradation by the proteasome. NFκB can then translocate into the nucleus where it transactivates pro-inflammatory genes. Inhibition of the proteasome prevents–IκB degradation, inhibits NFκB activation, and blocks inflammatory gene expression [54]. These anti-inflammatory properties have early been exploited to diminish the influx of leukocytes in a model of allergen-induced pulmonary eosinophilia in sensitized rats [55]. The therapeutic targeting of NFκB signaling in asthma has been "rediscovered" ten years later in an excellent review by the group of Sebastian Johnston [56]. The recently proposed new paradigm of asthma as a disease initiated by persistent dysfunction of the respiratory epithelium may add a new aspect to proteasome function in this disease with regard to MHC class I antigen presentation [57]: The defective behavior of the epithelium to viral infections and air pollutants may involve alterations in MHC I antigen presentation. Subsequent recruitment of CD8-positive cytotoxic T cells to the airways will then contribute to epithelial damage as suggested recently in a mouse model of allergic airway inflammation [58]. Thus, it is well feasible that this type of immune response contributes to the initiation of epithelial dysfunction and repeated airway damage in virus-mediated exacerbations in asthma. As inhibition of the proteasome has been shown not only

to attenuate virus replication in acute lung pneumonitis but also to affect antigenic peptide processing and subsequent CTL-responses, this may add to the therapeutic potential of proteasome inhibitors in asthma [59, 60]. Only recently, the rational for therapeutic application of proteasome inhibitors in asthma has been extended to the idea of depleting Ig-secreting plasma cells. Treatment of ovalbumin-sensitized mice with bortezomib did not, however, attenuate chronic asthma in mice [61].

3.3. Pulmonary Fibrosis

Data from cardiac, liver, and renal models of fibrosis indicate that non-toxic doses of proteasome inhibitors effectively reduce deposition of collagens, expression of matrix metalloproteinases, and TGFβ signaling thereby counteracting development of fibrosis in the respective organs [62]. Accordingly, Mutlu et al. only recently reported that the clinically approved proteasome inhibitor Bortezomib promoted normal repair and prevented lung fibrosis after 21 days in bleomycin-treated mice. Importantly, this antifibrotic effect was observed with-Bortezomib given only twice at day 7 and 14 after the initial lung damage by bleomycin [46]. In contrast, coapplication of both, Bortezomib and bleomycin, resulted in excess mortality in these mice [46]. Fineschi et al., reported that the daily application of Bortezomib starting one day after bleomycin instillation did not show any protective effects on the development of bleomycin-induced lung fibrosis [63]. These - on first sight - conflicting data may be reconciled by the above mentioned notion that the divergent cellular effects of proteasome inhibitors ranging from cytotoxic to anti-inflammatory and anti-fibrotic have been shown to be dose- and cell type dependent and are strongly determined by the degree of proteasome inhibition in the target cell type: sustained inhibition of the proteasome induces apoptosis, while partial inhibition is nontoxic and exerts beneficial effects [41, 42, 64]. Accordingly, inhibition of the proteasome at a defined degree is crucial to achieve a desired therapeutic effect in a particular disease. While sustained inhibition and cytotoxic effects are desirable in the setting of lung cancer it might be adverse in other chronic lung diseases such as asthma and pulmonary fibrosis. Partial inhibition of the proteasome, however, exerts anti-inflammatory and anti-fibrotic effects in the absence of toxicity [65, 66]. For that reason, it is of major importance to carefully monitor the degree of proteasome inhibition in the particular cell type and animal model used and adjust the dose of inhibitor correspondingly.

3.4. Cystic Fibrosis

The prominent role of the proteasome in cystic fibrosis is well known and has been covered by several excellent reviews [67-69]. Proteasomal degradation of both, Cystic Fibrosis Transmembrane Regulator (CFTR) and epithelial Na+ channel (ENaC), is part of the ERAD system for disposal of misfolded ER proteins involving polyubiquitination and retrotranslocation of these proteins into the cytosol as described above [70, 71]. Again, inhibition of the proteasome has been proposed as a strategy to rescue degradation of rapidly degraded CFTR folding mutants (specifically the Δ508CFTR mutant), to counteract inflammation and partially restore ion currents in the respiratory epithelium [72]. Only recently, proteasome inhibitors have been used for nanoparticle-based targeted drug delivery in a mouse model for cystic fibrosis [73]. Loss of functional CFTR has been associated with intracellular aggregate formation, accumulation of polyubiquitinated proteins, and aberrant autophagy in lung epithelial cells [74]. It needs to be further investigated whether proteasome function is also impaired in CFTR-aberrant cells as was shown for mutant surfactant protein C and aggregated neuronal proteins [75-78]. Such a scenario is very reminiscent of protein quality diseases of the brain and heart, where reduced proteasome activity exaggerates cellular stress and contributes to a vicious cycle of cellular dysfunction [3, 28].

3.5. COPD

Proteasome function has been investigated in COPD patients and corresponding mouse models with regard to lung remodelling and diaphragm atrophy.

Diaphragm muscle atrophy in COPD patients correlated with increased expression and activity of the ubiquitin proteasome system [79-81]. This finding was further substantiated by animal experiments where proteasome inhibitors efficiently counteracted increased protein turnover in a model for diaphragm atrophy indicating a causal role for increased proteasome activity for diaphragm atrophy [82]. The data are in accordance with previous reports on enhanced proteasome activity at conditions of increased muscle turnover in cachexia and cardiac hypertrophy [83, 84]. In contrast, proteasome expression and activity is downregulated in the lungs of COPD patients and inversely correlates with lung function [85]. In this study, reduced expression of proteasomal subunits correlated with decreased expression of the anti-oxidant transcription factor Nrf2 in lungs of COPD patients. However, while patients' data suggested a direct correlation between smoking and emphysema status of the patients with diminished proteasome function, cigarette smoke exposed and emphysematous mice showed increased proteasome expression and activity, suggesting an adaptive response of the lung to cigarette-smoke induced stress. Despite these conflicting

data, the concept of proteasome dysfunction contributing to COPD disease progression is well in agreement with the observed changes in proteasome activity in protein quality diseases as outlined above. As the proteasome takes centre stage in the degradation of oxidatively modified and misfolded proteins it is reasonable to assume that cigarette smoke challenges the proteolytic capacity of this system. Accordingly, a number of studies have demonstrated the importance of proteasomal degradation of modified and misfolded proteins in response to cigarette smoke exposure: oxidative modification of histone modifying enzymes such as HDAC2 and SIRT1 as well as of signaling mediators such as interferon γ and VEGF-receptor, Akt kinase, glutaredoxin-1, and the NFκB family member relB impairs the function of these molecules and makes them prone for proteasomal degradation [86-94]. The consequences of the non-timely degradation of central signaling mediators and the accompanying impairment of epigenetic, oxidative, inflammatory, and growth factor signaling for the pathogenesis of COPD are evident and have been excellently reviewed elsewhere [95-97].

Cigarette smoke mediated oxidative modification and loss of function may also apply to the protein quality control system itself such as the proteasome. Indeed, oxidative modification and impaired proteasome function have been observed in several cell culture models and also in patients with myocardial infarction or neurodegenerative disorders [73, 98]. One might speculate that chronic oxidative stress as seen in COPD affects proteasome function in the lung which ultimately tips the balance from an adaptive stress response of lung cells towards a vicious cycle of detrimental accumulation of oxidatively modified proteins, cellular dysfunction, and cell death. A scenario of decreased proteasome function in COPD is also fully in line with the concept of accelerated aging of the lung in response to chronic oxidative stress, as loss of proteasome activity has been identified as a strong and independent marker for aging [99-103].

4. Concluding remarks

In summary, there is accumulating evidence for a central role of proteasome function in chronic lung disease (Figure 3): on the one hand, the proteasome is a feasible target for therapeutic intervention in lung disease beyond its sole application in lung cancer. On the other hand, alterations in proteasome function in the lung emerge as a new pathomechanism for chronic lung diseases. The consequences of proteasomal dysfunction are deleterious as the central protein recycling machinery of the cell is affected. This results in accumulation of protein waste within the single cell and exacerbation of cellular stress. A second and currently neglected aspect of proteasome function is related to its role in MHC class I antigen

presentation. As the products of proteasomal degradation are employed for communication purposes to report the immune system about foreign or abnormal proteins, it is well feasible that mutated or modified proteins are differentially processed by impaired proteasome activity and result in the generation of non-self antigenic MHC I epitopes that betray the stressed cell to the immune system. This may then represent some form of communication to the immune system such as "Houston, we have a problem".

Acknowledgement

Table 1: Proteasome Function in Chronic Lung Disease

Disease	Effects	References
Lung Cancer	Therapeutic application of proteasome inhibitors inhibits lung tumor growth, induces apoptosis, reduces metastatic potential, overcomes drug resistance	[48, 49]
Asthma	Proteasome inhibitors reduce allergen-induced pulmonary eosinophilia in sensitized rats	[55]
	Rationale for proteasome inhibition as a therapeutic approach to counteract NFκB signaling in asthma	[56]
	Bortezomib treatment fails to ameliorate chronic asthma in mice	[61]
Pulmonary Fibrosis	Proteasome inhibition does not reduce bleomycin-induced pulmonary fibrosis in mice	[63]
	The proteasome inhibitor Bortezomib attenuates bleomycin-induced pulmonary fibrosis	[46]
Cystic Fibrosis	Proteasomal degradation of mutant CFTR and ENaC via the ERAD pathway	[70, 71, 104]
	Proteasome inhibition rescues CFTR degradation and partially restores cell function	[72, 73]
COPD	Diaphragm atrophy is associated with increased proteasome activity in COPD patients	[79]
	Proteasome inhibition counteracts diaphragm atrophy in mice	[82]
	Downregulation of proteasome expression and activity in lungs of COPD patients	[85]

Figure Legends

Figure 1: Ubiquitin-mediated degradation of proteins.

Proteins are tagged with multi-ubiquitin chains and targeted for degradation by the 26S proteasome. The 26S proteasome consists of a catalytic core, the 20S particle, and two 19S regulatory complexes. Upon binding of the protein substrate to the 26S proteasome, ubiquitin chains are recycled, the protein is unfolded, and degraded into small peptide fragments. The 20S core has a barrel-like structure with two outer α and two inner β rings consisting of seven different subunits each.

revised Figure 1

Figure 2: Interplay of protein quality control systems within the cell

Cellular protein quality control involves the ER stress pathway, the ubiquitin-proteasome system, and autophagy. These pathways are closely interconnected and all together serve as an adaptive system for protein disposal within the cell. Cytoplasmic proteins that become misfolded are hydrolyzed by the proteasome into small peptides. Misfolded secretory proteins are retrotranslocated from the ER into the cytoplasm where they are degraded by the proteasome. This route is known as the ERAD pathway. At certain conditions, misfolded proteins form aggregates that are disposed by the autophagosome. Disturbance of one or the other protein quality pathway results in accumulation of misfolded proteins within the cell, proteotoxicity, and cellular dysfunction.
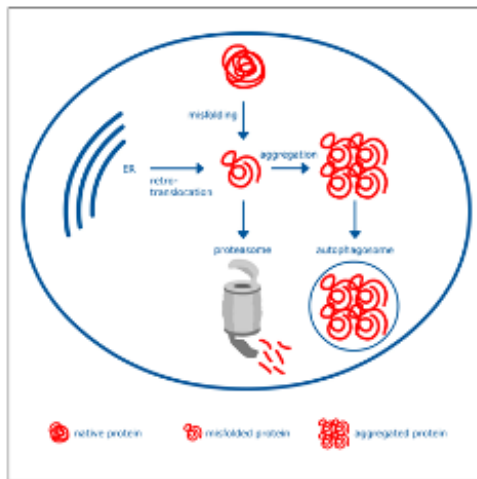
revised Figure 2

Figure 3: Proteasome Function in chronic lung disease: therapeutic target and pathologic dysfunction

Proteasome inhibitors have been successfully applied for the treatment of asthma, IPF, and lung cancer in animal models and clinical studies. Proteasome function has been shown to be relevant for CF and COPD pathogenesis.
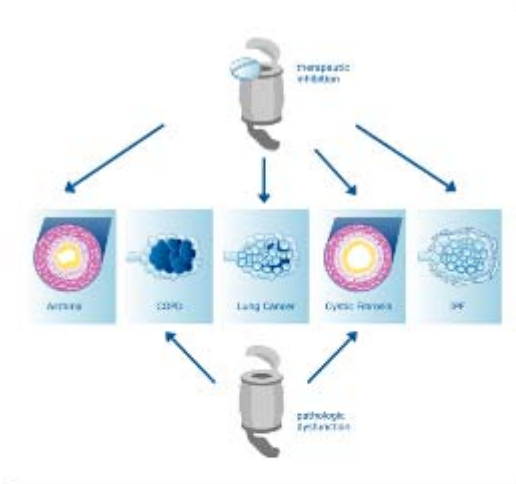
Figure 3

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