COMMENTARY

Leprosy Susceptibility—A Matter of Protein Degradation? The Role of Proteasomes in Infection and Disease

A recent study conducted in Vietnam and Brazil revealed a significant association of leprosy susceptibility with the Parkinson´s disease (PD) gene PARK2 and PARKG. Variants in the regulatory region shared by these genes turned out to be a major risk factor for leprosy ([9]). Although the mutation of the PARK2 (Parkin) gene responsible for familial early onset of PD is not identical with the nucleotide polymorphism found in leprosy patients, it is not surprising that malfunction of a central enzyme results in disease or enhanced disease susceptibility. Parkin is a ubiquitin-protein ligase that controls—together with other ubiquitin-conjugating enzymes—the degradation of proteins by proteasomes. In the last years, it became clear that the ubiquitin-proteasome complex is a hot topic in biological science, because a breakdown of this central catabolic system is associated with severe human diseases, including neurological disorders, inflammation, cancer, and susceptibility of infection.

Proteasomes are the enzymatic heart of the cells. Protein synthesis and degradation are metabolic processes equally essential for prokaryotic and eukaryotic cells. As for the catalytic pathway, lysosomes and proteasomes are two major proteolytic machineries that are involved in protein degradation. While extracellular and cell-surface membrane proteins are mainly targeted to lysosomes, the vast majority of cytoplasmic proteins are degraded by proteasomes.

The enzymatic activity of proteasomes is strictly regulated and acts in concert with the ubiquitin pathway, which primarily tags proteins for degradation ([1]). Proteasomes are found in archaebacteria, some eubacteria (e.g., Actiomycetes) and eukaryotes. While their role in prokaryotes is not fully understood, they perform multiple functions in eukaryotic cells: degradation of damaged and abnormal proteins into small peptides and processing of proteins thereby yielding proteins of different biological activity including cell-cycle regulators, oncogens, tumor suppressors and transcription factors. Finally, MHC class I restricted cytolytic $CD8^+$ T cells recognize peptides from self- and non-self proteins that are generated by proteasomes. This enables $CD8^+$ T cells to control for and eliminate altered and infected cells. All this crucially depends on the precise function of the ubiquitin-proteasome system and thus, it is not surprising that aberrations lead to pathological reactions and disease ([2]).

The first step in the substrate selection for proteasomal degradation is mediated by the addition of poly-ubiquitin chains. This "kiss of death" is triggered by the successive action of several enzymes including the Ub-activating enzyme (E1), Ub-conjugating or carrier enzyme (E2), and Ub-protein ligase (E3). Ubiquitin tagged proteins are then recognized and digested by the proteasome, a multiprotein complex ([10]). The catalytic active sites of the eukaryotic proteasome is housed in a barrel shaped 20S core complex, which is composed of 28 subunits arranged in 4 stacked heptameric rings. The outer rings contain the a-subunits which shape the gates of substrate entry and product release. The two inner rings harbor the β subunits (β1–β7) of which the β1, β2, and β5 subunits are catalytically active. In contrast, proteasomes of prokaryotes encode only one type of α-subunit and one type of β-subunit. Despite this difference the overall architecture of these complexes is conserved. It seems that in eubacteria, proteasomes are not necessary for intracellular proteolysis as most bacteria rely on other cytosolic proteases for protein turnover.

Interestingly, the only eubacteria known to contain proteasomes are the family of actinomycetes to which *M. tuberculosis* and *M. leprae* belong. *M. tuberculosis* is unusual for a bacterium because it lacks two proteases of the HslUV and Lon family ([3]). Both mycobacteria are intracellular pathogens that spend most of their life inside cells, primarily macrophages. A recent study by Darwin, *et al*. provides an explanation of the strategy used by *M. tuberculosis* to avoid killing in the phagosome ([4]). They could demonstrate that transposon mutants with insertions in proteasome associated genes of *M. tuberculosis* are highly sensitive to reactive nitrogen intermediates which are produced as major defense mechanism by infected host cells. However, the type of damage that would target a protein for proteasomal degradation is not well understood, yet. Perhaps modifications such as nitrosylation are recognized by the eukaryotic ubiquitin-proteasome system as suggested for proteins with oxidative damage ([5]). Since the gene products of noxR1 and noxR3 have also been implicated in resistance to nitric oxide it is unclear whether proteasome associated mutations directly affect the degradation of modified proteins or whether the proteasome is needed to convert precursors into active forms of noxR proteins. Moreover, the mycobacterial proteasome is essential for the refolding of proteins that have been damaged by reactive nitrogen intermediates (RNIs) as demonstrated *in vitro*.

The coevolution of host cells and pathogens involves also the ubiquitin-proteasome system. Many viruses need the ubiquitin-proteasome in order to form correct virus particles (Ros), express components of this system as virulence factor (ubiquitin ligase) ([6]), or modulate the proteasomal activity by directly interacting with defined proteasome subunits ([7]). On the other hand the ubiquitin-proteasome system is also crucial for infected host cells to fight against invaders by processing and presenting their antigens to cytolytic T cells ([8]).

At first glance this seems to be paradoxical but taking into account that the ubiquitin-proteasome pathway acts on proteins, a central component of life, it adds up that this system evolved and is used beyond the barrier of species and even different phyli.

CONCLUSION

The ubiquitin-proteasome system plays a key role in a broad array of basic cellular processes with protein quality control as central function. Loss or impairment of this function is associated with many different types of diseases. Although we currently do not understand the molecular mechanisms of mutated PARK2 and PACRG and enhanced susceptibility to leprosy, it is interesting to note that PD and leprosy are diseases that both affect the nervous system which seems to be extremely sensitive to aberrations in the ubiquitin-proteasome system. Although accumulation of ubiquitin conjugates and/or inclusion bodies is characteristic for many neurodegenerative diseases, a firm and direct pathogenetic linkage to aberrations in the ubiquitin-proteasome system has not been established yet. So far, we can only speculate how mutations in PARK genes relate to leprosy susceptibility. Controlled degradation of proteins derived either from the pathogen *M. leprae* or infected host cells might be fundamental for the integrity of infected cells as well as induction of immunity against leprosy. As consequence, the failure of ubiquitination may result in accumulation of toxic proteins in highly sensitive nerve cells which, once damaged, cause paralysis and disfiguration typical for leprosy patients.

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