

# A new garbage disposal system – cancer cells unveils a new trick?

## Abstract

Proteasomes play an important role in maintaining cellular homeostasis by degrading unwanted and misfolded proteins in cells through regulated proteolysis. The increased dependence of cancer cells on proteasomes to drive their rapid proliferation have been successfully exploited in developing anti-cancer therapies aimed at targeting proteasome function. However, recent reports highlighting emergence of drug resistance to existing proteasome inhibitors together with undesired side-effects associated with these drugs as a result of inhibiting proteasomes in normal cells have underscored the need for strategies that can disrupt proteasome function selectively in cancer cells. The recent discovery of a new proteasome isoform in human cells (' $\alpha$ 4- $\alpha$ 4' proteasomes) and their potential role in enabling cancer cells adapt to cellular stress has opened up new potential avenues for targeting proteasomes in cancer. This review highlights this discovery and discusses the potential of targeting these novel proteasome isoforms in cancer.

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## Introduction

Cancer cells lack the regulatory mechanisms present in normal cells that ensure controlled growth and proliferation. As a result, they grow and divide faster than normal cells in the body. The consequence of being in a state of constant overdrive is that cancer cells produce much more waste, which if not removed efficiently could end up being toxic to them.<sup>1</sup> This makes cancer cells more dependent on the cell's primary waste disposal units - large multi-protein complexes known as proteasomes.<sup>1</sup> Proteasomes are large barrel shaped structures in cells that breakdown defective proteins and remove them before they become toxic.<sup>2</sup> In normal cells they play an important role in maintaining cellular homeostasis by turning over unwanted and misfolded proteins in cells. Proteins destined for degradation are usually targeted to the proteasome by covalently attaching a small polypeptide called ubiquitin on the target protein.<sup>3</sup> In most cases, a chain of ubiquitin on a protein is recognized as a signal for degradation and the target protein bearing this modification is transported to the proteasome. The proteasome has receptors that recognize polyubiquitinated proteins. Once at the proteasome, the polyubiquitin chains are removed and the target protein is unfolded and threaded into the catalytic core of the proteasome, where it is cleaved to smaller peptides.<sup>2</sup> The level of a number of proteins is regulated in the cell with the help of the ubiquitin-proteasome pathway. This includes several key oncogenes and tumor suppressor proteins.<sup>4-8</sup>

Since cancer cells are in an accelerated metabolic state required to support their rapid rate of proliferation, they are highly dependent on the proteasome function for their survival. Disruption of proteasome activity would result in build-up of cellular waste, which would overwhelm the cancer cells and cause cell death.<sup>9</sup> This makes cancer cells more sensitive to proteasome blockade compared to normal cells. As expected, drugs that block proteasomes activity such as bortezomib and carfilzomib are currently being used as an effective therapeutic strategy in several cancers, particularly hematological malignancies such as multiple myeloma and mantle cell lymphoma.<sup>9,10</sup> However, since proteasomes are also critical to normal cells in the body, this strategy leads to unintended killing of some non-cancerous cells

leading to undesired side effects. Further, increasing resistance to the extant proteasome inhibitors is also a growing concern.<sup>10</sup> To overcome these concerns it is important to develop new strategies to target the cancer cell's waste disposal system in a more specific manner.

A potentially important discovery that could pave for the development such effective therapeutics is the finding that not all proteasomes present in our cells are same.<sup>2</sup> In fact, cells in our body can assemble a few different types of proteasomes. These different proteasomes differ in the way they degrade proteins and thus help our cells perform different functions. For instance, it has been well documented that immune cells in our body assemble a specialized type of proteasome called immunoproteasome.<sup>12</sup> These immunoproteasome contain immune cell specific catalytic subunits that enable these specialized proteasome to produce peptides that are more suitable for antigen presentation by the MHC class-I molecules. Cells in thymic cortex are also known to contain another specialized proteasome called the thymoproteasome which are important in positive selection of CD8+ T-cells.<sup>1</sup>

In a recent research published in the journal *Cell Reports*, scientists at Yale University discovered a new type of proteasome that exists in human cells.<sup>14</sup> These new proteasome isoforms, called the ' $\alpha$ 4- $\alpha$ 4' proteasomes, lack the  $\alpha$ 3 proteasome subunit in the core particle. Instead, an additional  $\alpha$ 4 subunit occupies the position previously occupied by the  $\alpha$ 3 subunit. These proteasomes previously shown to exist in yeast, where they were shown to help the yeast cells resist cadmium induced stress.<sup>15,16</sup> Similar to yeast, human cells designed to assemble the ' $\alpha$ 4- $\alpha$ 4' proteasomes also showed enhanced resistance to toxic metals.<sup>14</sup> Heavy metals are known to cause oxidative stress in cells. That ' $\alpha$ 4- $\alpha$ 4' proteasomes enables cells to survive better under conditions that induce oxidative protein damage suggest a potential role for these proteasomes in degrading oxidatively damaged proteins. The study also showed that these unique proteasomes could potentially be assembled at a higher level in certain cancers.<sup>14</sup> They were also found to be more efficient in degrading peptide substrates compared to the regular proteasome suggesting enhanced proteolytic activity. Thus, by helping cells achieve elevated proteolytic capacity, the ' $\alpha$ 4-

$\alpha 4'$  proteasomes could play an important role in enabling cancer cells overcome oxidative conditions, which is frequently encountered within a growing tumor. Since the activity of these proteasomes peaks in certain cancer cells, targeting them specifically, instead of all proteasomes in these cancer cells, would provide us a more specific therapeutic option. Such strategies could potentially overcome the disadvantages of the current methods and become frontline therapy for subset of cancer where ' $\alpha 4$ - $\alpha 4'$  proteasomes are important. However, before we make the giant leap of targeting these alternative proteasomes in cancer, we need to understand these proteasomes and their role in cancer better.

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## Conflict of interest

The author declares no conflict of interest.

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