# Lysosomal Digestion of Cellular Debris and Neurodegenerative Diseases: A Breakdown

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## Background

One hallmark of many neurodegenerative diseases, such as Parkinson's and Alzheimer's disease, is the presence of the aggregation of abnormal proteins. These proteins have been explored in previous articles. Today, they are being scrutinized in ongoing research aimed at developing treatments for these diseases. Although they may not ultimately become the underlying cause of the disease, these abnormal clusters do indeed harm neighboring brain tissue.

If familiar with some degree of high school biology, unwanted cellular debris, such as these clusters of proteins, should be cleared out by the cell's waste management system. That said, the main and most well-known component of that waste management system is known to be carried out by lysosomes. However, due to the continued presence and the failure to clear these abnormal proteins, the lysosome may be something worth exploring in the context of neurodegenerative diseases.

## Lysosomes

Lysosomes, part of the endomembrane system, are membrane-bound organelles that specialize in the digestion of cellular materials. Specifically, the lysosome is a vesicle that contains digestive enzymes called hydrolytic enzymes. Inside the vesicle, the environment is more acidic than its surroundings, as these enzymes primarily use hydrolysis to break down organic molecules into their elements or monomers, which can later be reused by the cell. Thanks to this digestive function, not only are lysosomes used to defend against pathogenic invaders such as bacteria and viruses, but they are also used to recycle. In some cases, which could be applied to cancer research, when the cell is severely damaged and may pose a risk to

surrounding healthy cells, lysosomes can release digestive enzymes to digest the entire cell, a process known as apoptosis, or cell death.

**ALP**

The autophagy-lysosomal pathway (ALP) is the main process by which lysosomes degrade material. There are multiple distinct mini-pathways within this general pathway, including macroautophagy, microautophagy, and chaperone-assisted autophagy. However, all these pathways share the common feature that digestion always occurs in the lysosome (Finkbeiner, 2020).

**Macroautophagy**

Macroautophagy is one of the more common pathways, beginning with the formation of a regular vesicle that contains materials to be broken down. This vesicle, called the autophagosome, does not digest the material. Rather, it contains it. Later, through fusion, the lysosome assimilates the autophagosome and digests its contents.

**Microautophagy**

Microautophagy functions in a similar way, except that there is no need for the formation of an autophagosome to temporarily store the cellular materials to be digested. As a result, materials slated for digestion are directly assimilated by the lysosome, a process similar to pinocytosis. Proteins, such as the Hsc70 protein family, may help transport misfolded proteins (Finkbeiner, 2020), and this pathway could play a role in why beta-amyloids tend to accumulate in patients with neurodegenerative diseases.

## Chaperone-Assisted Autophagy

When proteins are misfolded and therefore dysfunctional, those proteins must be eliminated in order to prevent buildup. In a routine method, lysosomes can digest these proteins using the chaperone-assisted autophagy pathway. Chaperones, which are proteins that assist in protein folding and transportation, bind to the misfolded proteins and transport them directly to the lysosome for destruction. Although this pathway specifically targets proteins, the transport process reduces its efficiency in clearing abnormal proteins. However, the activation of this pathway has been observed to help with the clearance of protein debris (Finkbeiner, 2020; Massey et al., 2006).

## ALP and Neurodegeneration

The ALP plays a major role in degrading materials that pose a threat to cell health, and in the context of neurodegenerative toxic protein buildup, the ALP becomes a more relevant player in the field. Mutations in genes that govern the pathways have been identified as a possible factor in the correlation with Alzheimer's (Kegel et al., 2000). Specifically, the inability of the pathway to keep up with clearing beta-amyloid proteins, especially with the overproduction of these toxic proteins, contributes to the onset of diseases such as Alzheimer's.

However, it is observed that there are differences in how neurons, post-mitotic cells, use lysosomes. Because of the neuron's special structure, with regard to its long extensions, autophagosomes were observed to be created in the long arms of the neurons (axon terminals) and transported to the main cell body, where the lysosomes digest the contents held inside (Maday & Holzbaur, 2014). As a result, it can be postulated that, because axon terminals and dendrites can end up being extremely long, the movement of autophagosomes may be prolonged

and therefore extend the length of the process of digestion. In addition, mutations in the ALP pathway may compound the issue. Therefore, mutations in the ALP may prove more detrimental than normal due to the vulnerability of the neuron in the context of the ALP.

To corroborate this, mutations in ALP were observed, in multiple studies, to be strongly correlated and linked to neurodegenerative diseases. In mouse models, ATG7, a gene that regulates autophagy, was silenced, and the results were observed. Motor neurons, because they could no longer process the buildup of waste, were quickly affected, and abnormal behavior was recorded.

Conversely, the stimulation of the pathway could prove to assist in the treatment of symptoms of neurodegenerative diseases like Alzheimer's disease. However, this field is extremely complicated, and the targeting of the ALP could result in unintended side effects. There have been no human trials on this type of treatment, and there is uncertainty about accidentally inhibiting other important functions of other organelles. There has been evidence that even suggests that targeting the ALP could result in the propagation of cancer cells (Shintani & Klionsky, 2004), as well as the overaccumulation of autophagosomes.

**References**

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