A Deeper Understanding of Misfolded Enzymes and Lysosomal Storage Disorders
Historically, lysosomal storage disorders have been described as a group of disorders caused by missing enzymes. This description suggests that enzyme is missing from the body completely. While some individuals with lysosomal storage disorders do not make any enzyme, many individuals do make enzyme. However, the enzyme that is made is unstable and unable to get to the lysosome where it is needed to breakdown substrate.

This booklet offers a deeper understanding of the underlying cause of lysosomal storage disorders. The following pages describe what enzymes do, how they are made, and what happens when they are not made correctly. This deeper understanding has the potential to lead to new therapeutic approaches for lysosomal storage disorders.
The cell is the functional unit of all living organisms. The human body is estimated to contain at least 100 trillion cells and each type of cell has a specialized function. While cells differ in their size, shape, and function, they are typically made up of the same components and organized similarly.

Cells contain internal compartments called organelles (see the figure below). Each organelle has a specific role in carrying out the vital functions of a cell.

The human cell is organized into compartments called organelles. Some key organelles include:

- **Nucleus** – contains the cell’s genetic material
- **Endoplasmic Reticulum (ER)** – involved with making proteins, including enzymes
- **Golgi Apparatus** – serves as central delivery system for cell by delivering enzymes to their intended destination
- **Lysosome** – contains enzymes that break down substrate into smaller components
One vital function of cells is to make proteins. Proteins are essential components of the human body. Proteins perform specific biological functions within a cell and each type of protein has a unique function.

Enzymes are proteins that have a special job in the cell. Enzymes help biochemical reactions to occur within the body. When enzymes are missing, the biochemical reactions that they help may not be able to be completed.

Enzymes that carry out biochemical reactions in the lysosome are called lysosomal enzymes. Lysosomal enzymes help the cell break down substrates in the lysosome. Substrates are materials that need to be broken down into smaller components that can be recycled by the cell or eliminated if they are not needed.

If lysosomal enzymes are missing from lysosomes, substrate will accumulate since there is no enzyme to break it down. This may lead to a lysosomal storage disorder.
We all possess inherited information called DNA. This genetic material contains the instructions for making all of the necessary components in the body, including lysosomal enzymes.

All proteins and lysosomal enzymes are made up of biological chemicals called amino acids. Amino acids are assembled into a long chain in the cellular organelle known as the Endoplasmic Reticulum (ER).

As the chain of amino acids is being assembled, it folds around itself into a unique three-dimensional shape. This process is referred to as enzyme folding. In order to exit the ER and move to other parts of the cell, an enzyme must be correctly folded and stable.

**Nucleus and Endoplasmic Reticulum**

According to the DNA genetic code contained within a cell's nucleus, the Endoplasmic Reticulum makes enzymes by assembling a long chain of amino acids.

**Correctly folded, stable enzyme**

The long chain of amino acids twists and folds until it reaches a stable three-dimensional shape that is unique to that particular enzyme.
Lysosomal enzymes carry out their biochemical reactions in the lysosome. Since these enzymes are made in the ER, they need to be transported within the cell in order to reach the lysosome.

The cell has developed signals to help direct the movement of enzymes in the cell, similar to how traffic signals direct the movement of cars on roadways.

The ER contains a quality control system that acts as a traffic signal for the cell. Only correctly folded and stable lysosomal enzymes are given the green light and are sent, or “trafficked,” to the lysosome.

Lysosomal enzymes are made in the ER and then are sent to the Golgi. Only correctly folded and stable enzymes are given the green light and released by the ER. The Golgi ensures that the enzymes are directed to the lysosome, where they are needed to break down substrate.
what happens when lysosomal enzymes are made incorrectly

Mutations are changes in the DNA that may alter the instructions for making enzymes. There are many different types of mutations. Some mutations are very severe and do not allow any enzyme to be made. Other types of mutations allow enzyme to be made but there may be errors in how the enzyme is assembled. If amino acids are not assembled in the correct order, the chain of amino acids may not fold into the correct three-dimensional shape. Enzymes that do not achieve their correct three-dimensional shape are referred to as misfolded enzymes.

Misfolded enzymes may be unstable and given a red light by the ER quality control system. Consequently, most misfolded lysosomal enzymes are not trafficked to the lysosome. As a result, substrate may accumulate within the lysosome and cause a lysosomal storage disorder.

Misfolded Enzymes May Lead to a Lysosomal Storage Disorder

Misfolded enzymes may be given a red light by the ER quality control system. Since most misfolded enzymes are never sent to the lysosome, substrate may accumulate within the lysosome, damage the cell, and cause the signs and symptoms of a lysosomal storage disorder.
Lysosomal storage disorders are a group of more than 40 disorders. Each disorder involves a different lysosomal enzyme. A deficiency of a particular enzyme results in the build-up of that enzyme’s specific substrate.

**What’s “Missing”?**
The cause of lysosomal storage disorders traditionally has been attributed to “missing” lysosomal enzymes. If a lysosomal enzyme is missing, substrate may accumulate within the lysosome. Accumulation of substrate within the lysosome leads to the symptoms associated with lysosomal storage disorders.

**A Deeper Understanding**
Recent evidence reveals that many individuals who have lysosomal storage disorders do make lysosomal enzymes. However, the enzyme being made may be misfolded and unstable, and therefore it may not be trafficked to the lysosome. Thus, many individuals do make enzyme but it is “missing” from the lysosome, which allows substrate to accumulate within the lysosome.
Currently, treatment is available for several lysosomal storage disorders. There are different approaches to treatment, some of which have been in use for many years and others which are under investigation:

**Enzyme replacement therapy (ERT)**
ERT involves the regular intravenous (IV) infusion of enzyme that is made using recombinant (genetic) technology. ERT aims to reduce the amount of substrate accumulation in the lysosome by providing a manufactured source of enzyme to the cells to break down the substrate. IV infusions of ERT have been approved for several different lysosomal storage disorders.

**Substrate reduction therapy (SRT)**
SRT uses oral medication to reduce the amount of substrate that is made by cells. SRT aims to reduce the amount of substrate made by cells so there is less substrate for the enzyme to break down. SRT has been approved for the treatment of two lysosomal storage disorders.

**Pharmacological chaperone therapy**
Pharmacological chaperone therapy is an investigational approach using oral medications that bind to misfolded enzyme. Many individuals with lysosomal storage disorders do make lysosomal enzymes, however, they make misfolded enzyme. The binding of the pharmacological chaperone to the misfolded enzyme is thought to help stabilize an individual’s naturally occurring misfolded enzyme and “chaperone” the enzyme to the lysosome where it can break down substrate. Pharmacological chaperones are under investigation as potential therapy for several different lysosomal storage disorders. In addition, research is being conducted to explore the use of pharmacological chaperones in combination with enzyme replacement therapies.
**Amino acids** – the basic building block of proteins

**DNA** – basic unit of heredity that allows for the transmission of genetic information from one generation to the next and contains instructions for making proteins and enzymes

**Enzyme** – a special type of protein that speeds up a biochemical reaction that takes place within cells

**Endoplasmic Reticulum** – cellular organelle that assists with protein production

**Golgi Apparatus** – cellular organelle that serves as the central delivery system for the cell by delivering proteins to their intended cellular destination

**Lysosome** – cellular organelle that breaks down substrate into smaller components

**Organelle** – specialized compartment within a cell that carries out a specific function

**Protein** – component of the human body that performs a specific biological function within cells

**Protein Folding** – process by which proteins achieve their three-dimensional shape. Enzymes, special types of proteins, fold in this manner.

**Protein Trafficking** – process of moving proteins from one cellular organelle to another

**Substrate** – cellular material that needs to be broken down into smaller components so they can be recycled by the cell or eliminated if they are not needed
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