Fatty Acids Synthesis L3

The pathway for fatty acid synthesis occurs in the cytoplasm, whereas, oxidation occurs in the mitochondria. The other major difference is the use of nucleotide co-factors. Oxidation of fats involves the reduction of FAD and NAD^+. Synthesis of fats involves the oxidation of NADPH. However, the essential chemistry of the two processes are reversals of each other. Both oxidation and synthesis of fats utilize an activated two carbon intermediate, acetyl-CoA. However, the activated form of acetyl-CoA in fat synthesis exists temporarily bound to the enzyme complex as malonyl-CoA.

The synthesis of malonyl-CoA is the first committed step of fatty acid synthesis and the enzyme that catalyzes this reaction, acetyl-CoA carboxylase (ACC), is the major site of regulation of fatty acid synthesis. Like other enzymes that transfer CO_2 to substrates, ACC requires a biotin co-factor. Acetyl-CoA carboxylase is called an ABC enzyme due to the requirements for **A**TP,Biotin, and **C**O_2 for the reaction (ABC enzyme are a family of ATP-dependent transporters that pump amino acids, proteins e.t.c. out of cells against a concentration gradient). The synthesis of fatty acids from acetyl-CoA and malonyl-CoA is carried out by fatty acid synthase, FAS. Fatty acid synthase is encoded by the FASN gene which is located on chromosome 17q25 and is composed of 43 exons that encode a protein of 2511 amino acids.

Lipid Storage disease

Lipid storage diseases are a group of inherited metabolic disorders in which harmful amounts of fatty materials (lipids) accumulate in various tissues and cells in the body. Lipids are important parts of the membranes found within and between each cell and in the myelin sheath that coats and protects the nerves. Over time, this excessive storage of fats can cause permanent cellular and tissue damage, particularly in the brain, peripheral nervous system, liver, spleen, and bone marrow. Lipid storage diseases are inherited from one or both parents who carry a defective gene. Symptoms may appear early in life or develop in the teen or even adult years. Neurological complications of the lipid storage diseases may include lack of muscle coordination, brain degeneration, seizures, loss of muscle tone, learning problems, spasticity, feeding and swallowing difficulties, slurred speech, hypersensitivity to touch, pain in the arms and legs, and clouding of the cornea.

Inheritance of Lipid Storage disease

Lipid storage diseases are inherited from one or both parents who carry a defective gene that regulates a particular protein in a class of the body's cells. They can be inherited in two ways:

- Autosomal recessive inheritance: this occurs when both parents carry and pass on a copy of the faulty gene, but neither parent is affected by the disorder.

- X-linked inheritance; this occurs when the mother carries the affected gene on the X chromosome that determines the child's gender and passes it to her son. Sons of carriers have a 50 percent chance of inheriting the disorder. Daughters have a 50 percent chance of inheriting the X-linked chromosome but usually are not severely affected by the disorder. Affected men do not pass the disorder to their sons but their daughters will be carriers for the disorder.

Some forms of lipid storage diseases

1. **Gaucher disease:** is caused by a deficiency of the enzyme glucocerebrosidase. Fatty material can collect in the spleen, liver, kidneys, lungs, brain, and bone marrow. Symptoms may include enlarged spleen and liver, liver malfunction, skeletal disorders and bone lesions that may cause pain and fractures, severe neurologic complications, swelling of lymph nodes and adjacent joints, distended abdomen, a brownish tint to the skin, anemia, low blood platelets, and yellow spots in the eyes. Persons affected most seriously may also be more susceptible to infection. The disease affects males and females equally. Gaucher disease has three common clinical subtypes. ***Type 1*** **(or *non-neuropathic* type)** is the most common form of the disease in the United States. It occurs most often among persons of Ashkenazi Jewish heritage. Symptoms may begin early in life or in adulthood and include enlarged liver and grossly enlarged spleen, which can rupture and cause additional complications. Skeletal weakness and bone disease may be extensive. The brain is not affected, but there may be lung and, rarely, kidney impairment. Individuals usually bruise easily due to low blood platelets and experience fatigue due to anemia. Depending on disease onset and severity, those with type 1 may live well into adulthood. Many individuals have a mild form of the disease or may not show any symptoms. ***Type 2 (*****or *acute infantile neuropathic*** **Gaucher disease)** typically begins within 3 months of birth. Symptoms include an enlarged liver and spleen, abnormal eye movement, extensive and progressive brain damage, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow. Affected children usually die before age 2. ***Type 3*** **(the *chronic neuronopathic* form)** can begin at any time in childhood or even in adulthood. It is characterized by slowly progressive but milder neurological symptoms compared to the acute or Type 2 Gaucher disease. Major symptoms include eye movement disorders, cognitive deficit, poor coordination, an enlarged spleen and/or liver, seizures, skeletal irregularities, blood disorders including anemia, and respiratory problems. Individuals who are successfully treated with enzyme replacement therapy generally live into adulthood. For those with type 1 and most type 3 Gaucher disease, enzyme replacement treatment given intravenously every two weeks can dramatically decrease liver and spleen size, reduce skeletal abnormalities, and reverse other manifestations. Successful bone marrow transplantation cures the non-neurological manifestations of the disease. However, this procedure carries significant risk and is rarely performed in individuals with Gaucher diseases. Surgery to remove the whole or part of the spleen may be required on rare occasions (if the person is anemic or when the enlarged organ affects the person's comfort). Blood transfusion may benefit some

anemic individuals. Others may require joint replacement surgery to improve mobility and quality of life. There is currently no effective treatment for the brain damage that may occur in types 2 and 3 Gaucher disease.

2. **Niemann-Pick disease:** is actually a group of autosomal recessive disorders caused by an accumulation of fat and cholesterol in cells of the liver, spleen, bone marrow, lungs, and, in some patients, brain. Neurological complications may include ataxia, eye paralysis, brain degeneration, learning problems, spasticity, feeding and swallowing difficulties, slurred speech, loss of muscle tone, hypersensitivity to touch, and some corneal clouding. A characteristic cherry-red halo develops around the center of the retina in 50 percent of patients. Niemann-Pick disease is currently subdivided into four categories. Onset of *type A*, the most severe form, is in early infancy. Infants appear normal at birth but develop an enlarged liver and spleen, swollen lymph nodes, nodes under the skin (xanthemas), and profound brain damage by 6 months of age. The spleen may enlarge to as much as 10 times its normal size and can rupture. These children become progressively weaker, lose motor function, may become anemic, and are susceptible to recurring infection. They rarely live beyond 18 months. This form of the disease occurs most often in Jewish families. In the second group, called *type B* (or juvenile onset), enlargement of the liver and spleen characteristically occurs in the pre-teen years. Most patients also develop ataxia, peripheral neuropathy, and pulmonary difficulties that progress with age, but the brain is generally not affected. Type B patients may live a comparatively long time but many require supplemental oxygen because of lung involvement. Niemann-Pick types A and B result from accumulation of the fatty substance called sphingomyelin, due to deficiency of an enzyme called sphingomyelinase. Niemann-Pick disease also includes two other variant forms called *types C* and *D*. These may appear early in life or develop in the teen or even adult years. Niemann-Pick disease types C and D are not caused by a deficiency of sphlingomyelinase but by a lack of the NPC1 or NPC2 proteins. As a result, various lipids and particularly cholesterol accumulate inside nerve cells and cause them to malfunction. Patients with types C and D have only moderate enlargement of their spleens and livers. Brain involvement may be extensive, leading to inability to look up and down, difficulty in walking and swallowing, and progressive loss of vision and hearing. Type D patients typically develop neurologic symptoms later than those with type C and have a progressively slower rate of loss of nerve function. Most type D patients share a common ancestral background in Nova Scotia. The life expectancies of patients with types C and D vary considerably. Some patients die in childhood while others who appear to be less severely affected can live into adulthood. There is currently no cure for Niemann-Pick disease. Treatment is supportive. Children usually die from infection or progressive neurological loss. Bone marrow transplantation has been attempted in a few patients with type B. Patients with types C and D are frequently placed on a low-cholesterol diet and/or cholesterol lowering drugs, although research has not shown these interventions change the abnormal cholesterol metabolism or halt progression of the disease.

3. **Farber's disease:** This is also known as Farber's lipogranulomatosis, describes a group of rare autosomal recessive disorders that cause an accumulation of fatty material in the joints, tissues, and central nervous system. The disorder affects both males and females. Disease onset is typically in early infancy but may occur later in life. Children who have the classic form of Farber's disease develop neurological symptoms within the first few weeks of life. These symptoms may include moderately impaired mental ability and problems with swallowing. The liver, heart, and kidneys may also be affected. Other symptoms may include vomiting, arthritis, swollen lymph nodes, swollen joints, joint contractures (chronic shortening of muscles or tendons around joints), hoarseness, and xanthemas which thicken around joints as the disease progresses. Patients with breathing difficulty may require insertion of a breathing tube. Most children with the disease die by age 2, usually from lung disease. In one of the most severe forms of the disease, an enlarged liver and spleen (hepatosplenomegaly) can be diagnosed soon after birth. Children born with this form of the disease usually die within 6 months. Farber's disease is caused by a deficiency of the enzyme called ceramidase. Currently there is no specific treatment for Farber's disease. Corticosteroids may be prescribed to relieve pain. Bone marrow transplants may improve granulomas (small masses of inflamed tissue) on patients with little or no lung or nervous system complications. Older patients may have granulomas surgically reduced or removed.

The **gangliosidoses** are comprised of two distinct groups of genetic diseases. Both are autosomal recessive and affect males and females equally.

1. The **GM1 gangliosidoses** are caused by a deficiency of the enzyme beta-galactosidase, resulting in abnormal storage of acidic lipid materials particularly in the nerve cells in the central and peripheral nervous systems. GM1 gangliosidosis has three clinical presentations: early infantile, late infantile, and adult. Signs of *early infantile* GM1 (the most severe subtype, with onset shortly after birth) may include neurodegeneration, seizures, liver and spleen enlargement, coarsening of facial features, skeletal irregularities, joint stiffness, distended abdomen, muscle weakness, exaggerated startle response, and problems with gait. About half of affected patients develop cherry-red spots in the eye. Children may be deaf and blind by age 1 and often die by age 3 from cardiac complications or pneumonia. Onset of *late infantile* GM1 gangliosidosis is typically between ages 1 and 3 years. Neurological signs include ataxia, seizures, dementia, and difficulties with speech. Onset of *adult* GM1 gangliosidosis is between ages 3 and 30. Symptoms include muscle atrophy, neurological complications that are less severe and progress at a slower rate than in other forms of the disorder, corneal clouding in some patients, and dystonia (sustained muscle contractions that cause twisting and repetitive movements or abnormal postures). Angiokeratomas may develop on the lower part of the trunk of the body. The size of the liver and spleen in most patients is normal..
2. The **GM2 gangliosidoses** also cause the body to store excess acidic fatty materials in tissues and cells, most notably in nerve cells. These disorders result from a deficiency of the enzyme beta-hexosaminidase. The GM2 disorders

include:

- ***Tay-Sachs disease*** (also known as GM2 gangliosidosis-variant B). Tay-Sachs and its variant forms are caused by a deficiency in the enzyme hexosaminidase A. The incidence is particularly high among Eastern European and Ashkenazi Jewish populations, as well as certain French Canadians and Louisianan Cajuns. Affected children appear to develop normally for the first few months of life. Symptoms begin by 6 months of age and include progressive loss of mental ability, dementia, decreased eye contact, increased startle reflex to noise, progressive loss of hearing leading to deafness, difficulty in swallowing, blindness, cherry-red spots in the retinas, and some paralysis. Seizures may begin in the child's second year. Children may eventually need a feeding tube and they often die by age 4 from recurring infection. No specific treatment is available. Anticonvulsant medications may initially control seizures. Other supportive treatment includes proper nutrition and hydration and techniques to keep the airway open. A rarer form of the disorder, called late-onset Tay-Sachs disease, occurs in patients in their twenties and early thirties and is characterized by unsteadiness of gait and progressive neurological deterioration.

- **Sandhoff disease** (variant AB). This is a severe form of Tay-Sachs disease. Onset usually occurs at the age of 6 months and is not limited to any ethnic group. Neurological signs may include progressive deterioration of the central nervous system, motor weakness, early blindness, marked startle response to sound, spasticity, myoclonus (shock-like contractions of a muscle), seizures, macrocephaly (an abnormally enlarged head), and cherry-red spots in the eye. Other symptoms may include frequent respiratory infections, murmurs of the heart, doll-like facial features, and an enlarged liver and spleen. There is no specific treatment for Sandhoff disease. As with Tay-Sachs disease, supportive treatment includes keeping the airway open and proper nutrition and hydration. Anticonvulsant medications may initially control seizures. Children generally die by age 3 from respiratory infections.

Below table summarizes lipid storage diseases, the deficient enzyme and their symptoms.

Table 25-2 **Sphingolipid Storage Diseases**

Disease	Enzyme Deficiency	Principal Storage Substance	Major Symptoms
G_{M1} Gangliosidosis	G_{M1} β-galactosidase	Ganglioside G_{M1}	Mental retardation, liver enlargement, skeletal involvement, death by age 2
Tay–Sachs disease	Hexosaminidase A	Ganglioside G_{M2}	Mental retardation, blindness, death by age 3
Fabry's disease	α-Galactosidase A	Trihexosylceramide	Skin rash, kidney failure, pain in lower extremities
Sandhoff's disease	Hexosaminidases A and B	Ganglioside G_{M2} and globoside	Similar to Tay–Sachs disease but progressing more rapidly
Gaucher's disease	Glucocerebrosidase	Glucocerebroside	Liver and spleen enlargement, erosion of long bones, mental retardation in infantile form only
Niemann–Pick disease	Sphingomyelinase	Sphingomyelin	Liver and spleen enlargement, mental retardation
Farber's lipogranulomatosis	Ceramidase	Ceramide	Painful and progressively deformed joints, skin nodules, death within a few years
Krabbe's disease	Galactocerebrosidase	Deacylated galactocerebroside	Loss of myelin, mental retardation, death by age 2
Metachromatic leukodistrophy (Sulfatide lipidosis)	Arylsulfatase A	Sulfatide	Mental retardation, death in first decade

Table 25-2