

# Learning of Multitasking from the Liver

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## **The liver:**

The liver is the main organ of intermediary metabolism. It consists of several different cell types. The predominant cell type is the hepatocyte (60-65 %). In addition, endothelial cells (20-25 %), Kupffer cells (8-12 %) and hepatic stellate cells are present.

Amino acids, proteins, lipids and carbohydrates are synthesized, degraded or modified in the liver by hepatocytes. For example, gluconeogenesis generates glucose, a central carbohydrate in the metabolism of the organism which, above all, represents the main energy source for neuronal tissue. On the other hand, glucose is also degraded by hepatocytes via glycolysis. Glycolysis in the liver generates precursors for the synthesis of amino acids and lipids, and delivers energy for metabolism under low oxygen tension. The degradation of fatty acids ( $\beta$ -oxidation) occurs in the liver, which yields acetyl-CoA. However, acetyl-CoA is also the precursor for fatty acid synthesis in this organ. Several amino acids are generated in the liver. The major amino acid in blood plasma is glutamine (Gln), which is synthesized from ammonia and  $\alpha$ -ketoglutarat by glutamine synthetase (GS) in liver. However, glutaminase, also present in liver degrades Gln to ammonia and glutamate. In addition hepatocytes metabolize drugs in biotransformation reactions, synthesizes bile acids and hormones. These examples show that, both synthesis and degradation of the same molecules, i.e. anabolism and catabolism, can take place in liver. Both may take place at the same time. These reactions are performed mainly by hepatocytes. Consequently liver can be characterized as a multitasking organ.

## **Organization of liver tissue:**

In order to fulfil these tasks the liver is a highly structured organ, although morphology is rather uniform. The smallest subunit within the organ is the lobulus. Each lobulus consist of afferent vessels which form portal fields. The surrounding area is named periportal region. Blood flows from the portal field into the tissue and is drained through a centrally located efferent vessel, branches of the hepatic vein. Around these central veins the area is called pericentral region. In cross-sections a hexagonal arrangement, consisting of a central vein surrounded by 3 to 6 portal fields can be observed. During passage from the portal field to the central veins blood flows through the sinusoids, passing approximately 20-25 hepatocytes., Within this distance of 20-25 hepatocytes all metabolic functions of the liver are localized. Due to the presence of multiple lobuli (more than thousand), the liver has the capacity to keep the composition of blood fairly constant.

Interestingly, some metabolic pathways are present in all hepatocytes and some are present only in a subset of hepatocytes in the periportal or the pericentral area of the lobulus. In particular, anabolic and catabolic pathways are separated. This concept is called metabolic zonation. This zonation is for some functions static (confined to a fixed number of hepatocytes only), or can be dynamic for others depending on the physiological demand. Based on this spatial arrangement of different metabolic pathways among hepatocytes, which allows a metabolic zonation, the liver is an organ predestined to exert multitasking capabilities.

### **Glutamine metabolism:**

Glutamine (Gln) is the main amino acids in blood plasma (20 %) and represents two-thirds of all amino acids in cerebrospinal fluid in man. Gln serves as donor of nitrogen groups in the synthesis of purines and pyrimidines, is substrate in several other biosynthetic reactions, and is the major energy source in kidney, small intestine and bone.. Most importantly, however, Gln is synthesized from glutamate or  $\alpha$ -ketoglutarate, thereby removing toxic ammonia from the circulation.

Glutamine is synthesized in liver by a small subset of hepatocytes located around the central veins. Newly synthesized Gln is immediately drained from the liver and is distributed in the organism. Gln can re-enter the liver via the portal veins . Subsequently, Gln is almost completely degraded by glutaminase to ammonia and glutamate in the periportal region. Ammonia may be removed by fixation in the urea cycle. Remaining ammonia is then removed from the blood in the pericentral area by specific  $\text{NH}_4^+$ -carriers and is converted to Gln by glutamine synthetase. This new glutamine again enters the circulation.

### **Glutamine synthetase:**

In liver, glutamine synthetase (GS) is expressed only in a small subpopulation of pericentral hepatocytes representing a static localization. Periportal hepatocytes are free of GS. Therefore, GS can be used as a model enzyme to investigate factors responsible for metabolic zonation. Several different mechanisms seem to be involved in the induction of GS. A soluble factor, most likely generated by endothelial cells can induce GS [1]. This factor might activate the Wnt/ $\beta$ -catenin pathway, which seems to be involved in the induction of GS [2]. Recently a model of interacting factors of the Wnt/ $\beta$ -catenin pathway was calculated, based on Affimetrix gene array data [3]. In addition Gaunitz and co-workers [4] demonstrated that the expression of GS is repressed in periportal hepatocytes due to a silencer element and a silencer binding protein.

From these data it is obvious that the regulation of the multitasking capabilities of liver tissue, based on the heterogeneous gene expression is a complex process. GS seems to be an appropriate model enzyme to investigate factors involved in these processes. Especially since other heterogeneously expressed proteins seem to be regulated by similar processes [5].

### **Reference List**

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