Lu *et al. Metab Target Organ Damage* 2023;3:3
DOI: 10.20517/mtod.2023.11

Metabolism and Target Organ Damage

Editorial

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Are hepatocytes endocrine cells?

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How to cite this article: Lu Y, Zheng MH, Wang H. Are hepatocytes endocrine cells? *Metab Target Organ Damage* 2023;3:3. https://dx.doi.org/10.20517/mtod.2023.11

Received: 21 Mar 2023 **Accepted**: 27 Mar 2023 **Available Online:** 31 Mar 2023

Academic Editors: Luigi Elio Adinolfi, Amedeo Lonardo **Copy Editor:** Ying Han **Published:** Ying Han

While exocrine glands secrete substances onto an epithelial surface through the ducts, endocrine glands are ductless and secrete their products directly into blood or lymph. These secretions are produced by specific cells, which either live in groups to form specific organs or tissues, called endocrine glands or endocrine organs, or scattered in other organs, such as cells secreting gastrointestinal hormones in gastrointestinal mucosa. These secretions were initially named "hormones" by two British physiologists - William Mortlock Bayliss and Ernest Henry Starling, in the early 20th century. Hormones enter target cells of distant organs through blood circulation and exert their unique biological effects through either binding with their membrane receptors to activate intracellular second messengers, such as protein kinases and calcium, or interacting with nuclear receptors, leading to changes in the expression and/or activity of target genes at the transcription and/or protein modification levels. Traditional endocrine organs are hypothalamus, pituitary gland, pineal gland, thyroid gland, parathyroid gland, adrenal gland, pancreatic islets, testis (male), and ovary (female). Due to the discovery of Leptin in 1994 and subsequent molecules such as Adiponectin and Resistin, adipose tissue, which stores triglyceride and energy, is also considered as an endocrine organ.

These molecules secreted by adipose tissue are collectively termed adipokines. With the development of RNA-sequencing, mass spectrometry, and single-cell sequencing technologies, it has been shown that the liver can also express and secrete many molecules, including cytokines, metabolites, and exosomes, and miRNAs [Figure 1]. These molecules not only play autocrine and paracrine roles in the liver but can also enter into the blood circulation and reach distant organs. Especially the hepatocytes-derived cytokines are collectively named "hepatokines"[1-3]. One of the well-established hepatokines is the fibroblast growth factor 21 (FGF21), which regulates hepatic and systemic homeostasis in response to environmental changes, such as diets, exercise, and cold exposure[4]. Moreover, the importance of other hepatokines, including Kisspeptin, Fetuin B, SerpinB1, Follistatin, Gpnmb, Tsukushi, SMOC1 and ORM2, has been identified in recent years[5-12]. In light of these, we may raise the question: are the hepatocytes novel endocrine cells? To explore this issue, we would compare hepatocytes with traditional endocrine cells as follows:

First, the function of secretion, especially endocrine, is the most important characteristic of endocrine cells. At this point, hepatocytes can secrete multiple hepatokines mentioned above into the blood. In particular, these hepatokines, similar to hypothalamic hormones and insulin, are structurally polypeptides, and proteins and are transcribed and expressed by specific genes (that are not synthesized through biochemical reactions). However, it should be noted that the substances secreted by traditional endocrine cells are tissue-specific. Insulin is mainly secreted by pancreatic beta cells, and thyroid hormone can only be secreted by thyroid follicular epithelial cells. However, the specificity of hepatokines is relatively weak. The mRNA of hepatokines mentioned above is also expressed in other tissues or organs. For example, FGF21 is also enriched in the adipose tissues and skeletal muscles[4]. Therefore, specific expression and secretion of certain cytokines in the liver remains to be identified.

Second, traditional hormones and endocrine organs can respond to changes in the internal and external environments. For example, insulin is expressed and released from pancreatic b cells in response to increased circulating glucose concentrations. The molecular mechanisms of expression and secretion of hepatokines remain poorly understood. Especially while insulin can be released into the blood 5-10 min after a meal, whether secretion of hepatokines is a fast reactive process needs to be determined.

Third, all of the traditional endocrine hormones have crucial physiological functions, including growth, development, and reproduction. However, studies on hepatokines now focus more on pathophysiological conditions, such as obesity and overnutrition. Great effects have been made to explore their roles and mechanisms in metabolic diseases, including type 2 diabetes and nonalcoholic fatty liver disease. However, the physiological roles of hepatokines are seriously ignored.

Fourth, one of the important differences between the endocrine system and the cardiovascular, digestive, and immune systems is that it depends on feedback regulation. In the hypothalamic-pituitary-adrenal axis or the hypothalamic-pituitary-gonadal axis, the secretion of downstream hormones is often positively regulated by the upstream hormones, while the upstream hormones are negatively regulated by the downstream hormones, thus ensuring that the expression and secretion of hormones are properly controlled in a relatively stable concentration range. Whether positive and/or negative feedback loops for the expression and secretion of hepatokines exists needs to be determined.

In summary, hepatocytes are similar to traditional endocrine cells in many aspects, which makes us reasonably propose that they are novel endocrine cells. However, some differences still exist between hepatocytes and traditional endocrine cells, as mentioned above. Nevertheless, both the metabolic and endocrine functions of hepatocytes are crucial for the regulation of hepatic and systemic homeostasis

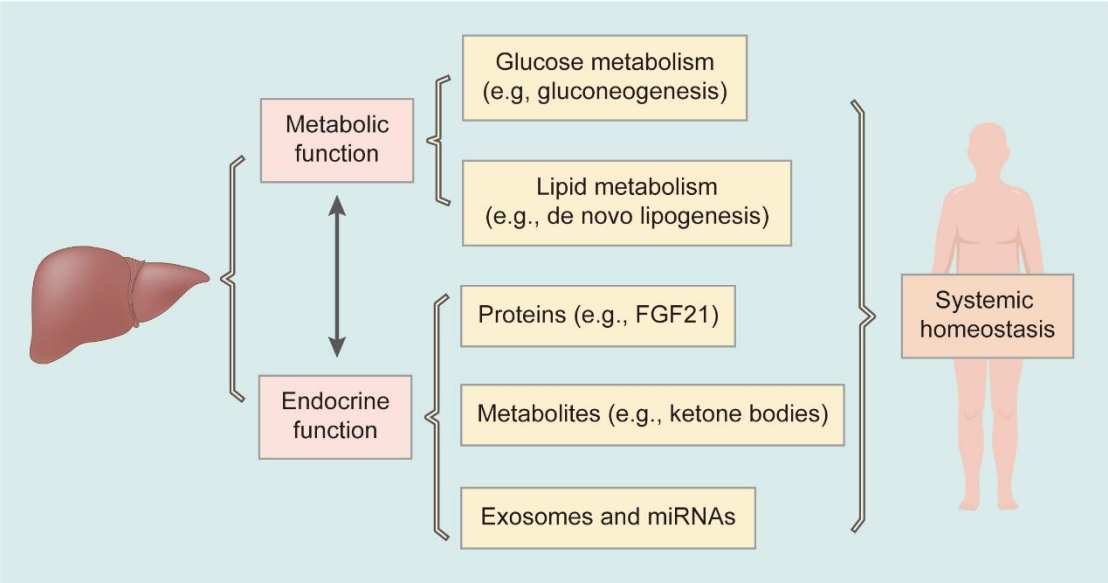

Figure 1. The liver has both metabolic and endocrine functions to regulate hepatic and systemic homeostasis.

[Figure 1]. Therefore, it has recently been proposed that the liver can be considered a metabolic organ with important endocrine functions, especially in the maintenance of metabolic homeostasis and the development of metabolic disorders. We also believe that with the update of molecular biology technologies, the endocrine functions of hepatocytes, also named hepatocrinology[13], including the regulatory mechanisms of hepatokines and the identification of novel specific hepatokines, will be gradually uncovered.

DECLARATIONS

Authors' contributions

Conceived the design of this article and wrote the first draft. He also participated in the process of revising and editing the manuscript and approved the submitted version of the manuscript: Lu Y
Involved in discussion and revision of the manuscript, approval the submitted version of the manuscript: Zheng MH, Wang H

Availability of data and materials

Not applicable.

Financial support and sponsorship

National Key Research and Development Program of China (2018YFA0800402).

Conflicts of interest

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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