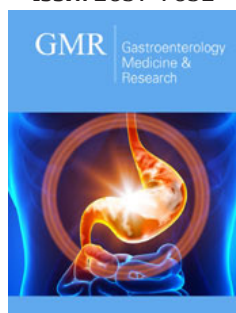



# Age-Related Changes in the Liver: On the Way to Ontogenetic Bioregulation

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## Abstract

This short communication aims at describing age-related changes of liver functions, focusing on our own studies performed earlier in primary cultures of liver cells obtained from fetal and prepubertal rats. In addition, our recent theoretical constructs are discussed, outlining the new general concept of ontogenetic bioregulation.

**Keywords:** Hepatocytes; Hormonal regulation; Ontogeny; Primary cell cultures

## Introduction

This story began long time ago, at the end of eighties of the last century. At that time we worked in the laboratory for biological research of hormonal compounds at the institute of experimental endocrinology in Moscow, Russia, being quite successful in studying hormonal secretion by pituitary cells of adult rats in primary cultures. However, since one colleague had an intention to go away from laboratory, our chief, Prof. Viktor P. Fedotov asked us to elaborate primary cultures of rat liver cells. After 3 months of reading many articles in the National Library, we were sure that:

- A. Trypsin, used for isolation of pituitary cells is completely inadequate for isolating the liver cells;
- B. Collagenase had to be used by perfusion of its solution to adult rat liver-a procedure that was too expensive for us at that time;
- C. Fortunately, in the case of fetal rat liver batch-type incubation in solution of collagenase could be employed.

Therefore, the first results were obtained on primary cultures of fetal rat liver cells enriched with hepatocytes. However, soon an obvious question emerged: for how much the hormonal regulation of fetal liver is mature? As a result of this doubt, we had to elaborate primary cultures of liver cells obtained from prepubertal rats by means of perfusion with collagenase solution, using a protocol of other researchers for adult mice of approximately the same size. All these circumstances paved our way to age-related comparisons of hormonal regulation in primary cultures of rat liver cells.

## Why are age-related changes so important?

In parallel to our studies on primary cultures of liver (and subsequently pituitary) cells obtained from rats of different age categories, a group of English epidemiologists headed by David J.P. Barker performed a series of investigations that resulted one-two decades later in organization of International Society for DOHaD (Developmental Origins of Health and Disease) and its journal. At present this Society is a unique world-wide entity in studying development and aging in conjunction.

At least two reasons were decisive for our association with this Society since 2009:

- a) shortly after arriving to Brazil in 1993, we performed the experiments *in vivo*, demonstrating much higher sensitivity of neonatal rats to growth-inhibitory action of Glucocorticoids (GC), thus reproducing long-known data of Widdowson and McCance on malnutrition (see discussion in [1]);
- b) on the other hand, GC are considered at present to be the principal candidates to mediators of programming / imprinting phenomena in DOHaD concept [2].

### Age-related changes in the liver

The most essential process in this regard is polyploidization, when diploid hepatocytes (2n) are transformed to polyploid ones (4n-8n and higher ploidy) by a phenomenon similar to mitosis, but without cytokinesis. This process is accompanied by more than two-fold increase in cell size (from approximately 10 to 20-30 micrometers). Exactly because of this peculiarity, we did not use the incorporation of <sup>3</sup>H-thymidine as an indicator of cell proliferation in our experiments on primary cultures of liver cells obtained from fetal and prepubertal rats. Instead of this, we employed double labeling with <sup>3</sup>H-uridine and <sup>14</sup>C-L-leucine, in order to evaluate the biosynthesis of total RNA and proteins respectively. It is important that monolayer cultures possess an advantage of much more simple procedure for evaluating the incorporation of labeled precursors to acid-insoluble cellular material. The comparison of fetal and prepubertal hepatocytes has demonstrated the most expressive stimulatory effect of GC on total RNA and protein biosynthesis, without notable age-related differences. Moreover, several other hormones, such as insulin, growth hormone and tri-iodothyronine were able also to stimulate the biosynthesis of macromolecules in hepatocytes, sometimes with potentiated action [3].

On the other hand, we studied the hormonal regulation of production by hepatocytes of immunoreactive Serum Albumin (SA), the principal protein of blood serum or plasma. Again, GC possessed the most expressive stimulatory influence on SA production, without notable differences between hepatocytes of fetal and prepubertal rats [4]. Since there remained a small contamination of primary liver cell cultures by Kupffer cells, we have elaborated also their cultivation in selective medium containing GC and barbiturate. In this case GC have lost their ability to stimulate biosynthesis of total RNA and proteins during subsequent incubation in non-selective medium, what was interpreted by us as some sort of imprinting phenomenon [5]. Later on we suggested the involvement of interleukins produced by contaminating Kupffer cells in hormonal regulation of hepatic functions in primary cultures. Moreover, just recently we reviewed these data, together with hypotheses of other authors, in order to justify the possibility of programming/imprinting phenomena *in vivo* [6].

### Tissue streaming and proteostasis in the liver

At present two processes are discussed, as referred to tissue self-renewal in general: tissue streaming and proteostasis. Tissue streaming, as related to the liver, was explored by Gershon Zajicek

and his colleagues in Israel during the eighties of the last century (see discussion in [7]). This process is described as slow cellular translocation from cambial layer of stem or progenitor cells to the layer of terminally differentiated cells that are subjected finally to apoptosis and subsequent phagocytosis. It appears that in the liver cambial layers are located closely to vessels originating from portal vein, whereas terminally differentiated hepatocytes are proximate to reticulo-endothelial spaces occupied by Kupffer cells. It is important also that with aging the velocity of tissue streaming appears to diminish substantially. On the other hand, proteostasis in hepatocytes is quite intensive. In fact, the proteolysis rate their is close to 4-5% per hour, therefore protein pool is renewed by protein resynthesis almost entirely during one day (24h) [8]. Just recently we have proposed the concept of hormonal regulation for tissue streaming that tries to reunite two smaller concepts, of episodic hormonal secretion in homeokinetic (or homeodynamic) mode and tissue streaming [9]. Now we are ready to adjust this concept by adding hormonal regulation of proteostasis. At least in the liver this regulation should include insulin and glucagon. Finally, let's discuss now, why the even larger concept of ontogenetic bioregulation may be especially important.

### Final remarks

Previously we have proposed the necessity of amplifying and broadening the disciplines of gerontology to the science of whole ontogeny and of endocrinology to the science of bioregulation. The concept of ontogenetic bioregulation is exactly at the intersection of these amplified versions of gerontology and endocrinology. As referred to the liver, three important endeavors are essential for elaboration in the near future:

- A. Clarifying the mechanisms of programming/imprinting and embedding in perinatal and early development;
- B. Studying the causes of lower tissue streaming with aging;
- C. Their interactions with proteostatic regulation in the liver.

In conclusion, we are sure that these investigations may help a lot in the treatment and prevention of chronic liver disorders, such as non-alcoholic steatohepatitis as a consequence of metabolic syndrome.

### Conflicts of Interest

The author declares that does not have affiliation or participation in organizations with financial interests.

### Ethical Approval

This report does not contain any study of human or animal subjects carried out by the author.

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