Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.63.009851

Biological Information Transmission Modalities in the Normal Liver and in the Cirrhotic One. From Ligand Molecule to Oscillations, Waves and Fields

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ARTICLE INFO

Received: August 02, 2025

Published: September 04, 2025

Citation: Mihaela Gheorghiu. Biological Information Transmission Modalities in the Normal Liver and in the Cirrhotic One. From Ligand Molecule to Oscillations, Waves and Fields. Biomed J Sci & Tech Res 63(2)-2025. BJSTR. MS.ID.009851.

ABSTRACT

All physicians were used to approaching hepatic pathophysiology from the macroscopic level down to the level of molecular signaling and hepatocyte genomic response, where they stopped. This paper aims to approach the fractal reality called Life at an even deeper level. More specifically, this article is one of the few that aims to present the connection between biochemical and biophysical phenomena. Thus, we will try to present the spectacular events of intrahepatic signaling from the cellular to the quantum level. We believe it is extremely important for a physician to understand that normal and disease are actually particle-wave phenomena of informational exchange. We will first present how any signal from an extracellular ligand is transformed in the hepatocyte into calcium oscillations and waves, a phenomenon known for a long time.

We will descend into the fractal and see how, under normal conditions, these calcium oscillations and waves are entangled with the oscillations and waves of ROSs generated in the mitochondria and how the entanglement disappears in liver pathology. We will see how the oscillations and intra- and intercellular waves of calcium and ROSs generate electromagnetic waves and how, at this level, the laws of quantum physics manifest themselves. Then how these electromagnetic (energetic) fields associate torsion (informational) fields, confirmed by the physics of recent years. Although torsion fields are classically considered pseudoscience because they lack sufficient experimental support, although torsion fields were classically considered pseudoscience because they lacked sufficient experimental support, this approach is now increasingly being disproven. Readers should remember that quantum mechanics was founded on a single empirical prouve: the double slit experiment. This is where Normal begins, this is where Disease begins.

Keywords: Extracellular Ligand; Calcium Oscillations and Waves; Reactive Oxygen Species Oscillations and Waves; Electromagnetic and Torsion/Spinor Fields; Quantum Entanglement

Abbreviations: FGF: Fibroblast Growth Factor; HGF: Hepatocyte Growth Factor; PDGF: Platelet Derived Growth Factor; TNFα: Tumor Necrosis Factor Alpha; VEGF: Vascular Endothelial Growth Factor; APC: Antigen Presenting Cells; GPCRs: G Proteins Coupled Receptors; ER: Endoplasmic Reticulum; SERCA; Sarcoplasmic/Endoplasmic Reticulum; TRKp: Tyrosine Kinase Receptors

Introduction

If, until the '70-'80 years, the pathophysiological mechanisms of liver cirrhosis were understood and explained at the systemic, humoral level, by detailing the specific syndromes, the following decade brought the great victory of the discovery and description of membrane receptors and of the intracellular signaling mechanisms. It was the opening of a new and unexpected path. Optical and electron microscopy had already provided information about the organelles and tissue function, but intracellular functional details had not been glimpsed yet. To date, a lot of intracellular signaling mechanisms have been described that basically follow the following pattern: ligand → receptor → cell membrane → adapter proteins → initiator enzymes → many enzyme cascades, basically kinases and intracytosolic mediators, which amplify the response → transcription factors → nucleus → genomic response by RNA... → final cell response by protein synthesis. This paper aims to present and argue the idea that the transmission of

biological information in an organism means much more than a biochemical reaction. It means oscillation, wave, coherence, quantum entanglement, quantum tunneling... We are not in a science fiction scenario, but we are recalling, in passing, essential operating principles, discovered and experimentally confirmed after the 1990s. However, the information explosion has culminated in the last 7-8 years, after the acquisition of research technologies unimaginable a decade ago.

Intercellular Information Transmission Under Normal Conditions and in Liver Cirrhosis

The liver consists of parenchymal cells (hepatocytes, which constitute approx. 70% of the liver's cellularity) and non-parenchymal ones. Three of the non-parenchymal cell types are arranged in the wall of the liver sinusoids: sinusoidal endothelial cells, Kupffer cells (resident liver macrophages), and hepatic stellate cells [1].

Apart from these, there are four other types of non-parenchymal cells: intrahepatic cholangiocytes, progenitor stem cells (also called oval cells), fibroblasts and a local lymphocyte population. Before going into the details of this paper, it is essential to deeply understand the functional structure of the liver lobule (Figure 1). Portal venous branches join at the periphery of the lobule with branches of the hepatic artery, giving rise to a perilobular arteriovenous network [1]. From this network arise the sinusoidal capillaries, with a radial arrangement, towards the centrilobular vein. The direction of blood circulation is from the periphery of the lobule to the centrilobular vein. Hepatocytes are arranged in cords around the sinusoidal capillaries. The latter therefore make the connection between the perilobular arteriovenous network and the centrilobular vein, which flows into a hepatic vein. Hepatocytes have a vascular pole, oriented towards sinusoidal capillaries and lateral walls [1]. Between the side walls of the hepatocytes, narrow spaces are formed, into which the bile flows and which, at first, do not have their own walls (the hemispace from one hepatocyte joins the hemispace of the neighboring hepatocyte, creating a canalicular structure without having own walls). They converge towards the periphery of the lobule, emptying into intralobular canaliculi with their own walls (cholangiole) [1]. The cholangioles of several neighboring lobules converge into a perilobular bile duct. It forms the hepatic triad in the portal space, along with the branch of the portal vein and the arterial branch. So, the circulation of bile is opposite to the circulation of blood. Under normal conditions, all of the aforementioned cell types exchange information that generates reciprocal functional regulation loops (Figure 1).

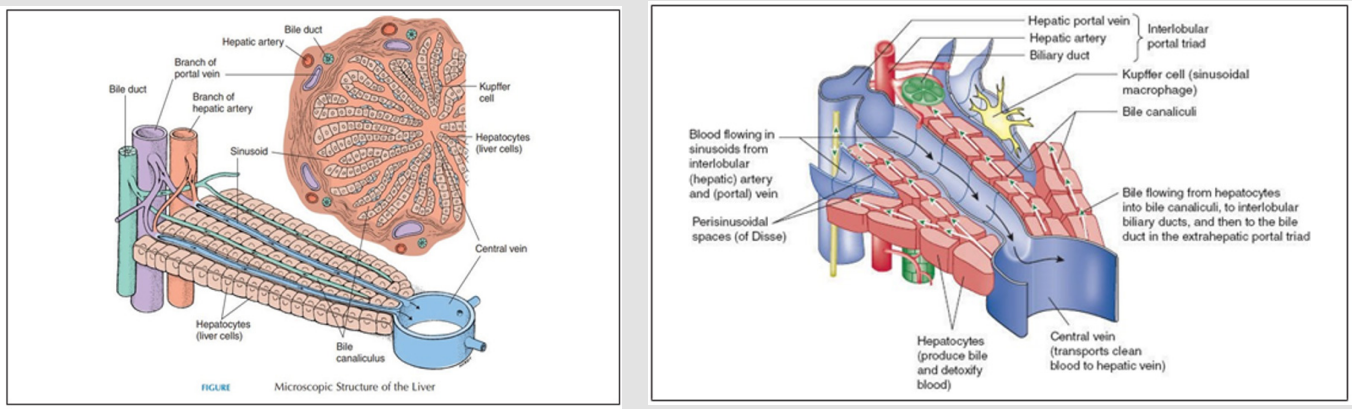

Figure 1: Section through the liver lobule; functional diagram of the bile and blood flows [1].

But What Happens in Cirrhosis?

Before leading the discussion at the intra- and extracellular level, it is useful to briefly present the chronic inflammatory environment that precedes the onset of cirrhosis. The etiological factor triggers a chronic inflammatory reaction, developed following the classical model and involving all parenchymal and non-parenchymal liver cell types. Blood leukocytes (neutrophils, monocytes, lymphocytes) are added to these cells, being attracted to the inflamed liver tissue by various signal molecules with a chemotactic role. The inflammatory phenomenon triggered by the repetitive action of the causative agent is self-perpetuating, through the chronic release of inflammatory mediators, cytokines and growth factors (having prototypes TGFβ-transforming growth factor beta and FGF-fibroblast growth factor). FGF and TGFβ stimulate the activity of fibroblasts and hepatic stellate cells → increase collagen production → hepatic interstitial fibrosis and the emergence of connective septa. On the other hand, HGF (hepatocyte growth factor) is released from the hepatocytes destroyed by apoptosis or necrosis and stimulates hepatocyte regeneration, with the emergence of regeneration nodular foci. The parallel processes of fibroblastic proliferation and anarchic hepatocytic regeneration cause the disorganization of the liver architecture and the progressive decrease in the number of hepatocytes. Fibrosis (without clinical mani-

festations) precedes cirrhosis, being the essential pathologic process common to all chronic liver diseases that progress to cirrhosis. Therefore, the fibrosis mechanism should be understood in all the intercellular information exchange complexity that generates it. Hepatic stellate cells, sinusoidal endothelial cells, Kupffer cells and hepatocytes participate in this exchange

Hepatic Stellate Cells (HSCs)

They are also known as perisinusoidal cells, lipocytes (fat-storing cells), Ito cells or vitamin A-rich cells [2]. They are located in the space of Disse (perisinusoidal space), which is formed between the wall of a sinusoidal venule and the wall of hepatocyte cords. Their main function is to store retinoids, mainly vitamin A. Significant amounts of PDGF (Platelet-derived growth factor), TGFβ, TNFα (Tumor necrosis factor alpha), IL-1β (Interleukin-1 beta) are produced from liver inflammation [3]. These cytokines and growth factors stimulate HSCs that transition from the latent to the activated form, which allows them multiple possibilities of evolution:

- They become precursors of new hepatocytes;
- Proliferate and then migrate, also like HSCs;
- Turns into myofibroblasts that secrete collagen and other components of the extracellular matrix, with the generation of fibrosis. The transformation into myofibroblasts is also induced by prolonged vitamin A deficiency [4].

Sinusoidal Endothelial Cells (SECs)

They are fenestrated cells, meaning they have spaces with dimensions of 150-175 nm that act as a filter for water, electrolytes and particles. They have an increased endocytosis capacity [5]. Fenestrations are lost in chronic alcoholism and LC (defenestration), when a continuous basement membrane appears that makes it very difficult for nutrients to enter the hepatocytes. The newly formed basement membrane is the result of collagen synthesis by hepatic stellate cells transformed into myofibroblasts. SECs have a very interesting dual behavior [5]:

- When they are activated in chronic inflammation, they begin to secrete IL-33 (Interleukin-33), which activates HSCs, thus the appearance of fibrosis;
- When are stimulated only by VEGF (Vascular endothelial growth factor), they start to secrete NO (nitric oxide), which induces the reversion of myofibroblasts into HSCs.

Kupffer Cells (KfCs)

They are macrophages that belong to the RES (Reticuloendothelial System) and are located among sinusoidal endothelial cells. Are frequently activated by viruses, alcohol, bacterial lipopolysaccharides, fatty diet, iron deposits etc. The results of activation are the inflammatory mediator's synthesis and discharge that destroy both the etiological agent and hepatocytes. In infections-induced acquired immunity, they also play the role of antigen presenting cells (APC) [6]. To KfCs are added blood monocytes and neutrophils, which are attracted and activated in the liver. KfCs synthesize cytokines, primarily TGFβ (the most potent inducer of fibrosis), which activate HSCs. It also secretes IL-6 (Interleukin-6) and IL-1β, which induce the cholangiocytes proliferation, with the appearance of a ductular reaction [6]. KfCs phagocytize apoptotic bodies and produce cell death ligands, such as FasL and TNFα, which bind to the death receptors Fas and TNFR and induce apoptosis in the cells displaying these receptors [6]. They can also synthesize thromboxane A2 (TxA2), which stimulates the microthrombi formation and generates an increase in portal pressure [7].

Hepatocytes

They are the primary targets of viruses, ethanol metabolites, bile acids, and mediators released in the inflammation that precedes and/or is associated with LC. In LC, they progress either towards necrosis/apoptosis or regeneration. When severely "damaged" and hypoxic, they secrete ROSs (reactive oxygen species) and TGFβ (Transforming growth factor beta), which stimulate HSCs to transform into myofibroblasts and to secrete collagen. They control the extracellular matrix production through the secretion of a large content of metalloproteinases, but also of their inhibitors [4]. If this hepatic intercellular communication was long considered to be achieved only through isolated peptide molecules, hormones and cytokines, in recent decades communication through extracellular vehicles (EVs), which are particles initially attached to the outer membrane and then released into the environment, has also been proven and extensively described [4,8,9].

The Great Importance of The Mechanism is Given by the Possibility of Transferring the Vesicular Content of Proteins and DNA and RNA Fragments [8]

There are three types of EV known: exosomes, microvesicles (microparticles) and apoptotic bodies. Exosomes are the smallest EVs (around 100 nm) and are formed in the endoplasmic reticulum, then fusing with the outer cell membrane and remaining attached to its outer face, from where they detach, under certain conditions [8, 9]. Microvesicles (0.1-1 μ) are formed by the phenomena of "budding" and fission of the outer membrane. Like exosomes, they contain proteins, DNA and RNA and are released by a "donor" cell and taken by an "acceptor" cell. Apoptotic bodies (1-4μ) are released by apoptotic cells onto the outer membrane, with the participation of the cytoskeleton, which directs various structural fragments into this type of microvesicles. Apoptotic bodies are taken up and engulfed by macrophages, along with the entire apoptotic cell [8,9]. Intercellular communication through EVs is actually done through exosomes and microvesicles, the mechanism having a particular importance in the development and spread of a disease. It is also carried out under physiological conditions, ensuring functional connections at a distance between organs [9] (Figure 2).

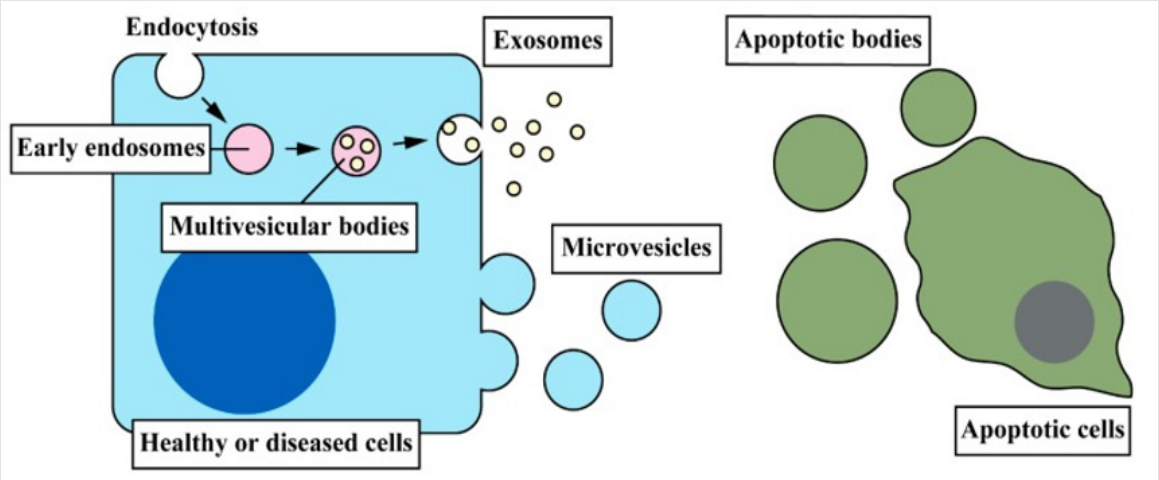

Figure 2: Intercellular communication through extracellular vesicles [9].

Examples:

- In the liver, the largest number of EVs is secreted by hepatocytes and, in this way, they transmit information to HSCs, endothelial cells and Kupffer macrophages. In the case of LC, the phenomenon ensures the perpetuation of the inflammatory process, fibrosis and angiogenesis [9].

- Experimental injection of EVs into the tail vein of mice was followed by the EV distribution in the liver, spleen, intestine, lungs, pancreas and kidneys [8,9].

- The liver and the intestine mutually coordinate in the processes of enterohepatic circulation and metabolism of bile acids, through the secretion and absorption on cellular receptors of EVs containing bile acids [9].

- Intestinal microbiota influences the liver function through the secretion of EVs with bacterial compounds that bind to the receptors of liver parenchymal and non-parenchymal cells [8,9] (Figure 3).

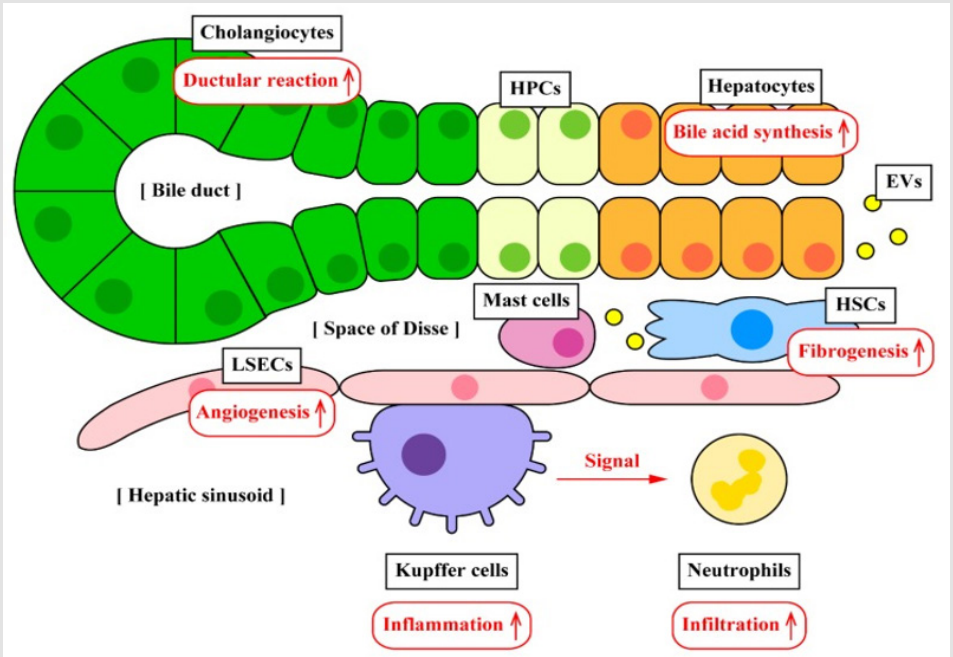

Figure 3: Communication between different types of hepatic cells through extracellular vesicles, HPC – hepatic progenitor cells; EVs –extracellular vesicles; LSEC – liver sinusoidal endothelial cells [9].

The fundamental novelty of this biological information transfer mechanism between cells and organs is the fact that DNA and RNA fragments can be transferred paracrine or at distance (even between organs). If, under normal conditions, this transfer "coherentizes" cells and organs, in the case of a pathological process, the disease spreads rapidly from an affected donor to a healthy receiving cell. Consequently, EVs have become very important therapeutic targets.

Intracellular Transmission of Information Under Normal Conditions and in Liver Cirrhosis

All hormones and neurotransmitters use G proteins coupled receptors (GPCRs).

How Does a Cell "Know" Which Ligand is Attached on its Membrane, if Lots of Different Ligands Use the Same Type of Cellular Receptors?

How Does the Hepatocyte Manage to Distinguish these Signals?

The answer is: at a Basal Level, Through Calcium Oscillations and Waves.

According to classical information, it is known that many of the liver's functions are controlled by Ca^{2+}, as in the myocardial cell and many other cell types:

- Glucose and glycogen synthesis;
- Bile secretion (vesicles motion, canalicular exocytosis, permeability of junctions between cholangiocytes, canalicular contraction);
- Regulation of cell growth;
- Cell division;
- Apoptosis;
- Necrosis.

Therefore, Calcium has a Fundamental Role in the Control of Cell Functions.

What are the "Strategies" Employed by the Normal Hepatocyte to Exert Control Through Calcium?

How does this Control Mechanism "Work"?

The cytosolic calcium level is maintained low (100–200 nM), while in the other two compartments with which it communicates, the extracellular environment and the endoplasmic reticulum (ER), the concentrations are much higher (1–2 mM and 0.5 mM, respectively) [9,10]. Being located between these two compartments very rich in calcium, the cytosol constantly registers rapid variations in calcium concentration through the transfer of small amounts from the extracellular environment or from the ER. These variations are induced by hormones and neurotransmitters, through GPCRs stimulation, and are described as calcium signals [10,11]. Calcium signals are recorded throughout the body, from subcellular components to organs and systems. Moreover, they are very well organized in space and time. In the hepatocytes stimulated by different classes of GPCR-bound ligands, as in all other non-excitable cells in the body, the predominant pathway for increasing cytosolic calcium is the activation of the inositol triphosphate (IP3) system. IP3 is therefore synthesized secondary to signaling through the GPCR pathway, which involves the following steps: Ligand-GPCR → G protein synthesis → PLC (phospholipase C) activation → PIP2 (phosphatidyl inositol diphosphate) cascade activation → IP3 synthesis, which binds to receptors (IP3Rs) on the ER membrane. IP3Rs are, in fact, channels through which calcium is released into the cytosol [11,12].

It has been experimentally shown that the hormonal stimulation of hepatocytes generates calcium signals in the form of oscillations with a period of several seconds to several minutes. Each calcium oscillation is spatially organized: first it grows locally, then, it propagates throughout the cell, like a wave, at a speed of 10-20 μ/sec [11]. We have previously seen how the different types of liver cells communicate indirectly, through mediators and released EVs, which bind to receptors and trigger intracellular transduction signals. All these signals are "translated" into the cell through calcium waves, which propagate not only in cell, but also between cells, through gap junctions [13] (Figure 4). Therefore, it should be understood that, following a ligand attachment to a hepatocyte receptor, the "message" carried by the ligand is translated in the cell into a universal language: calcium oscillations and waves. Intra- and intercellular calcium oscillations and waves are closely dependent on the properties of inositol triphosphate receptors, IP3Rs (calcium release channels). By special recording techniques, very discrete variations in cytosolic calcium have been detected. Thus, signals given by increases in cytosolic calcium level determined by a single IP3R channel were called "Ca^{2+} blip", and those originating from a small group of channels were called "Ca2+ puff" [11,13,14]. IP3R is a heterotetramer, so it contains four calcium receptor units. The operation of IP3R channels is essential, so it is subject to strict regulation mechanisms by:

- Cytosolic Ca^{2+} level. The open-closed state of IP3R units depends on this level. IP3Rs open when calcium decreases, as a result of SERCA (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase) activation, that reintroduces it into the ER, and close in opposite situations.;
- Particularities of calcium diffusion in the cytosol;
- Synthesis, metabolism and intracellular movement of IP3Rs;
- Activity of many intracellular kinases that phosphorylate and, secondarily, open IP3Rs [15].

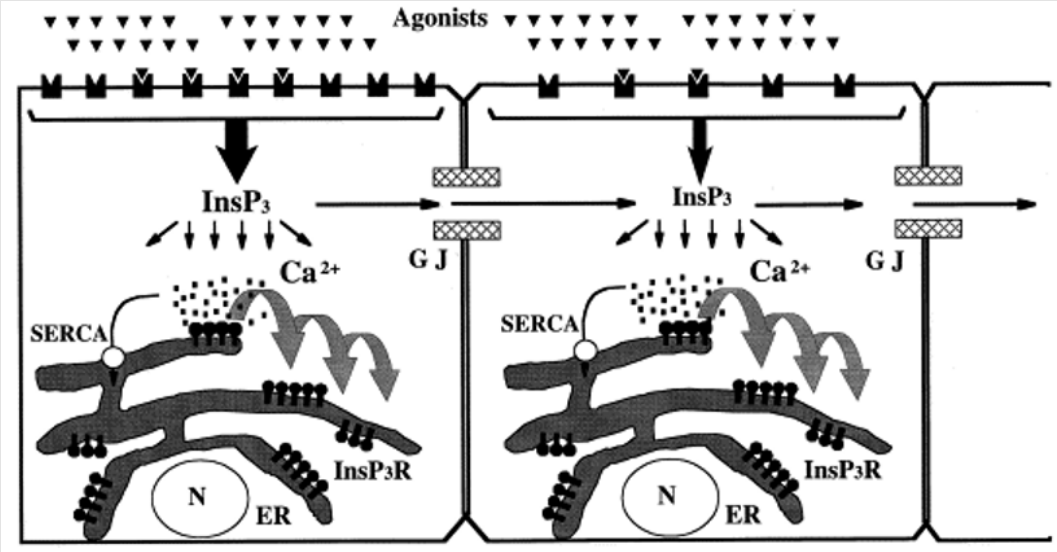

Figure 4: Calcium signals inside the hepatocytes [12].

What are the Particularities of Calcium Oscillations and Waves in Hepatocytes?

- Oscillations

They are generated by IP3 and SERCA operation.

These oscillations are of two types: sharp peaks and sinusoidal oscillations [12,16].

a) In most cases, calcium oscillations take the form of sharp, repetitive spikes, preceded by a slight "pacemaker-like" increase in cytosolic calcium. These periodic increases in calcium concentration from 0.1 µmol to 1 µmol have been observed in response to the stimulation of hepatocytes with hormones (NA-noradrenalin, A-adrenalin, ADH-antidiuretic hormone etc.) and correspond to low cytosolic concentrations of IP3 (variant A in the graph). Depending on the type and concentration of membrane ligands, the period of oscillations varies from several tens of seconds to several minutes [12,16]. The general property of these oscillations is that their frequency increases proportionally to the level of stimulation exerted by ligands on the outer membrane, a phenomenon called "frequency-encoding" (the level of the external stimulus is "encoded" in the frequency of calcium oscillations).

b) In certain situations, ligand stimulation of receptors generates oscillations of cytosolic calcium concentration in the form of small and symmetrical fluctuations, against a background of an increased basal calcium level. These are called sinusoidal oscillations and are based on moderate IP3 concentrations (variant B in the graph) [12] (Figure 5).

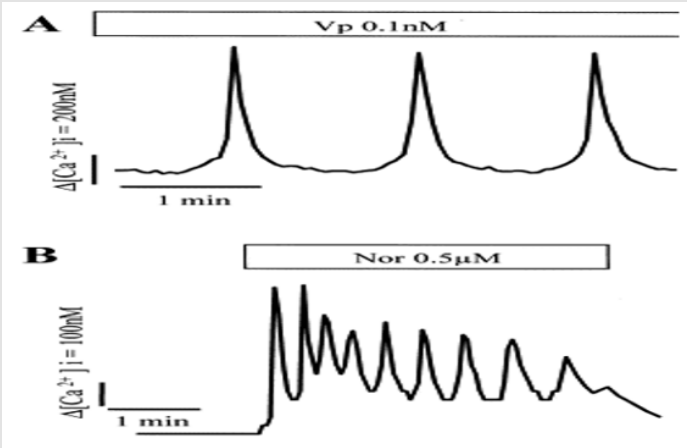

Figure 5: Calcium oscillations in an isolated hepatocyte [12].

Systematizing the experimental observations, it should be remembered that the particularities of cytosolic calcium oscillations in hepatocytes depend on:

- The level of external stimulation (through ligands);
- The cytosolic concentrations of IP3;
- The ligand type - generates a certain pattern of the downward slope;
- The level of extracellular calcium (i.e. the rate of calcium influx into the cell directly proportionally influences the frequency of oscillations);
- The level of calcium in the deposits controls the entry of calcium from outside the hepatocyte. A low level in the deposits stimulates the entry of extracellular calcium, a phenomenon called capacitative entry [12];
- Mitochondria modulate both calcium oscillations and waves [17]. The mitochondrial outer membrane is very tightly attached; it is contiguous with the endoplasmic reticulum. The influx of calcium into the mitochondrion is done through a pore (uniporter), and the efflux through the $Na+/Ca^{2+}$ exchanger (NCX) and through the mitochondrial transition pore, which is a high-conductance channel for calcium. This exchange is done according to mitochondrial biochemical needs (without calcium, the Krebs cycle cannot function, but with too much calcium, apoptosis is triggered). However, the concentrations of calcium that enter and leave the mitochondrion under normal conditions are very small, compared to the calcium supplied by the ER, so that they can only exert a modulatory role on the general cytosolic calcium level [12,17];
- CAMP and cGMP regulate IP3Rs activity by activating protein kinases that, in turn, phosphorylate IP3R.
- Over time, IP3R becomes desensitized to the action of an external ligand. This contributes to the mechanism of stopping oscillations, along with IP3Rs inhibition by elevated cytosolic calcium concentrations [17].

- Calcium Waves

1. They spread intracellularly and intercellularly.
2. Intracellular waves

Each cell is an inhomogeneous space. Although the ER is present in almost all cell types, IP3Rs channels are not uniformly distributed. IP3Rs are more abundant at the apical regions of hepatocytes, that is, in the vascular pole (toward the sinusoids), and this arrangement is the result of membrane lipid rafts action. The number of simultaneously open IP3Rs is less than 100, although the average diameter of a hepatocyte is around 20 μ [18].

The coherent behavior of the cell in calcium signaling is generated by the fact that both IP3 and Ca^{2+} diffuse into the cytoplasm starting from the apical region, which allows each calcium oscillation to propagate like a wave through the cell. This behavior was observed in the case of hepatocyte stimulation through GPCRs, but also through tyrosine kinase receptors (TRK), cytokine (CKR) or toll receptors (TLR) [12,19]. When the width of the calcium wave front is approximately equal to the hepatocyte dimensions (20 μ), the wave has the appearance of a tide traveling at 20 μ/sec. This rate does not depend on the ligands concentration [12]. We have stated above that calcium waves are generated by the intracellular diffusion of IP3 and calcium. Which of these two factors takes precedence for wave propagation? The answer has been provided experimentally: a non-metabolizable analog of IP3 was introduced into hepatocytes, and yet calcium waves were produced. It means that it is calcium (and not IP3) that has the main role in the wave propagation [12,20].

Inter Hepatocytes Calcium Waves

The study of communication between hepatocytes has confirmed the presence of calcium waves at the intercellular level as well [11,12]. Throughout the normal liver there is the same coordination and organization of waves as within hepatocytes, confirming the integration of the wave response at the organ level [21]. From a biochemical point of view, the explanation lies in the diffusion of calcium and intracellular mediators (including IP3) through gap junctions. Each gap junction contains two hemichannels, called connexons, one from each cell. Each connexon consists of six protein molecules, called connexins, arranged in such a way as to constitute a lumen through which small molecules of 1-1.5 kDa can pass [22,23]. Communication through these junctions is modulated by cytokines, growth factors and NO, so it can be easily altered by various forms of aggression or cellular stress (Figure 6). So far it has discussed in detail the generation of calcium oscillations and waves in the microdomains between the endoplasmic reticulum membrane and the outer mitochondrial membrane, and the control of these waves. The time has come to present how the nucleus can generate its own calcium waves, although it also receives waves generated in the cytoplasm. These nuclear waves are considered to "dictate" to DNA the information on which gene transcription is based [24-26]. How are calcium waves generated in the nucleus? It is known that, in addition to the endoplasmic reticulum, there is also a nuclear reticulum (nucleoplasmic reticulum, RN), whose membrane is continuous with the endoplasmic reticulum membrane and the nuclear membrane (Figure 7).

DOI: 10.26717/BJSTR.2025.63.009851

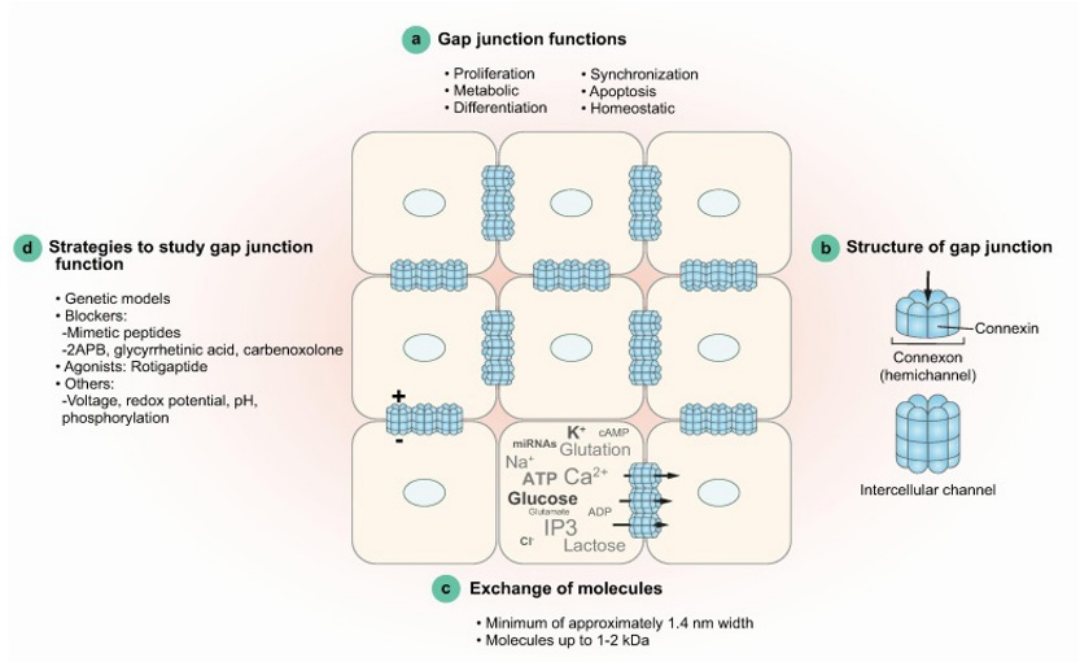

Figure 6: Gap junctions between hepatocytes [23].

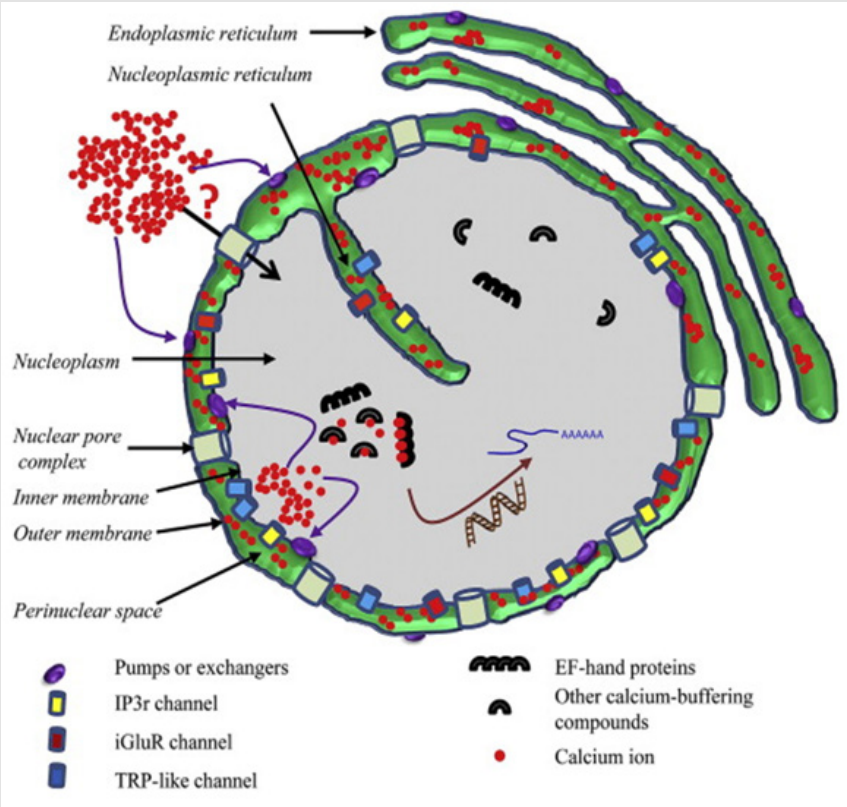

Figure 7: The nucleoplasmic reticulum and its contiguity with the endoplasmic reticulum [29].

Two forms are known: RN type 1, which consists of invaginations of the inner nuclear membrane, and RN type 2, which contains both the outer and inner nuclear membranes. The two types coexist in the same nucleus and are constantly remodeling [27]. This structure allows calcium to simultaneously regulate multiple and independent processes in the nucleus. The biological actions of nuclear calcium are known, but the mechanism by which Ca^{2+} is maintained at permanently elevated concentrations in the nucleoplasm is not entirely clear. Initially, it was thought to be a passive diffusion of cytosolic calcium across the nuclear membrane [28]. The nuclear membrane contains pores permeable to molecules up to 60 kDa. But the calcium ion has 40 Da!!! Such dimensions of the nuclear pores would allow a rapid equilibration of the calcium concentration between the nucleus and the cytosol [27,29]. Under certain conditions, for example in the stimulation of hepatocytes with antidiuretic hormone, ADH, this diffusion occurs, causing rapid calcium waves to appear in the nucleus. However, most of the time, a nucleo-cytoplasmic calcium concentration gradient is maintained, which means that pore permeability is controlled [27,29]. In the space between the two nuclear membranes, there is a high concentration of calcium. In fact, calcium enters this space through two pumps: SERCA, located in the outer membrane, and $Na+/Ca^{2+}$ exchanger (NCX), in the inner membrane. The removal of calcium from the nuclear membrane is done through IP3-sensitive channels (IP3R), present in both membranes [27,29]. Have you already read about this organization anywhere in this review? In addition, the nuclear membrane contains all the necessary equipment for IP3 synthesis (PIP2 and PLC). It has been shown that these channels release calcium from the nuclear membrane into the nucleoplasm [30]. Apart from the nuclear membrane, the RN is also involved in the spatiotemporal regulation of calcium-dependent events.

Arguments

- Both IP3R and RyR are present in the RN;
- SERCA is also present along the RN invaginations;
- IP3Kinase, which inactivates IP3 by phosphorylation, is present in the RN and plays a role in stopping calcium signals [30].

Conclusions

- The structural and functional organization of the nuclear reticulum is very similar to that of the endoplasmic reticulum;
- The nucleus has its own way of generating calcium signals, independent of the cytosolic ones.

The hepatocyte nucleus has very unexpected ways of responding to environmental stimuli. Thus, stimulation of tyrosine kinase receptors (RTK) on the outer membrane with growth factors (HGF, insulin), an essential phenomenon in regeneration, is followed by some known events and others, more difficult to predict:

- The RTK-generated stimulus involves cytosolic activation of the PIP2 cascade, followed by IP3 signaling and the appearance of cytosolic calcium waves that propagate throughout the cell. In addition, the calmodulin-transcription factor system is activated, with the subsequent entry of the latter into the nucleus. This pathway was known [30,31].
- !!! One of the RTKs are rapidly translocated from the outer membrane into the nucleus. [31,32] It is a relatively newly discovered phenomenon, unsuspected until now. "Plunge" receptors from the outer membrane into the nucleus? Are they the same receptors that the growth factors have fixed on? Are there some "unused" ones? It is not yet known.
- !!! MAPK family kinases are rapidly relocated from the cytosol to the nucleus, where they activate PLC, with the production of IP3 and intranuclear calcium release. Intranuclear calcium waves are generated, which activate various transcription factors at this level [30,24-26].
- !!! Nuclear calcium waves are very important for the liver cell to enter the cell cycle and for regeneration. Without them, the G1→S and G2→M transitions cannot be achieved. The same calcium waves work, much more intensely, in tumor cells [30,32].

What is Not Yet Known

- What does the genome "read"? Nuclear calcium waves or their interference with cytosolic calcium waves?
- How are these waves "decoded" by the genome, under normal conditions and how does it happen in pathology?

Calcium Oscillations and Waves in Liver Cirrhosis

The liver cell is poorly supplied with oxygen and nutrients, through multiple mechanisms:

- Sinusoids endothelium defenestration and the basal membrane emergence;
- In the normal liver, sinusoidal fenestrated capillaries control HCS, inducing their senescence. Defenestration greatly decreases the sinusoids ability to inhibit HSC activity and thus collagen production. This way, fibrosis disseminates between hepatocytes and sinusoids, further altering cellular exchanges [2,5,23];
- The vascular tone is increased in LC due to the decreased NO (the main vasodilator) synthesis in defenestrated endothelial cells → vasoconstriction amplifies hypoxia being an inflammation-inducing mechanism.

The liver cell reacts to hypoxia by decreasing the mitochondrial respiratory chain activity → decreases the ATP supply in the hepatocyte → decreases the SERCA activity → excessively increases the cytosolic calcium concentration. Oxygen-depleted mitochondria produce large amounts of ROSs, which initially stimulate calcium uptake into mitochondria, followed by its massive "shedding" into the cytosol [33]. All inflammatory cytokines and ROSs in the extracellular en-

vironment signalize inside hepatocytes through kinase cascades that phosphorylate IP3Rs, inducing calcium release from the ER. Extracellular vesicles originating from apoptotic or necrotic hepatocytes, HSC or Kupffer cells transfer to the "acceptor" hepatocytes modified DNA and RNA fragments. These further inhibit the synthesis and function of enzymes, including ATPases that control cytosolic calcium concentrations [8,9]. All the mentioned mechanisms converge towards the excessive accumulation of calcium in the hepatocyte cytosol, with a decrease in the frequency and velocity of calcium waves. Gap junctions are altered or destroyed by multiple phenomena in LC: fibrosis, the alternation between healthy hepatocytes and necrotic or apoptotic hepatocytes. In addition, certain types of gap junction connexins are predominantly synthesized in cirrhosis (e.g., Cxs 43) and enter the composition of extracellular vesicles, thereby stimulating CHS and fibrosis [9,21]. This alteration of gap junctions induces a decrease and disruption of calcium wave transmission throughout the organ.

Conclusion

1. Regardless of the extracellular ligand that transmits information by binding to a membrane receptor, the information is translated inside the hepatocyte into a new language: calcium oscillations and waves.

2. The frequency, velocity and shape of these oscillations are the ways in which the hepatocyte encodes the messages received from each type of external ligand.

3. Calcium oscillations and waves are also strongly influenced by intracellular activity, primarily by ROSs produced in mitochondria (details will be presented below).

4. Calcium waves propagate throughout the liver cell and by their characteristics influence the entire activity: calcium-dependent proteins (calmodulin, calcineurin), transcription factors, nuclear activity, the functioning of mitochondria, cytoskeleton, lysosomes, etc.

5. Calcium waves also propagate intercellularly, through the gap junctions, functionally uniting the entire organ.

6. In liver cirrhosis, the cytosolic calcium level increases excessively. Consequences: alteration of the calcium wave pattern and, in severe cases, hepatocytes apoptosis or necrosis.

7. The structural changes of the intercellular junctions and the pericellular space in cirrhosis also induce the alteration of the calcium waves intercellular transmission.

8. The same principle of converting external information into calcium oscillations and waves has also been identified in the other types of liver cells, as well as in many other cells types in the body.

Calcium…the Last Frontier?

Calcium oscillations and waves are doubled by H_2O_2 oscillations and waves

Calcium oscillations and waves have been talked about for at least 30 years. Their role is overwhelming, because they have "pushed" the understanding from the biochemical level to that of vibration and wave. In the myocardium, brain, liver, as well as in the kidneys, immune cells and, in fact, in all body structures. The principle of fractal functioning in biology, and especially the fractal nature of regulatory mechanisms, has been discussed for some time. This approach helps us understand that there is always a new frontier in knowledge. Calcium oscillations and waves represent only a deeper level of understanding that is, by no means, the ultimate one. They are controlled from an even more subtle level. During the calcium signals dissemination, microdomains with high calcium concentration are formed at the interface between the endoplasmic reticulum and the mitochondria [30] (Figure 8). They were initially described in the cardiac cell, but also exist in the hepatocyte. In these calcium microdomains there are nanodomains with H_2O_2 (ROS) [34]. Therefore, calcium and ROSs sources "come together" to cooperate functionally. However, ROSs are in much lower concentrations than calcium, on a different fractal scale. Here it is an experimentally demonstrated model of cooperation. The mitochondrion needs these calcium microdomains juxtaposed to its membrane to take up Ca^{2+} through the uniporter. Without this calcium, the Krebs cycle does not work [34,35]. During the ATP synthesis, the mitochondrial electron chain "leaks" electrons from complexes I/III, forming superoxide anion -2O. in the mitochondrial intermembrane space. This phenomenon is not accidental and neither does it represent any malfunction. These electrons are needed to induce the folding of the proteins synthesized at the mitochondrial level (electrons oxidize these proteins, an essential process for their folding). The superoxide anion is dismutated to H_2O_2, which in turn increases the permeability of the uniporter for calcium [36]. Therefore: calcium from the microdomains enters the mitochondria and stimulates the Krebs cycle → electrons are transported from the respiratory chain of cytochromes into the mitochondrial intermembrane space → the structure of some proteins is finalized and superoxide is formed → the superoxide anion undergoes a dismutation reaction into H_2O_2, which, in turn, increases the uniporter permeability for calcium. The mechanism also has a mechanical interpretation: Ca^{2+} enters the mitochondrion through uniporter ◊ this calcium entry attracts K+ locally ◊ both calcium and potassium rapidly increase the osmolarity at the entry site and attract H_2O_2 formed in the mitochondrial cristae ◊ the local volume increases rapidly and pushes the H_2O_2 content into the nanodomains at the ER-mitochondrion interface [34,36] (Figure 8). When H_2O_2 variations stop, calcium oscillations stop as well, throughout the hepatocyte [37,38].

How does it, happen?

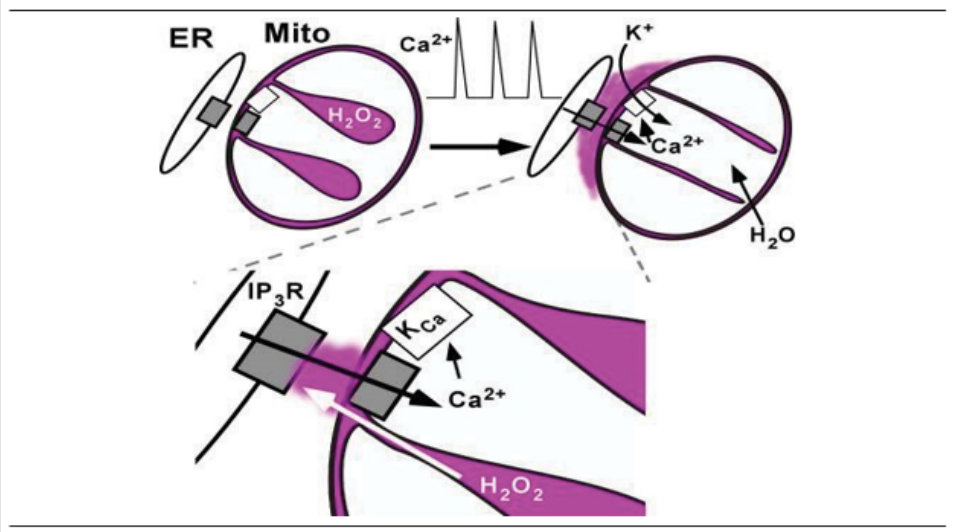

Figure 8: Mechanism of hydrogen peroxide elimination at the level of mitochondrial membrane [34].

Intra- and Intercellular Communication Through Quantum Mechanisms

Mitochondria communicate both with each other and with other organelles through nanotunnels, through which atoms and small molecules, including ATP, Ca^{2+} and other ions, ROSs, water, etc., circulate. These molecules dimensions and the nanotunnels lumen are so small that the phenomena can occur delocalized, in a quantum manner [39,40]. Calcium and H_2O_2 are well below 25 kDa, the maximum molecular weight for which dual wave-particle behavior was demonstrated in 2019 [41]. Thus, H_20_2 can propagate through quantum tunneling in these nanotunnels, making practically instantly coherent the activity of all mitochondria, but also of all other cellular sectors to which they are physically connected. We must not forget the dimensions of gap junctions that allow extremely fast passage of atoms and molecules up to 1-1.5 kDa. Isn't very fast functional synchronization possible, through tunneling and quantum entanglement, at this level as well? [42-44]. Phenomena occur at the dimensional scale to which the principles of quantum physics can be applied without fail. Coming back to calcium and hydrogen peroxide. So "someone", a much higher energy molecule, a reactive oxygen species formed in the mitochondria, "orchestrates" the undulating behavior of calcium. Even though it has a much lower concentration. It is as if, regardless of the nature and significance of the membrane ligand message, the calcium wave must also bear the imprint of the "energy citadel". This imprint is also undulatory: increases and decreases in the H_2O_2 concentration. Let's try to decipher the message of the hydrogen peroxide molecule even more deeply: in fact, through the oxygen in its composition, it contains the initial information, coming both from the oxygen in the inhaled air (also, very probable, transported through a quantum mechanism at the level of the alveolar-capillary membrane), as well as from food. We can now reconfigure the conclusion regardless of the nature and significance of the membrane ligand's message, the calcium wave must necessarily bear both the imprint of the "energy citadel" (mithocondrion) and the imprints of "heaven and earth" (atmospheric air and food).

On the other hand, reactive oxygen species "reveal" unexpected functional valences. Some molecules that we knew only generated tissue damage and defended us from pathogens control the fundamental processes of the cell??? Current knowledge clearly differentiates free, destructive ROSs from molecular-ionic, signaling forms of ROSs (low concentrations of superoxide anion and H_2O_2). ROSs are destructive only in high concentrations and/or in free radical forms [33,34,36]. For decades, it has been believed that the only source of energy in the cell is ATP, and the production of ATP in mitochondria is strictly based on chemical energy transformation. The classical, unanimously accepted understanding is that ROSs are produced in mitochondria, as manifestations of dysfunctions in normal electron conjugation, and that they must be neutralized by antioxidants, such as catalases, SOD, peroxidases, etc. The latest research shatters this dogma, proving that variations in the ROSs concentration, through the oscillations and waves created in the cell, are vital for the metabolism functioning, and the increase in their cytosolic concentration precedes fundamental processes: maturation, cell division, aging, apoptosis [45,46]. Another essential aspect proven very recently was the intercellular rapid propagation of H_2O_2 waves [47]. The following question arises: How can some oscillations, some waves of H_2O_2 control cell division, for example? I recommend you an exceptional video that introduces us to cymatics. It is a must-watch because it suggests the answer: https://www.youtube.com/watch?v=GtiSCBXbHAg

We can observe how sound waves "dictate" the symmetrical spatial organization of the sand powder. The only difference is that in the video there are sound waves, the experiment being much simpler to perform this way than with electromagnetic waves. But the similarity is perfect. Moreover, the possibility of interconversion between mechanical (sound) and electromagnetic waves has long been known [48-50].

Do Such Phenomena Occur During Normal Liver Regeneration?

How Would the Wave Patterns be Altered in Liver Cirrhosis?

If the discovery of calcium waves and oscillations leaves behind the exclusivity of the material, biochemical, explanation for the understanding of the Livingness, the discovery of the fundamental role of ROSs in all cellular regulation mechanisms leaves behind another frontier: that of identifying the trigger mechanism for the development of metabolic processes. This mechanism is not carried out by reactive oxygen species, *per se*. They are just electron receptors, structures that contain electrons from the environment, which our body takes from oxygen anions in the air, water, and food. To them are added electrons from terrestrial electromagnetic radiation. Modern biology claims that respiration, digestion, liver processing are nothing but forms of repetitive conversion of electrons from the environment into electrons generated in the Krebs cycle and the respiratory chain and that, in fact, the trigger element for cellular metabolism is the entry of these electrons, of these particle-waves, into the body [51-53]. It's as if external oxygen creates a "mirroring", a "signature" inside the body, through another form of oxygen, reactive oxygen species. Or, better said, we live by the constant conversion of high-energy electrons. That is, the conversion of particle-waves

Biological Electromagnetic Waves…the Last Frontier?

The Biological Spinor/Torsion Fields

As previously presented, neither calcium and its waves, nor even the electronic waves of our metabolism, represent the final frontier. For several years, we have already experienced the possibility of experimentally stimulating cells and cellular components with laser beams, that is, stimulation with coherent electromagnetic beams [54,55]. It can be done so precisely that cytosolic or nuclear calcium discharges induced by these waves can be made punctual, identical to discharges through IP3R. Certain gene regions can also be stimulated with precision [54,55]. These technological possibilities have generated a new science, called optogenetics [56]. But it must not be forgotten! For two structures, a transmitter and a receiver, to exchange information, they must use the same "language". If a particular cell or intracellular region responds to a laser beam, it means that that cell or intracellular region itself emits electromagnetic radiation. Why not laser? If calcium waves can be stimulated by the electromagnetic laser beam, as has been easily achieved, it means that "behind the calcium wave" there is also an electromagnetic undulatory phenomenon hidden. If a fragment of the genome stimulated with a laser beam responds by transcription, it means that also the genome has its proper electromagnetic emission. So are we somehow, at the end of the fractal progression of biological events in our body, wave structures? The emission of bioelectromagnetic fields has been experimentally proven for a long time, and an indirect proof of their existence is the effect on cellular biochemical reactions exerted by applied external electromagnetic fields. This is also how radiological procedures (X-ray and CT scans) are explained. If living structures did not emit such fields, they could not interact with external ones [57]. The emission of acoustic (mechanical) waves by living molecules and structures has also been confirmed, which explains their possibility of interaction with external acoustic waves, especially ultrasound [58]. If our structures did not permanently emit electric and magnetic fields, ECG, EEG and nuclear magnetic resonance procedures would not be possible. Another form of field proven to interact with living structures is the spinor field (according to Western nomenclature), also named torsion field (according to Russian scientific nomenclature). In Russia, torsion fields have been intensively studied since the 1960s. Applying the same reasoning as for electric, magnetic, electromagnetic and acoustic fields, it is clear that living structures also emit a torsion field, characterized by spin angular momentum and the vacuum polarization effect [59-62].

What is the Spinor/Torsion Field?

The electric charge and gravitational field of all rotating objects generate a torsion field. So, from galaxies and planets in motion, to electrically charged subatomic particles that spin, a torsion field is emitted [61-64].

If we try to describe the presence of torsion fields at the biological level, we must refer to small-sized structures. Every elementary particle, starting with electrons, exhibits spin, that is a rotational movement around its own axis which generates a torsion field. Depending on the orientation of the rotational motion, the spin can be right-handed or left-handed. The intensity of the torsion field emitted by a molecule is given by the superposition of each nuclear and atomic torsion field in its composition [64,65]. So, each molecule type has a different torsion field!! For a very long time, the torsion field was considered a mere theoretical subject or a pseudoscience. The explanation was given by the fact that torsion field interactions were calculated to have a force 30 orders of magnitude smaller than the gravitational force. Later, physicists realized that this aspect was only valid for static torsion fields. They also found the presence of dynamic torsion fields, which have completely different properties. These fields propagate through space-time as a rotational wave. The cumulative properties of torsion fields deserve special attention [65]:

1. All substances have their own non-zero torsion field. The characteristics of this field depend on the chemical composition and spatial structure of the molecules or the crystal lattice of the substances.

2. Torsion fields of the same sign attract, and those of opposite sign repel. This behavior is completely opposite to that of electric charges generating electromagnetic fields.

3. The torsion field of an object is generated by classical spin, so when an external torsion field impacts an object, it will only interact with the object's torsion field, which will be modified.

4. Torsion fields traverse physical media without interaction with them, i.e. without loss and without being shielded. Thus, the absence of loss allows communication between torsion fields over very long distances.

5. The estimated speed of torsion fields is 109 times the speed of light, so their transmission is instantaneous even between galaxies.

6. Torsion fields have information and memory. This property can be understood as follows: a certain torsion field, with a certain spatial structure and frequency, polarizes the Physical Vacuum in a certain way. When the source of the torsion field is removed, the induced change in the Physical Vacuum is preserved.

From the above, it follows that physics has confirmed that any electric charge that spins and moves in space generates both an electromagnetic field (energy field) and a torsion field (informational). Simply put, any electromagnetic field associates a torsion field [66-70]. So, although propagated at a speed close to the speed of light in vacuum, the electromagnetic field permanently generated during cellular activity has only energy, while the associated torsion field is purely informational. This is not semantic or IT information, but a biological one [71-73]. Let's return to the liver and try to approach the phenomena through the prism of torsion fields. The microscopic observing of hepatocyte regeneration after different types of aggression has led to a surprising conclusion: regeneration mechanisms differ depending on the type of aggression.

a) In an acute aggression (partial surgical resection), the remaining intact liver regenerates very quickly (7-10 days), through the multiplication and hypertrophy of pre-existing hepatocytes, lacking inflammation and apoptosis [74]. The condition for regeneration to occur is the remanence of at least 25% of the initial liver volume. Sinusoidal endothelial cells (SECs) have a fundamental role in the regeneration of hepatocytes, through the discharge of HGF (hepatocyte growth factor). In fact, it is an information exchange between hepatocytes and SECs: outstanding hepatocytes release VEGF (vascular endothelial growth factor) and angiopoietin → stimulation of SECs regeneration → outstanding SECs and newly emerged SECs release HGF, which stimulates hepatocytes to enter mitosis [74].

b) In prolonged aggressions, there is an exaggerated and aberrant activation of SECs, which directs the liver response towards fibrosis. Moreover, a substantial increase in liver stem cells, also called oval cells, has been shown [75]. The origin of these cells is still much debated. Initially, it was believed that they originated in the hematogenous marrow, a hypothesis that has been disproven. Currently, it is believed that, under conditions of aggression, hepatocytes can "return" to the blastic, stem form, under the influence of SECs and Kupffer macrophages [75].

Why does the liver regenerate normally in acute conditions even if only 25% of it remains, and in prolonged aggressions, fibrosis degenerates into cirrhosis, and the liver's architecture no longer resembles normal? From the above listing of the torsion fields properties discovered by physicists, we saw that these are not only informational fields, but also have memory. Is it possible that when the liver regenerates normally, even after 75% of it is surgically excised, the arrangement of the new cellularity is done by "reading" the structuring information contained in the torsion field memory? Does the remaining fragment of 25% of the initial liver mass emit sufficient torsion field to allow access to this structuring information? Does prolonged infectious or toxic aggression somehow interrupt the ability to access information and memory of the normal torsion field? Does the torsion field of the pathogen or toxic compound cancel the ability to access the memory of the torsion field specific to a normal liver? Is the torsion field emission of the oval cells also added? These are hypothetical questions at the moment.

But let's address indubitable experimental arguments. In 2020, a study was conducted on the influence of torsion fields on mouse kidney cell cultures [76]. The results proved that mitochondria are clearly functionally influenced by applied torsion fields. In addition, cell metabolism, defense and stress resistance were significantly enhanced after short-term exposure to torsion fields. Another study was conducted on Arabidopsis thaliana seeds exposed to right and left torsion fields for varying periods of time [77]. Seeds exposed to both left and right torsion fields showed increased germination energy compared to unexposed seeds. The improvement in germination ranged from 29% to 55% depending on the exposure time. A recent study has proven the magneto-mechanical destruction of cancer-associated fibroblasts using ultra-small iron oxide nanoparticles and low frequency rotating magnetic fields [78]. Based on what was discussed above it is clear that low frequency rotating magnetic fields generate torsion fields. Moving back to the level of the Universe and galaxies, the torsion field is increasingly considered by physicists as a possible explanation for the existence of Dark Matter and Dark Energy [79-82]. Given that the physics of the Universe and galaxies gives such importance to the torsion field, is it possible that in biology it is just a meaningless notion, easily thrown into the trash can of pseudoscience [83]?

Conclusions

Let's try to go back in the human body. A ligand, that is an extracellular molecule, attaches to a cell membrane, on a structure called receptor, which is another molecule or a molecular assembly. The extracellular ligand's message is translated into the cell in calcium oscillations and waves, which reach the nucleus, but also unify all

cellular compartments, as well as several cells, even an entire organ. At a deeper fractal level, calcium oscillations and waves are doubled by oscillations and waves of reactive oxygen species (hydrogen peroxide), which necessarily implies the participation of mitochondria. What is the mitochondrion? Besides the fundamental aspect of being the energy citadel of the cell, it is also the place where oxygen from atmospheric air and brought by erythrocytes joins with oxygen coming from the Earth, through food. Some of this oxygen will be found in reactive oxygen species. At a deeper fractal level than the previous one, "behind" the reactive oxygen species, lie the electrons. Both calcium, reactive oxygen species, and electrons have quantum, particle-wave behavior. "Behind" all these events are the fields: electric, magnetic, electromagnetic, mechanical (sound) and, uniting them all, the informational torsion field. These communication modalities are characterized by a certain "behavioral" pattern under normal conditions and another in pathology. There is no research conducted on the emission of torsion fields in the normal liver, let alone in the cirrhotic one. There are very few works that present the deep connections between the biochemical (material) and biophysical (subtle, through fields) levels that coexist in any living organism. This is one of them. But the approach of this work constitutes only a first step towards a deeper understanding of normal and pathological Life...

Data Availability Statement

We consent to data sharing in a publicly accessible repository.

Conflicts of Interest

The author declares no conflicts of interest.

Funding Statement

This research received no external funding.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.63.009851

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