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Oncogenesis, lipids rafts and liquid crystals: A nanoscopic supplementary field for applied researches and a new hope of advances in cancer

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Abstract

Liquid crystals (LC) are an intermediate state between an ordered crystalline solid and a more disordered liquid. LCs (or mesophases) are ubiquitous in living systems, optimizing multiple biological functions that could not operate in purely solid or liquid environments as both mobility and organization are needed. One of us recently suggested that there is an information vector, shared by neurodegenerative and infectious pathologies, to be found within lipid rafts in an ordered liquid (Lo) form mediated by cholesterol. Here we extend this underlying mechanism to oncogenic processes. The specificity of our approach lies in highlighting the direct involvement of liquid crystals in early carcinogenic processes, by identifying specific metabolic pathways, with the intention of focusing research effort on this level, now that this has become technically feasible. Exploring LCs in living bodies reveals links between numerous oncogenic mechanisms. The approach is based on the geometric properties of amphiphilic (hydrophilic and lipophilic) plasma and intracellular membranes, the phospholipids of which are an example of the lamellar LC phase. These LCs underlie cell signaling and signaling pathways disorders at

membrane level: consequently, they are directly concerned with deregulation underlying many cancerous processes.

We demonstrate the implication of cancer cell membranes mesophases. That is in the membranes mesophases that are initiated most of metabolic pathways, leading to downstream pathogenic intracellular mechanisms. The concepts of order and of symmetry, in the mathematical sense, involved in condensed matter accompany informed adaptive supramolecular chemical processes in forming self-organizing mesogenic molecular assemblies. Multidisciplinary teamwork combining knowledge from different fields holds out the hope of therapeutic progress upstream of irreversible cancerous processes, while conserving the physiological integrity of the cells themselves.

Keywords: Structural biology, Pharmaceutical science, Biophysics, Cancer research, Lipid raft, Liquid crystal

1. Introduction

1.1. Background

The term “liquid crystal” (LC) (Figs. 1 and 2) dates from the early 20th century, but their structures and functions in living systems only began to be commonly exploited in the closing two decades, even though it was quickly shown, for example, that most ion channels comprise various kinds of LCs [1]. It is established that mesophases contain the chemical information transmitted from the intramolecular microscopic level, where covalent bonds are applied. Information is then transmitted at the

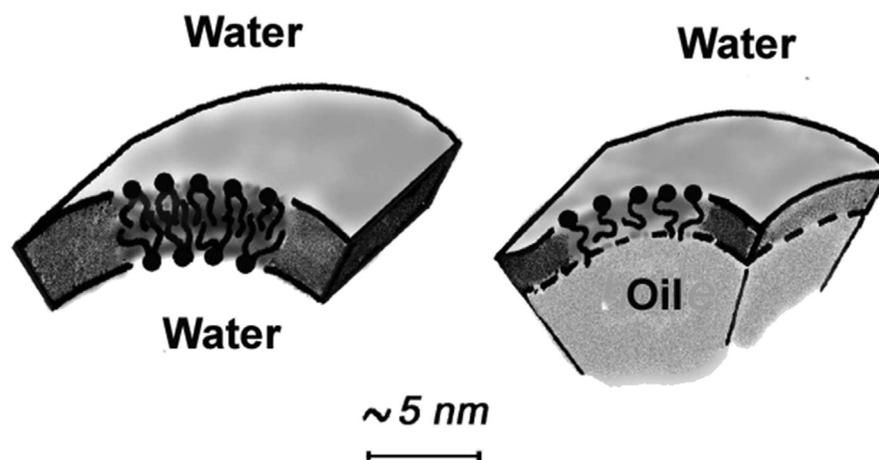


Fig. 1. *Left:* A liquid crystal film formed by a double layers of amphiphilic molecules (with polar heads and paraffinic tails) inside water. This is a very schematic approach of a cellular membrane. The film curvature is related to the ratio of the lateral area occupied by heads and tails. *Right:* A misceller cluster of oil whose surface is covered by a single layer of amphiphilic molecules with polar head outside, protecting oily medium from water.

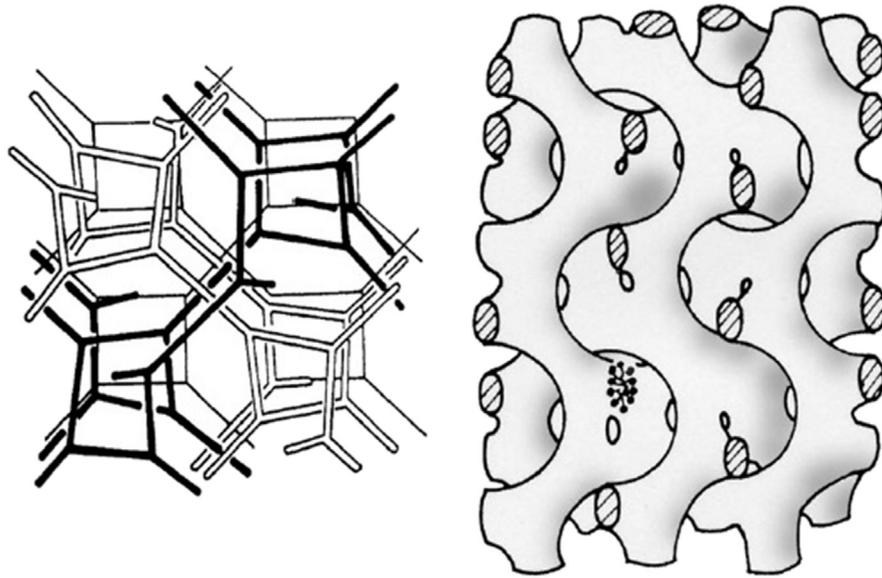


Fig. 2. Representation of a liquid crystal forming a "cubic phase". Amphiphilic molecules schematized by their polar heads and their parafinic tails form rods (right) which are organized as a connected network (left) surrounded by water.

intermolecular macroscopic level, where it is made up of informed, self-organized collections. Electrostatic interactions, coordination of metallic ions, van der Waals forces and donor–acceptor interactions of hydrogen bonding all come into play.

1.2. Theory

One of us put forward the idea of an information vector common to neurodegenerative and infectious diseases comprising membrane LCs in an ordered liquid (or "Lo") phase, mediated by cholesterol in lipid rafts. This hypothesis has been recently demonstrated, and is presently considered as a theory [2].

1.3. Hypothesis

As the mesomorphic LC state is ubiquitous in living systems [3], it may also constitute an information vector able to explore early oncogenic mechanisms. The specificity of our approach lies in highlighting the direct involvement of LCs in early carcinogenic processes, by identifying specific metabolic pathways, with the intention of focusing research effort on this level, now that this has become technically feasible. It is within plasmic and intracellular membranes that the multiple dysregulations leading to oncogenesis are initiated, and membrane amphiphilic phospholipid bilayers are in a lamellar LC phase [4]. Any geometric changes in these LCs can impact intracellular signaling pathways. Mesophase involvement in membrane

structure impairment and its functional consequences can induce early oncogenic processes.

Presented here is the hypothesis that it is possible to extend our above theory to cancerous phenomena. We show the importance of mesophases modifications in disturbing membrane organization, and the functional consequences, leading to premature oncogenic processes. LCs are implicated in many cases of deregulation underlying numerous cancerous diseases. New therapies, targeting mesogenic molecular assemblies, could protect physiological status, while acting on pathological processes upstream of traditional targets.

Might there be room for novel therapeutic approaches in the nanoscale areas where life perhaps begins ?

2. Material

The studied hypothesis is supported by detailed review of many publications on the physics of condensed matter [5, 6], cellular biology [7, 8] and clinical oncology [9, 10]. It emerges that certain properties commonly found in cancer cells concern underlying interconnected metabolic pathways related to membrane mesophases.

3. Methods

Our approach consists in demonstrating LCs involvement in interactions which, when deregulated, lead to oncogenic processes. These mechanisms initiate in plasma and intracellular membrane lipid rafts [11, 12].

We therefore propose:

- 1 **to highlight increased de-novo lipogenesis within cancer cells**, accompanied by increased absorption and consumption of glucose, and by active deregulation of cellular signaling, which inhibits apoptosis and induces angiogenesis, etc [13].
- 2 **and to relate 4 metabolic pathways**: Phosphoinositides, Phosphatidylinositol 3 Kinase (PI3K)/Protein Kinase B (Akt)/Mammalian Target of Rapamycin (mTOR), [11, 14, 15, 16], Sterol Regulatory Element-Binding Protein (SREBP), Cleavage Activated Protein (SCAP), Insulin induced Gene (INSIG), Hydroxymethyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) [17, 18, 19, 20, 21], and Rat sarcoma/Mitogen Activated Protein Kinase (RAS)/MAPK [22, 23] pathways.

Thus, we will show that these interactions are initiated in lipid rafts within plasma and intracellular membranes, and will trace these properties as far upstream of pathological manifestations as possible.

4. Results

4.1. Properties frequently observed in cancer cells

4.1.1. Fatty acid imbalance induces aggressive de-novo lipogenesis in lipid raft mesophases

Aggressive de-novo lipogenesis originating in endoplasmic reticulum (ER) lipid rafts is accompanied by imbalance between long-chain saturated fatty acids and shorter-chain non-saturated fatty acids, leading to lipotoxicity [20, 24]. It is cholesterol [2, 10, 25] that organizes membrane lipid distribution and phase separation, leading to the “Lo state” constituting lipid rafts. The association of cholesterol and saturated fatty acid chain lipids determines the conditions for localized Lo state formation [10]. The combination of glycosphingolipids with long aliphatic chains by multivalent ligands, in the presence of cholesterol, can cause membrane domain nucleation.

It is noteworthy that, in animal cells, cholesterol synthesis and regulation takes place entirely within the membranes.

4.1.2. SCAP-N glycolyzation is initiated by Epidermal Growth Factor Receptors (EGFRs) in the sER membrane

Increased glucose absorption generates the energy needed for lipid metabolism in the transformed cell. Within the ER membrane, EGFR [26] signaling, via promotion of glucose absorption, increases SCAP N-glycolysation¹⁷ involved in the tumoral process. Incidentally, one may remark that EGFRs are also used by many oncogenic viruses, such as human papillomavirus (HPV) [15] and other pathogens.

4.1.3. Lipid raft mesophase integrity is a prerequisite for normal signaling

Since the discovery of oncogenes and tumor-suppressor genes and thanks to the development of molecular biology, cancer is increasingly seen as a pathology of signaling [9, 26, 27, 28]. Signaling is initiated within the plasma membrane. The role of lipid rafts as a cellular signaling platform is well established. Moreover, lipid rafts are able to reprogram energy metabolism, leading to immune system escape processes. They have the essential property of selecting and gathering lipids for the purposes of a specific action.

We consider membrane mesophase integrity, including lipid raft Lo domains, to be a prerequisite for signal processing leading to the cascade of cellular and feedback reactions. Impairment of a pre-existing mesophase, or onset of a pathologic mesophase, can trigger or amplify well-known tumor-cell mechanisms, such as independence

between proliferation and anchoring signals, loss of contact inhibition, inhibition of apoptosis, induction of angiogenesis [13] and invasive potential.

4.2. Metabolic pathways are initiated in the mesophases of the membranes: their dysfunction can lead to oncogenic processes

As example, we describe these properties in four important metabolic pathways.

4.2.1. Phosphoinositides metabolism takes place within membrane nanodomains

The phosphoinositide pathway [14] notably coordinates intracellular signaling, cytoskeletal assembly, cellular polarity, ion channel control, vesicular trafficking, etc. Phosphoinositides are synthesized and degraded in nanoscale membrane domains. Phosphatidylinositol is a lipid synthesized in the ER, and particularly in plasma membranes associated with mitochondria. Phosphatidylinositol-4,5-bisphosphate (PIP₂) and Phosphatidylinositol-3,4,5-triphosphate (PIP₃) are mainly localized in the cell membrane, resulting from phosphorylation of PIP₂, binds to effector proteins via its Pleckstrin Homology domain (PH). Inositol phosphates (IP)s convert one to another under kinases and phosphatases [11, 12, 13, 14] induce synthesis and hydrolysis. IPs are able to organize cell dynamics spatiotemporally by forming protein complexes: relocation and reorganization of IP kinases and phosphatases rapidly and transiently generate membrane territories.

That is in the membranes mesophases that are initiated most of metabolic pathways: it is the starting point for our argument [10]

Our interpretation is in terms of formation of a lipid raft with mesomorphic organization resulting from the interaction between selected and locally assembled lipids and proteins. This state of affairs can emerge from non-mesogenic components subject to ordering, and hence disordering, governed by properties of symmetry in the mathematical sense. At this level, geometric factors govern supramolecular chemistry, giving rise to cellular functions and bearing information, notably adaptive self-organization information [29, 30, 31, 32].

This can be illustrated by a well-known experimental example of Human immunodeficiency virus (HIV-1) infection [33, 34] in the plasma membrane:

4.2.2. HIV-1 infection generates nanodomains on both sides of the plasma membrane

Self-assembly of the HIV-1 Gag polyprotein generates PIP₂/cholesterol nanoclusters; the gag polyprotein also binds to the PIP₃ membrane. Gag binding to membrane IPs locally reorganizes lipids, generating nanodomains on both sides of the

membrane, most probably involving curvature phenomena. Moreover, coordination between PIP2 and cortical actin is necessary for HIV-1 entry, leading to dynamic reorganization of the actin cytoskeleton governed by PIP2.

This mechanism concerning HIV may shed light on other interactions between proteins and membrane lipids liable to generate nanodomains relevant to oncology. The following example refers once again to the properties described in the previous paragraphs.

4.3. Activated PI3K generates PIP2 and PIP3 in the membrane

The PI3K/Akt/mTor pathway [11, 26, 27, 32, 33, 34, 35] is an intracellular signaling pathway initiated at the membrane, which is frequently activated in case of cancer. It is involved in cell growth and proliferation, angiogenesis, apoptosis and carbohydrate metabolism. A breakdown in the balance between cell survival and death leads to aggressive tumorigenesis and uncontrolled proliferation. Notably, PI3K/Akt/mTor pathway activation usually involves a tyrosine-kinase receptor, most often on the membrane, which is stimulated by upstream membrane factors. There are several proto-oncogenic tyrosine-kinase receptors, such as Epidermal Growth Factor Receptor (EGFR), in Human Epidermal Receptor (HER) family.

We think that mesophase formation may be involved in the following example, which may be assimilated to the previous case of HIV-1 and phosphoinositides: 1)- Activated PI3K stimulates membrane phospholipid inositol phosphorylation at position 3' of the inositol cycle and generates PIP2 and PIP3 membrane lipids; they are dephosphorylated by Phosphatase, tensin homolog deleted on chromosome ten (PTEN).; 2)-PIP3 activation generates a signal recruiting Akt at the cell membrane.; 3)-Akt binds to PIP3, and changes conformation, enabling activation, notably by 3-Phosphoinositide-Dependent Kinase-1 (PDK1). Thus raft integrity has to be taken into account: many possible dysfunctions can implicate its constituent LCs. Activated Akt is released in the cytosol, where it promotes cell survival by inhibiting pro-apoptotic proteins and/or transcription of their coding genes.

Besides these four examples, other independent Akt pathways have also been identified.

4.3.1. Lipid raft involvement in cell invasion by oncogenic viruses, such as HPV

Recent studies showed lipid raft involvement in cell invasion by oncogenic viruses such as HPV (benign papilloma, and tonsillar, tongue-base or cervical cancer). HPV activates the PI3K-kinase pathway [16]. It further activates PI3K, modulating the immune system [36] and limiting membrane inflammatory response. It has also been shown that the binding of a virus to its membrane receptor within the lipid raft

not only constitutes an entry point but also activates cellular signaling pathways promoting the viral infection. The PI3K/Akt/mTor pathway plays an essential role in the oncogenic viral cycle, from entry to protein synthesis transcription, apoptosis inhibition and oncogenic transformation. Further recent studies of Epstein Barr virus [37] also suggest primary membrane-related mechanisms, but which remain to be explored.

Membrane nanodomains seem to be the preferred pathway for many viruses. In our view, the rapid and transient nature of the development of these formations limits observation, leading to their being overlooked, despite an increasing number of studies of the involvement of lipid rafts, composed of LCs, in pathophysiology. Membrane proteins interact via their individual conformation. However, the order of these interactions may be overturned by a *collective* order emerging in membrane *clusters*: consequently, that can change the hierarchy of the instructions.

4.4. The SREBP, SCAP, INSIG, HMG-CoA reductase pathway depends on the ordered liquid state of the lipid rafts

This pathway is entirely dependent on Lo membrane nanodomains, initiating multiple downstream intracellular pathways [2, 17, 20, 21, 25, 38]. The LC structure of the lipid raft determines the multiple interactions within the pathway and their connections with the other pathways referred to above. All the regulation proteins are membrane proteins.

SREBPs regulate lipid homeostasis and glycogenesis and control fatty acid, triglyceride and cholesterol synthesis. Novel transcription targets have been identified, revealing the role of SREBP in cancer, type-2 diabetes, immunity, neuroprotection and autophagy. SREBP-1 is activated by the EGFR, PI3K/Akt signaling pathway. Unlike other Helice-boucle-Helice-l-Leucine Zipper (bHLH-LZ) family transcription factors, the newly synthesized SREBPs are inserted in reserve in the ER membrane as inactive precursors. Otherwise, glucose controls lipid metabolism, which is an important function in oncogenesis, relating EGFR signaling to glucose absorption and SCAP-SREBP complex activation. EGFR activation induces a response via phospholipid metabolism, by activating lipid-degrading membrane proteins, which in turn produce secondary messengers activating downstream signaling pathways. Besides, EGFR, for example, promotes SCAP N-glycosylation by increasing glucose absorption, thereby activating SREBP-1.

INSIG 1 and 2, which are also membrane proteins [39] essential to cholesterol concentration regulation, play an important role by inhibiting feedback from the final products (oxysterols and nanosterols) within cells and preventing toxic over-accumulation of cholesterol. INSIGs exert a dual function in cholesterol homeostasis, by interacting with SCAP and HMG-CoA reductase. INSIG 1 and 2 thus

influence cholesterol metabolism and homeostasis and lipogenesis in various tissues and are involved in numerous pathologies, and notably in oncogenic processes. Recent studies showed that INSIGs, and thus insulin, are pivotal to the metabolic pathways discussed here, influencing oncogenesis via the SREBP pathway.

Lipid rafts are thus platforms organizing the angiogenesis induced by Fibroblast Growth Factor₂ (FGF₂), which is also involved in glucose and cholesterol phosphate homeostasis. It is a glycoprotein, sequestered in the extracellular matrix; once released, it fixes to the cell surface, initiating a tri-complex with the Fibroblast Growth Factor Receptor (FGFR) membrane receptor, which notably activates Akt via PI3K. It has also been shown that Urokinase - type Plasminogen Activator Receptor (uPAR [40] or CD68) is a co-receptor for (FGFR₁), Vascular Endothelial Growth Factor Receptor (VEGFR₂) and EGFR. uPAR is a membrane glycoprotein attached to the cell membrane by a Glycosyl Phosphatidylinositol (GPI) anchor, and is abundant in lipid rafts. It is associated with various cellular signaling pathways, including PI3K/Akt, and regulates various tumor cell functions by forming membrane complexes with EGFR and integrins.

It is noteworthy that the structure of the ER membrane shows an LC state; via the structure-function relationship, this mesophase thus directly controls the above processes. The SREBP-SCAP-INSIG, HMG-CoA reductase pathway is an example of the link between an ER transmembrane regulatory protein and expression of genes involved in cholesterol synthesis and hydrolysis [2].

It is thus membrane LC status that needs exploring to diagnose early dysfunctions leading to oncogenic processes.

EGFR signaling, leading to the RAS/(MAPK) and PI3K/Akt pathways, is an example of membrane mesophase involvement in the interactions leading to cancerous processes, from the extracellular matrix to the nucleus.

4.5. RAS/MAPK pathway interactions are dependent on the plasma membrane

We remind that the membranous phospholipids constitute a LC state. The RAS/MAPK pathway [22, 23] is an intracellular signaling pathway notably involved in the regulation of proliferation, cell survival and angiogenesis, and is abnormally activated in many cancerous processes. The activated membrane receptors are usually tyrosine kinase proteins, themselves stimulated by various factors such as the growth factor EGFR. This is a transmembrane glycoprotein of the Human Epidermal Receptor (HER) family. The interactions resulting from these plasma and intracellular membrane-related processes trigger a cascade of phosphorylation of numerous intracytoplasmic proteins involved in signaling pathways that are disturbed in oncogenesis.

The proto-oncogene RAS family comprises 3 genes, with the corresponding proteins attached to the internal side of the plasma membrane by their C-terminal extremity, with activation triggered via membrane receptors, including EGFR, in the phospholipid layer, the lamellar phase of which is an example of LC state. MAPK (Extracellular-signal-Regulated Kinase ERK) pathway activation begins with RAS-mediated activation and membrane recruitment of RAF-1 protein, which activates MAPK kinase by phosphorylation. Then, in turn, this MAPK kinase governs translocation to the nucleus, by double phosphorylation of ERK. This leads to expression of early genes coding for transcription factors stimulating the expression of a large number of genes involved in RAS/MAPK and also PI3K/Akt signaling pathways (in association with other signaling pathways). It should be stressed that RAS proteins are small GTPases anchored in the plasma membrane by post-transduction covalent binding to the ER. It has been shown [23] that the oncogenic action of RAS depends on association with the inner face of the plasma membrane, notably involving the Cysteine, Aliphatic, amino-acid, X-terminal amino-acid (CAAX). Farnesyl transferase and methylation are involved, with negative charge neutralization, promoting interaction with the cell membrane. RAS has also been shown to be involved in macropinocytosis and endocytosis mechanisms in the plasma membrane, and especially in the lipid rafts, which are in Lo phase.

Furthermore, Duquesnes [26] showed that certain ligand precursors are located inside the extracellular matrix, providing extra regulation of metalloproteases, which are endopeptidases that degrade the matrix; thus interactions with the cytoskeleton, actin-myosin complexes and collagen need to be taken into account, with their respective mesomorphic phases, well documented in physics by J. Charvolin [29, 30], and also M. M. Giraud-Guille [41, 42]. Moreover, ligand binding to the receptor induces a change in conformation necessary for the formation of the active site of kinase domains: consequently, one may observe that some LC phase changes may underlie this essential step.

5. Discussion

What can systematic exploration of the LC phase tell us about pathophysiological phenomena? It broadens the field of investigation of many biological functions, to which it provides an underlying unity. LCs are omnipresent, determining the structure and hence the functions of the processes involved [43].

Although these processes differ according to the proteins concerned, the LC phase is a common underlying factor which, in our view, initiates and modulates pathophysiological events.

At the nanometric levels of lipid raft LCs, biological phenomena are observed far upstream of the cellular phenomena targeted by current therapies, the most advanced of which have in many cases transformed clinical practices in oncology. In general, this

progress has consisted in continuous improvement in means of observation and direct or indirect visualization of nano-level phenomena. The mesophases that we have discussed above, on the other hand, have been little explored in biological and medical research, despite being highlighted by physicists. However, the scientific community, and pharmacologists in particular, have for several decades [44, 45] been exploring mesophase properties for therapeutic purposes [46]. The mass of knowledge accumulated from this work [47, 48, 49] leads us to suggest opening up new lines of research focusing on mesophases involved in specifically carcinogenic processes. Collaboration with clinicians is necessary here, going beyond the usual multidisciplinary teamwork; but this in turn requires prior information regarding the concepts of soft matter, which are unfamiliar in current medical culture. The interest of our project lies in underlining the direct involvement of liquid crystals in early carcinogenic processes, by identifying specific metabolic pathways, with the intention of focusing research effort on this level: now, that has become technically feasible [12]. Yet it is within mesophases that most vital functions originate and/or dysfunction: one may think that LCs are implicated in deregulation underlying many cancerous processes. Because of their mechanical and architectural properties, the role of LCs in many of the phenomena of life is evident today to many young researchers. But why have these facts, known for decades, not yet led to practical, diagnostic or therapeutic applications? This may be for 2 reasons: 1)-because of the need for highly specialized teams in this field, they are often led by Physicist researchers, and are sometimes devoid of medical researchers, clinicians or biologists, capable of proposing medical applications taking advantage of these discoveries; 2)-but it is mainly because the observation of these phenomena of a few tens of nanometers has made enormous progress for a few years: until yesterday, to consider the medical utility of these LCs would have seemed quite utopian.

It is quite conceivable that focusing on them could open the way to progress that is at present unimaginable. However, at what steps of this waterfall of events would it be possible to act to prevent their progress, when they become pathological?

We have reported a series of studies [2], ready to be implemented that could launch this new line of research, and informed and adaptive chemistry [42] can now perform therapeutic experiments in animals. For results to come quickly, however, an interdisciplinary approach is needed to truly combine fields of knowledge, rather than simply juxtaposing them as is frequently the case [2].

Of course, this multidisciplinary integration includes informed adaptive supramolecular chemistry and the thermodynamics of non-equilibrium systems, with help of the power of present-day mathematical modeling and information technology [41, 42].

A mesophase could, by virtue of its geometric and kinetic properties, give rise to a structural, and thus functional, state that would be thermodynamically liable to induce the observed dysfunctions. This effect could be direct, modifying the cascade of interactions from extracellular matrix to intracellular sites, or indirect, for example

disturbing proto-oncogenes coding for RAS and Rat Fibrosarcoma Virus (RAF) proteins. Signaling, transcription and gene expression may be disturbed by a thermodynamic phase induced by an existing mesophase or by a pathogenic process [2]. An example of this could be a mesomorphic state maintaining increased EGFR stability and expression by increasing the number of membrane receptors.

These considerations can be related to the dynamic supramolecular processes described by Jean-Marie Lehn (*see (1) chap 9.4.2*), which play a crucial role in LC formation and characteristics. A supermolecule comprising a receptor and a substrate is conditioned by its geometric properties (structure, conformation, thermodynamics, stability, enthalpy, entropy of formation) and kinetics (formation and dissociation speeds). Changes in form can affect substrate fixation, especially in amphiphilic complexes. Amphiphilic molecules are liable to self-organize into different periodic structures. Hydrophobic effects, for example, alter the shape of the receptor. Physics, chemistry and biology meet at the metabolic crossroads of lipid rafts, the functions of which are determined by their mesomorphic state.

It is important to understand the organization of atomic patterns, in terms of the interactions between their constituent parts, molecule and self-organized assemblies, frequently show contradictory effects. Molecular-level recognition processes may emerge at the macroscopic level by inducing a mesomorphic phase within a supermolecule, with emergent properties determined by the molecular information present in the components. Cooperative processes involve phase changes that amplify recognition processes from the micro-to the macroscopic level. In this context, geometry leads to informed adaptive chemistry and the self-assembly and self-organization of matter [29, 30]. Structural organizations observed in physics generally result from contradictory constraints, which are conceptualized as geometrical frustration [5]. Living systems are subject to these constraints, but simply they optimize choices to be functional. Observed important dysfunctions, for instance in oncology, could result of light variation in choice optimization.

Subtle future therapeutic possibilities could be involved at this level. For example, papilloma viruses are non-enveloped icosahedra. The capsid is formed of pentamers of the major structural protein L-1 and, to a variable extent, L-2. Non-infectious particles of this type of virus, formed of L-1 and L-2, are the basis of present-day vaccines. The study of their properties can be done using geometrical symmetry properties of discrete protein set. This is incompatible with crystalline periodicity, but can develop in other forms of matter, including quasi-crystals and LCs.

6. Conclusion

Physics highlights the fact that mesogenic biological molecules, usually associated with mesophases, are strongly organized by their hydrophilic and hydrophobic

properties. This amphiphilic character and the geometry of the molecules give rise to a wide range of cellular and intercellular structures, combining antagonistic effects. These optimize multiple biological functions that could not operate in purely solid or liquid environments, as both mobility and organization are needed. It is important to take into account that molecules can interact with each other individually, but mainly interact globally, for instance through hydrophilic and hydrophobic mechanisms strongly governed by geometry, leading to competition between ordering and disordering. The cell membrane is an example, related to the concept of order, and is itself defined by symmetries in the mathematical sense. Order is symmetry, for instance between the two phases of the HPV membrane, characterized by its thickness. The 2-dimensional membrane liquid comprising molecules diffusing in parallel to the surface shows planar symmetry between the two interfaces. The richness of LCs, however, derives from the deviations from perfection known to physicists as topologic defects. This leads to membrane curvature, invagination and other components such as proteins and cholesterol, and symmetry-breaking between the interior and exterior of the cell.

Beyond the membrane, we need to integrate the biological networks giving rise to a given function, exploring other LC cell structures such as multilayers, cubic phases and micelles [28], whether included or not in organelle configurations. The competition between order and disorder also plays an important role in extracellular material. It is to be hoped that ongoing reflections will promote teamwork with physicists specializing in condensed matter and soft matter: polymers, gels, colloids and LCs. Using LCs geometric information vectors in nanotechnologies and the possibilities of the modern chemistry, exploration of mesophases should rapidly lead to therapeutic progress.

Before to conclude, a last point must be underlined: our suggestions to explore the nanoscales of lipid rafts and LCs in a therapeutic aim is not in opposition to the future cancer research priorities and investment for cancer in the USA [50], but in complement and addition to this project: this new kind of explorations must not be only considered as fundamental researches, but as applied researches.

However, to achieve this upstream efforts needs to bridge classical approaches, with statistical physics [51, 52] in both its classical and quantum aspects. It is via these multiple structural and functional explorations that the full complexity of living matter is revealed.

Declarations

Author contribution statement

Christiane Binot: Conceived the hypothesis and performed its demonstration. She analyzed and interpreted the data, and wrote the paper.

Claude-Henri Chouard: Organized the whole manuscript. He analyzed and interpreted the data; he contributed reagents, materials, analysis tools or data. He wrote the paper.

Jean-François Sadoc: Have redact the parts involving Liquid Crystals. He contributed reagents, materials. He analyzed the data. He wrote the paper.

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The authors declare no conflict of interest.

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