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For the section: PROBLEMS AND PARADIGMS

METABOLIC REPROGRAMMING IS A HALLMARK OF METABOLISM ITSELF

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Abstract

The reprogramming of metabolism has been identified as one of the hallmarks of cancer. It is becoming more and more frequent to connect other diseases with metabolic reprogramming. This article aims to argue that metabolic reprogramming is not driven by disease but instead is the main hallmark of metabolism, based on its dynamic behaviour that allows it to continuously adapt to changes in the internal and external conditions.

Keywords: metabolism; metabolic reprogramming; hypoxia; cancer; ultradian rhythms; immunometabolism

1. Introduction

The renewed interest in metabolic aspects of oncology and the accumulation of data on the topic since the 1990s led Hanahan and Weinberg to propose "*deregulating cellular energetics*" as one of the "new" emerging hallmarks of cancer in the 2011 revised version of their classic review on the hallmarks of cancer.[1,2] Currently, this deregulation of cellular energetics is commonly termed *"metabolic reprogramming"* and is widely accepted to be a common feature of clinically relevant cancers. In contrast, if we focus our attention on what is known regarding metabolism, the flexibility or plasticity of metabolism emerges immediately as an intrinsic property of metabolism itself, allowing living beings to adapt continuously to ever-changing internal and environmental conditions. This simple but underestimated idea will be the core concept discussed in the present article. Starting with limitations in the most accepted definitions of metabolism, and following with an overview of the ups and downs of the interest in the scientific study of metabolism, this article argues in favor of the understanding of metabolism as a complex dynamic network. Furthermore, it reviews evidence clearly pointing to the fact that metabolic reprogramming of cancer is but a consequence of the intrinsic capacity of the metabolic network to rewire itself dynamically.

2. The Concept of Metabolism: More than just Intracellular Biochemistry

Classically, metabolism has been understood in the terms in which Hans Kornberg still defines it today in the corresponding entry of the Encyclopaedia Britannica (electronic version): *"the sum of the chemical reactions that take place within each cell of a living organism and that provide energy for vital processes and for synthesizing*

new organic material".[3] Explicitly, this definition excludes such fundamental physical processes as the absorption of light in photosynthesis and all processes (yes, metabolic ones) that occur across the plasma membrane, on the cell surface or in extracellular spaces. Moreover, it is disturbing, to say the least, that the author discriminates against biosynthetic processes as if they did not belong to a larger group of "vital processes". The Spanish version of Wikipedia defines metabolism as: *"the set of biochemical reactions and physicochemical processes that occur in a cell and in the organism"*.[4] This definition seems more accurate than the one provided by the English version of Wikipedia, which still restricts its definition to chemical transformations occurring exclusively within cells: *"Metabolism (from Greek: μεταβολή metabolē, "change") is the set of life-sustaining chemical transformations within the cells of organisms"*.[5] My experience of decades of teaching metabolism allowed me to introduce a more complete and integrative definition of metabolism in the late 1980s, long before this approach started to make inroads into biochemistry textbooks and then into the largest of the generic encyclopedias, Wikipedia. The definition I propose for the concept of "metabolism" is based on the consideration of life as an open thermodynamic system, according to which a living being is a thermodynamic system far from equilibrium and in continuous exchange of matter, energy and information with its environment. Metabolism should be considered the "engine" of life, providing the complex set of physicochemical processes that guarantee that adequate exchange of matter, energy and information with the environment (see Box 1: Metabolism, the engine of life). However, this might not be enough. At the end of this article, I will argue why I am increasingly convinced that metabolism is more than the engine of life.

3. The Metabolic Network: Far from a Still Photo with Simple Dots and Lines

Metabolism is now seen as a complex network, as illustrated by the iconic metabolic map originally edited by Gerhard Michal and currently maintained in electronic format and navigable by the company Roche.[6] The overview map of the global metabolic pathways provided by KEGG (Kyoto Encyclopedia of Genes and Genomes) Pathway database [7] (Figure 1) is an abstraction of metabolism built as a network in which each node represents a metabolite and the edge connecting two nodes represents the biochemical reaction allowing the transformation of the first metabolite in the second. In this figure the different colors highlight the modularity of metabolism, in which sugar lipid, amino acid, nucleotide and energy metabolism modules, among others, are tightly interconnected. A much-simplified version of this map is currently used by two of the most popular biochemistry textbooks in their respective introductory chapters to metabolism, its design and its regulation.[8,9]

Modern network theory has confirmed that the metabolic network is more robust and resistant to "targeted attacks" than so-called "scale-free" networks, and that this is due to the special topological structure of the metabolic network, which is at once hierarchical and modular (Figure 2).[10-13] In fact, Barabasi's group was the first to report that the metabolic networks of a number of different organisms are organized into numerous highly connected topologic modules and that these modules hierarchically combine into larger, although less cohesive, units. Furthermore, the same study revealed that the hierarchical and modular topology of *E. coli* metabolic network reflects the true functional organization of metabolism.[10] More recently, it has been found that this particular robustness of metabolic networks is the consequence of an evolutionary process that acquires and increases functional redundancy based on gene duplication and redundant reaction rewiring.[14] Furthermore, in complex biological communities

such as those present in microbiomes, it has recently been shown that metabolic network percolation quantifies how robustly a global metabolic network can produce a given set of metabolic products in different environments and during environmental change.[15]

Unlike the usual representation of metabolic networks such as those provided by KEGG in which there is only one class of nodes (metabolites) and only one class of edges (metabolic reactions), Mark Newman suggests that the most natural network representation of metabolism and metabolic processes is as bipartite networks. In all bipartite networks, there are two different classes of nodes and edges run only between nodes of different classes. For the case of bipartite metabolic networks, both classes of nodes are metabolites and metabolic reactions. Edges join each metabolite node to the reaction nodes in which it takes part.[13]

However, any of the multiple versions of the metabolic map available on the Internet represents a "still photo", far removed from an essential peculiarity of the metabolic network: its dynamic character, essential to understand the "plasticity" of the metabolism to adapt continuously to changes in external and internal conditions.

4. The Ups and Downs of the Interest in the Scientific Study of Metabolism

The 1920s and 30s marked the first "golden age" of metabolism studies, defining and characterizing the main pathways thanks to the work of an exceptional generation of biochemists including Embden, Meyerhof, Warburg, Krebs, Szent-Györgyi and Lipmann, among many others. Major pathways of primary metabolism, such as glycolysis, fatty acid beta-oxidation, the urea cycle and the tricarboxylic acid cycle, among others, were elucidated in this period. In the fifties and sixties, a second "golden

age" of metabolism ushered in studies on bioenergetics, notable contributors being Nobel laureates Calvin and Mitchell, but also Lehninger, Kennedy and Crane, among others. Components of the electron transport chain were investigated and described, coenzyme Q was discovered, photophosphorylation and the photosynthetic assimilation of inorganic carbon to produce new organic matter were described and the chemosmotic theory was proposed (and many years after its initial description by Peter Mitchell was accepted) as one of the main unifying principles of biology.[16]

However, with the advent of the scientific-technological revolution of recombinant DNA in the mid-seventies, the scene changed under a paradigmatically powerful "genocentric" approach to Biology, which prevailed until the end of the twentieth century. This quarter century was a bit like the "Dark Ages" for metabolic studies, which were "discredited" as "old-fashioned" and outside of the mainstream dictated by fashion. Everything changed, and the metabolism was again in the spotlight (and so on to this day) with the "rediscovery" of the Warburg effect by a new generation of scientists interested in metabolism using the most current tools and techniques of biochemistry and molecular biology, including "omic" approaches.

5. Metabolic Reprogramming in Cancer: Substrate Shifts and the Modulation of Metabolism by the Microenvironment

More than 90 years ago, Otto Warburg observed that a rat carcinoma produced large amounts of lactate even in the presence of oxygen, in apparent contradiction with the so-called Pasteur effect -the inhibition of glucose consumption in the presence of oxygen.[17] Furthermore, Warburg observed that the production of lactate by malignant tumours was higher than that by benign, less aggressive ones. The identification of this

aerobic glycolysis (later known as the *Warburg effect*), a feature common to multiple tumour cell types was but the beginning of our current knowledge of the peculiarities of tumour metabolism.[18] Almost thirty years after his seminal observation of aerobic glycolysis, Warburg also observed that cancer cells obtain similar amounts of energy by oxidative phosphorylation and by aerobic glycolysis, in spite of the fact that the ATP yield of the first process is 15-16 fold that of the second process.[18]

In the midst of the "Dark Ages" of metabolic studies, evidence was presented that glutamine can supply glucose as the main source of energy in certain types of tumour cells, as is the case in HeLa cells.[19] Subsequently, it was demonstrated that elevated glutaminolysis is also a characteristic metabolic behaviour of many tumour cells.[20,21] A process of investigation into the interrelationships between glucose and glutamine metabolism in cancer was started, and finally concluded that the preferential use of glucose or glutamine as metabolic substrate depends on the specific context of a tumour cell.[21-25]

As stated above, the "rediscovery" of the Warburg effect at the dawn of the new millennium has proved to be a determining factor for the renewed interest in tumour metabolism that we witness today.[26-28] For those of us who studied tumour metabolism in the 1980s and early 1990s against all odds at the height of the genocentric approach to biology, it came as no surprise that the "rediscovery" of the Warburg effect was followed by the "rediscovery" of the relevance of glutamine metabolism in tumour metabolism.[29-31] It is now fully accepted that in cancer there is a general reprogramming of cellular metabolism, and that such metabolic reprogramming is, in fact, one of the "hallmarks" of cancer.[1] Indeed, we now know that cancer not only has altered metabolism of glucose and glutamine, but also that of other amino acids, fatty acids, cholesterol and polyamines.[31-39] In recent years there has been an increasing

number of articles analyzing the reprogramming of metabolism in different types of cancer -as well as its potential for targeting- or papers describing the role of specific drivers of such a reprogramming.[40-59]

But cancer does not grow in a vacuum, rather in the context of specific host tissues and organs. Therefore, it is necessary to reanalyse not only the metabolism of tumour cells but also the complex metabolic interrelations between the different cell types within the tumour microenvironment and between the tumour and the host organism: a clear manifestation of the concept that metabolism is not confined to the interior of a single cell.[60,61] Our group was the first to demonstrate 30 years ago that a change in the glutamine metabolism of the host organism occurs very early in the development of a tumour and that an exchange of amino acids is established between the host and the tumour to contribute to the growth of the tumour.[62-64] Lately there has been renewed interest in exploring the metabolic interrelationships in the tumour microenvironment.[65-73] Recently, our group has contributed with an updated and complete review on metabolism in the tumour microenvironment.[74] We have also reviewed the connections of redox metabolism reprogramming in the context of tumour angiogenesis.[75]

6. Metabolic Reprogramming as a Characteristic Property of the Dynamic Character of Metabolism

Authors as prominent as Craig B. Thompson, Mathew Vander Heiden, Ralph DeBerardinis, Karen Vousden, Eyal Gottlieb and Almut Schulze lead the legion of authors who in the last twenty years have gradually "rediscovered" the importance of reprogramming in the metabolism of carbohydrates, lipids and nitrogen metabolites in

cancer, finding welcoming homes for their work in the most important scientific journals.[76-85] Not wishing to deny the merit of the good science that all of them are carrying out, I insist on using the term "rediscovery" because a good part of these findings had already been made (albeit with less sophisticated technical procedures than the current ones) decades before, as exemplified by the little known and cited (and yet indispensable) book "*Biochemical Aspects of Tumour Growth*", by V.S. Shapot.[60] The increasing number of research groups involved in metabolic studies is a clear evidence of the current renewed interest in metabolism. To the list of brilliant scientists involved in metabolic studies mentioned above, it is fair to add the important contributions in the field published by Peter Carmeliet, whose group in the last decade has been mimetically reproducing the steps of metabolic reprogramming in endothelial cells during angiogenesis. In this way, and in but a few years, he has gone from remarking that glycolytic metabolism is essential for endothelial cells[86] to "discovering" the importance of the oxidation of fatty acids and, more recently, of the metabolism of amino acids such as glutamine, asparagine or serine in angiogenesis.[87-89] All this has contributed to the establishment of the concept of global reprogramming of metabolism in the tumour microenvironment.[65,74,90]

However, all these metabolic changes and adaptations that are "sold" as "exceptional" and as a distinguishing mark of the cancer itself are no more than the reflection of the complex and dynamic character of the metabolic network, and tis ability to adapt to the changes and the metabolic and bioenergetics demands of each situation.[74,91] According to this concept, metabolic reprogramming of cancer would simply represent a (certainly remarkable) example of the flexibility and adaptability of metabolism. In the rest of this section, I will comment on some other relevant examples

of the dynamic potential of metabolism to fine-tuning living beings with changes in both internal and external environments.

6.1. Metabolic reprogramming in the transitions between normoxia and hypoxia

We need to go back more than 40 years ago to identify one of the first published scientific papers illustrating this concept, when the group then led by Professor Federico Mayor Zaragoza demonstrated that the facultative anaerobic organism *Saccharomyces cerevisiae* (baker's yeast) adapted its metabolism in the transition from normoxia to hypoxia with a drastic reduction of 2-oxoglutarate dehydrogenase activity: in practical terms, the "rupture" of the Krebs cycle and its transformation into the two branches of a biosynthetic route (of glutamate and compounds of 4 carbons) that also operates in strict anaerobic organisms (see Figure 3).[92] Some years later, these observations were confirmed in another facultative anaerobic organism, the prokaryotic cell *Escherichia coli*.[93] Hypoxia induces HIFs (Hypoxia Inducible Factors), transcription factors that in turn modify the pattern of expression of many genes coding for proteins involved in metabolic processes.[94,95] In fact, not only hypoxia but also circadian and ultradian rhythms, immune system responses, exercise, hibernation and practically any other environmental or internal factor (including aging) involving a change in the energetic and biosynthetic demands of an organism are capable of modulating the gene expression and metabolic characteristics of cells, as briefly highlighted with the examples that follow.

6.2. Metabolic reprogramming is associated with circadian and ultradian rhythms

It is well known that the interaction of cell-autonomous circadian clocks with fasting/feeding and dark/light cells gives rise to the circadian oscillation of thousands of

genes, thus impacting on their biological function. Many of these genes with circadian oscillations are directly or indirectly related to metabolism.[96-99]

Besides circadian rhythms, plants and animals also exhibit other periodic oscillations, such as the half-a-day cell-autonomous clock linked to cycles of light-darkness and/or with a circatidal origin.[100,101] But even shorter metabolic oscillators have been described with periods of the order of minutes in yeasts. The so-called yeast metabolic cycle (YMC), with a 40-min period, is particularly well characterized.[102-104] It has been proposed that the logic of this YMC is to make possible a temporal compartmentalization of cellular processes.[103] However, this is only one of a group of metabolic oscillations with periods ranging from 1 min to several hours and collectively known as ultradian metabolic cycles.[105,106] These short period metabolic oscillations are not a consequence of the cell cycle, and thus they are deemed to be autonomous.[107]

Although widely studied in the present century, these ultradian metabolic cycles are far from being a novelty in science: damped and undamped glycolytic oscillations in budding yeast were initially described almost sixty years ago.[108-110] Since these pioneering studies, yeast has been the most frequently used model organism for studies of metabolic oscillations. However, these oscillations are not the prerogative of unicellular organisms, as revealed by Klevecz and Ruddle as early as 1968, when they described cyclic changes in enzyme activities in synchronized mammalian cell cultures.[111] Many other metabolic oscillations have been described in complex multicellular organisms, including plants and animals. For instance, photosynthetic oscillations are well documented, being initiated and supported by imbalances in NADPH and ATP supply to the Calvin cycle.[112] In the mid-nineties, 100-second oscillations of Ca^{2+} and cell membrane potential were found in heart myocytes under oxygen deprivation conditions.[113] Oscillations in the metabolic flux through the Krebs

cycle throughout the mammalian cell cycle have recently been revealed using temporal fluxomics.[114] These and other examples are presented and explained as autocatalytic reactions exhibiting nonlinear dynamic behaviour similar to those of the Belousov-Zhabotinsky chemical clocks in the classical Volkenstein's textbooks of Biophysics, as well as in the monumental *The Geometry of Physical Time* by Arthur Winfree.[115-117] The non-linear dynamics of these autocatalytic biochemical processes is connected with collective behaviours of auto-organization, as clearly exemplified by the auto-organized patterns of growth of the slime mold *Dictyostelium discoideum* in response to a wave of cAMP.[115-117] Based on this example, a tight connection could be suspected between metabolic oscillations and the deployment of patterns during morphogenesis, a research area that deserves to be revisited in the near future. These metabolic cycles can also have a role in fine tuning the synchronization of biological processes.[117,118] From the viewpoint of integrated regulation of metabolism, these metabolic oscillations are related to the general principle of metabolic regulation according to which organisms synchronously activate their catabolic processes and inhibit their biosynthetic processes under conditions of low chemical energy levels (for instance, due to nutritional deprivation). This is revealed by signals such as low ATP/AMP (or the equivalent energy charge) and NADH/NAD^+ ratios, and via the AMPK signal transduction pathway.[9,119] The converse -an activation of biosynthetic pathways and an inhibition of catabolic pathways- occurs when the aforementioned ratios are high. An interesting redox oscillatory cycle has been characterized by the group led by the Morré marriage in a number of extracellular NADH oxidases (ENOX), including the tumour-associated ENOX isolated and characterized from the HeLa cell surface.[105,120,121] In a recent Editorial in this journal, Andrew Moore has suggested that metabolic cycles could play roles in cancer cells, an idea that deserves to be explored.[122]

6.3. Metabolic reprogramming occurs in immune cells and immune system responses

In the last few years, the evasion of the immune response has transpired to be the hallmark of cancer that is most likely to yield promising results as a therapeutic target in clinical oncology, as revealed by the Nobel Prize in Physiology or Medicine 2018 awarded to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation.[123] Its connections with (lymph)angiogenesis and metabolic reprogramming (other two hallmarks of cancer) in the context of cancer initiation, progression and metastasis has been studied, and is currently well documented.[73,123-128] This has decisively contributed to a burst of interest in the connections between metabolic reprogramming and immune cells and immune system, giving rise to the growth of the new research area of immunometabolism. In this context, metabolic reprogramming of different types of immune cells (including B, NK, and T cells, as well as macrophages, among others) upon their activation and under different pathophysiological conditions (such as inflammation and exposure to pathogens) are also well documented.[129-146] The growth rate of immunometabolism research in the few last years is so high that metabolic reprogramming of immune cells has already become a hotspot similar to cancer metabolic reprogramming.

6.4. Plants reprogram metabolism in response to heat, water, salt and other environmental stresses.

Plants, along with fungi, are the eukaryotic organisms with the most complete and complex metabolic networks, possessing numerous pathways of secondary metabolism. Being rooted in the soil, plants cannot move or migrate in search of nutritional resources

or in response to changes in environmental conditions. Therefore, plants are exceptional models for studying the extremely high level of sophistication of metabolic responses that continuously fine-tune the biological conditions of the organism to these environmental conditions. Metabolic responses of plants to pathogens and to different kinds of abiotic stress are so well documented as to be included in the routine content of standard plant biochemistry textbooks.[100] It is well known that plant acclimation to heat stress involves the synthesis of several heat shock proteins with major functions in the control of protein activity, leading to many changes in cellular metabolism, albeit a great part of them are still poorly understood.[100,147,148] In the current scenario of climate change, the responses of plants to heat stress are particularly relevant.[149-152] However, metabolic responses to a number of other abiotic stresses, including flood, drought, salt, and cold stress, among others, have been reported.[153-156]

6.5. Other relevant metabolic reprogramming responses

Transitions between rest and exercise. The metabolic adaptations in the transitions rest/exercise, the differences of the metabolic modifications linked to training for strength exercise and endurance exercise and the different metabolic impacts of acute and chronic exercise are well documented.[8,9,157,158]

Hibernation. It is well known that hibernating animals depress their general metabolic functions. AMP kinase has an essential role in this metabolic depression.[159]

Aging. *Aging* is accompanied by a number of changes in metabolism. Some of these changes give rise to sarcopenia, a progressive loss of skeletal muscle strength and mass. It has been shown that the use of the metabolic modulator trimetazidine induces myogenesis though a metabolic reprogramming that stimulates differentation of skeletal

muscle progenitors and increases the levels and activity of proteins involved in the oxidative metabolism of aged myocytes.[160]

Integrated metabolic changes in different parts and organs of a pluricellular individual living being. Even in the same organism its different parts and organs respond autonomously but in concert with changes in bioenergetic and biosynthetic demands, as excellently illustrated by the spectacular variety of metabolic flow modes in which enzymes from the Krebs cycle may be involved in different plant tissues under different lighting conditions, nutritional stress, etc.[161]

7. Conclusions and Outlook

The notion of metabolic reprogramming as one of the hallmarks of cancer has had a big impact on basic, translational and clinical oncology research, giving rise to the concept of an "oncometabolite" and to the FDA approval of the first drugs targeting metabolism for the treatment of several types of cancer.[162-166] The characteristically elevated glucose uptake by many cancers is the foundation of the use of positron emission tomography (PET) for cancer diagnostic and treatment follow-up based in the use of the non-metabolizable glucose analogue 2-[^{18}F]-fluoro-2-deoxy-D-glucose.[167] In oncology, processes involving metabolic remodeling such as the so-called Crabtree and Chance effects remain to be "re-discovered".[168,169] And the metabolic connections between the tumor and its host deserve to be further investigated within the frame of the tumor macroenvironment concept.[170-172] The roles of cancer cell metabolic cycles in non-linear dynamics of autoorganization in tumors should be further explored.[115-117,120,122] Furthermore, the notion of metabolic reprogramming has pervaded the whole biomedical research arena, finding applications in the description of metabolic changes found between different diseases and the healthy state. Metabolic reprogramming has

been identified as occurring in alcoholic liver disease, aplastic anemia, inflammatory diseases, ischemic heart failure, ischemic-reperfusion injury, amyotrophic lateral sclerosis, bacterial infections, Zika virus infection, and lung disease, among many others.[74, 173-183]

The main conclusion derived from this article is that metabolic reprogramming is not only a hallmark of cancer or other diseases, but rather the main hallmark of metabolism itself: it is the consequence of the extraordinary capacity of the dynamic metabolic networks to readjust themselves by rewiring to reach optimal adaptation to each great or small change in the cell-external and -internal environments. Doubtless, a better understanding of metabolism and its remodelling potential will contribute to finding solutions to current challenges in biomedicine and beyond.

Under the present global climate change scenario, heat stress can have terrifying effects on world crop production. A better understanding on how plants reprogram their chloroplast metabolism under heat stress could contribute to finding new ways to counter the impact of global climate change on crop production.[153] Other environmental challenges could also be solved with the help of a better understanding of the metabolic adjustments (that is, the metabolic reprogramming) associated with them.

The potential and power of the metabolism as a genuine engine of life never ceases to surprise and amaze us. My view is that, indeed, metabolism cannot be considered metaphorically "just" the engine of life, rather it is also the complex and dynamic set of interconnected biomolecular machines including sensors that detect both internal and external changes (in terms of matter, energy or information), and central processing units, able to process inputs and to generate biological response, always connected to a continuous fine tuning of the engine of life (Figure 4). The current renewed interest in

metabolism should contribute to its re-positioning at the core of life. And not only at the core of each individual living being, but at the core of life as an emergent, collective phenomenon of the biosphere. Metabolism is intrinsically connected to life at all the scales. Nutrient cycles in the biosphere and the geophysiology inherent in the Gaia theory can be considered higher scale manifestations of metabolism.[184-186] I am sure that in the immediate future many new surprises await us in this exciting subject. Repositioning metabolism at the core of life will undoubtedly contribute to a better understanding of biological processes and life itself. Metabolism is the main hallmark of life.

Conflicts of interest

The author declares that he has no actual or potential competing financial interest.

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BOX 1: The metabolism is the engine of life.

In the last third of the 20th century, the Chilean neurobiologist Humberto Maturana introduced the concept of autopoiesis to refer to the inherent properties of life, a concept he developed extensively and lucidly in the book "*The Tree of Knowledge*",[187] co-authored by his disciple Francisco Varela. Here they point out that "*living beings are characterized because, literally, they continuously produce themselves, which we indicate when we call the organization that defines them autopoietic organization [...] In the first place, the molecular components of a cellular autopoietic unit must be dynamically related in a continuous network of interactions*". That dynamic network is the metabolism and its capacity to change by adapting to external and internal changes is what we call metabolic reprogramming. According with this and with the thermodynamics understanding of metabolism introduced in section (2), metabolism is essential to dynamically display the biological information contained in genes and to generate and maintain all the complex molecular machinery that performs the essential functions to keep us alive. In short, the metabolism is the real engine of life.

FIGURE LEGENDS

Figure 1. The metabolic network. A eukaryotic cell can produce about 30,000 different proteins, many of them enzymes that catalyze thousands of metabolic reactions involving many hundreds of metabolites. The depicted network is the overview metabolism map (map01100) provided by KEGG PATHWAY database (http://www.genome.ad.jp/kegg/pathway/map/map01100.htm). Each point (node) of this map represents a metabolite and each line (edge) connecting two metabolites represents the biochemical reaction corresponding to the transformation of one of the metabolites in the other. It is important to note that this representation is a fixed image, while a main feature of the metabolic network is its capability to change in time in response to changes in both the internal and external environments.

Figure 2. Network science identifies three main kinds of networks: random networks, scale-free Networks (also known as small-world networks) and hierarchical networks. As in the example depicted, hierarchical networks use to exhibit a remarkable modularity. The metabolic network is hierarchical and modular, and this fact renders metabolism a particularly robust network.

Figure 3. Energy metabolism reprogramming in yeasts. Under aerobic conditions, the tricarboxylic acid (or Krebs) cycle works as depicted in the left figure. The image inside the cycle is Sir Hans Krebs' photo, distributed by the Nobel Foundation when he was awarded with the Nobel Prize in Physiology or Medicine in 1953. The reader's attention is drawn to the fact that when Krebs initially described the tricarboxylic acid cycle the enzyme citrate synthase was still unknown. Under anaerobic conditions, the

enzyme alpha-ketoglutarate dehydrogenase becomes inactive and the Krebs cycle breaks and becomes a branched biosynthetic pathway, as initially demonstrated by the group led by Federico Mayor Zaragoza, a former UNESCO Director-General.[92]

Figure 4. A metaphor of metabolism as the complex, dynamic set of biomolecular machines comprising the sensors (A) able to detect changes in both external and internal signals (in terms of energy, matter or information), the CPUs (Central Processing Units) (B) able to process and integrate these signals producing messengers and biological responses continuously fine-tuning the engine (C) of life, yielding final biological responses always associated with dynamic metabolic changes. (Figure designed by María Medina Amores).

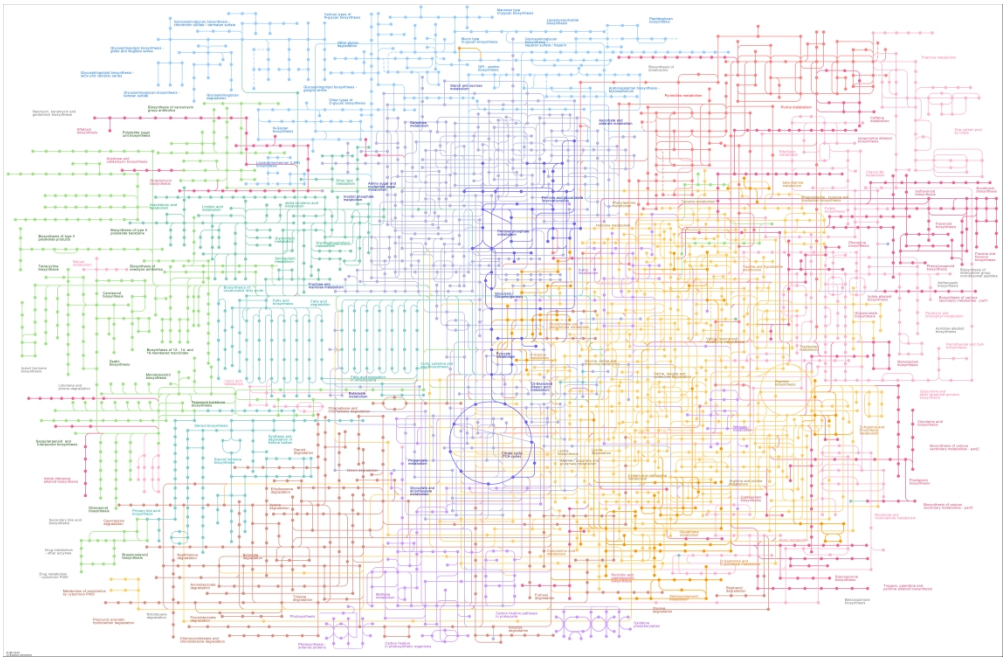

Figure 1

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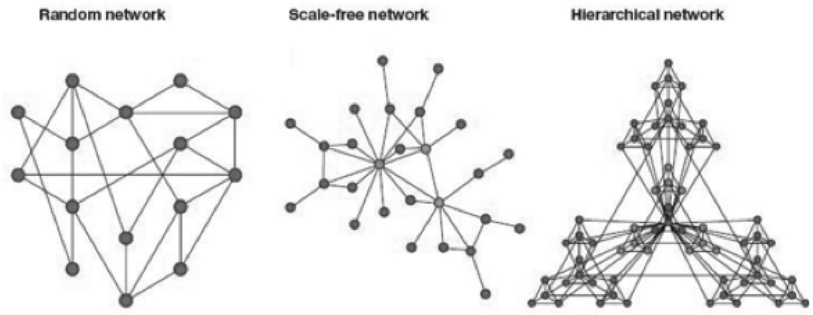

Figure 2

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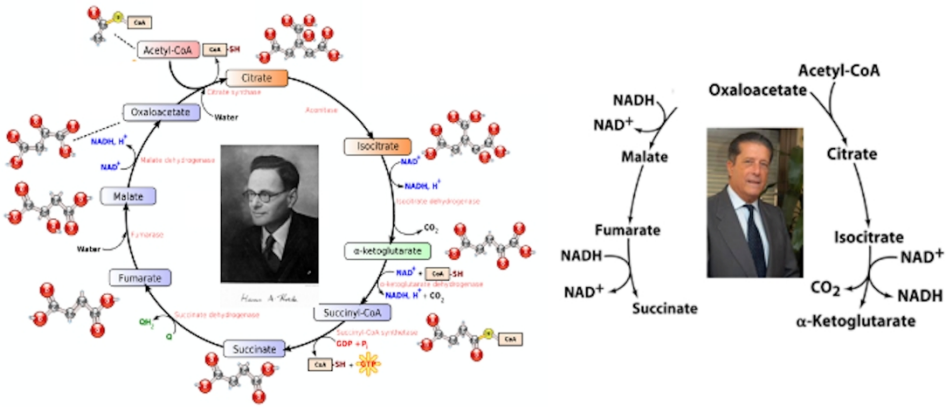

Figure 3

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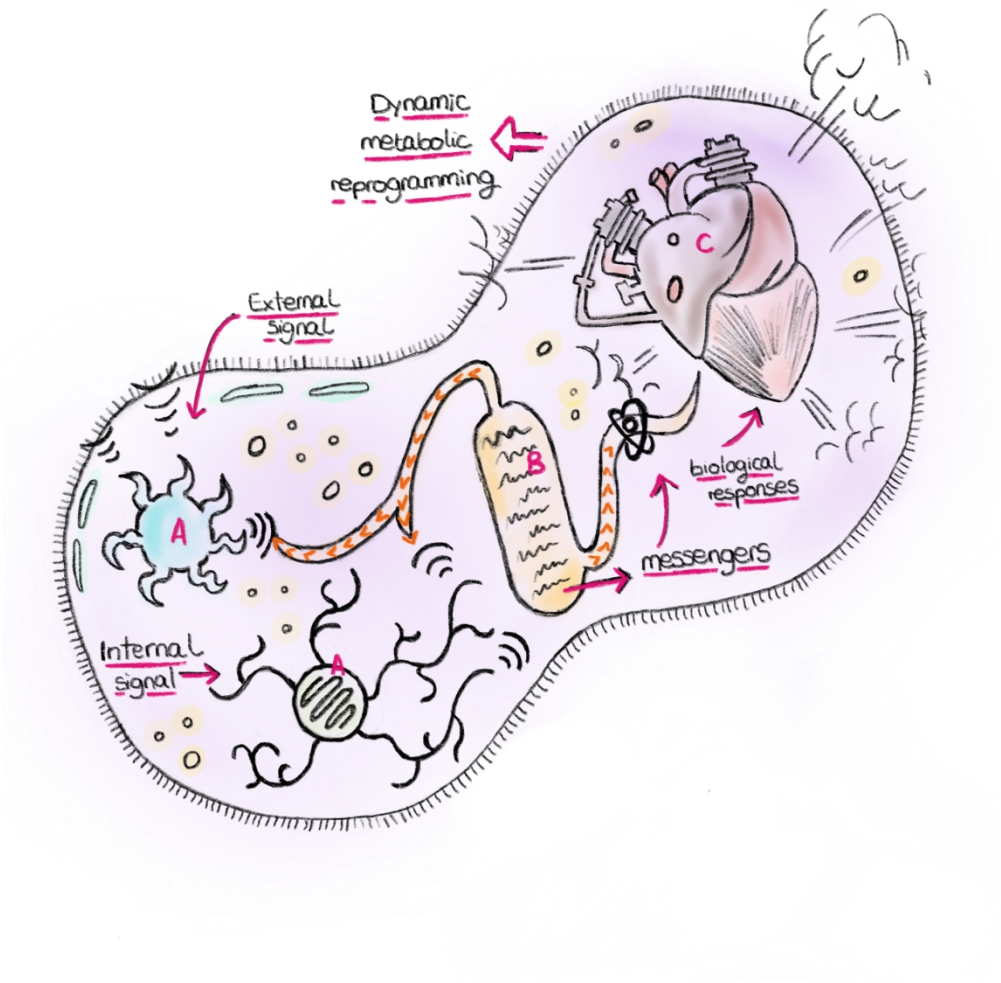

Figure 4

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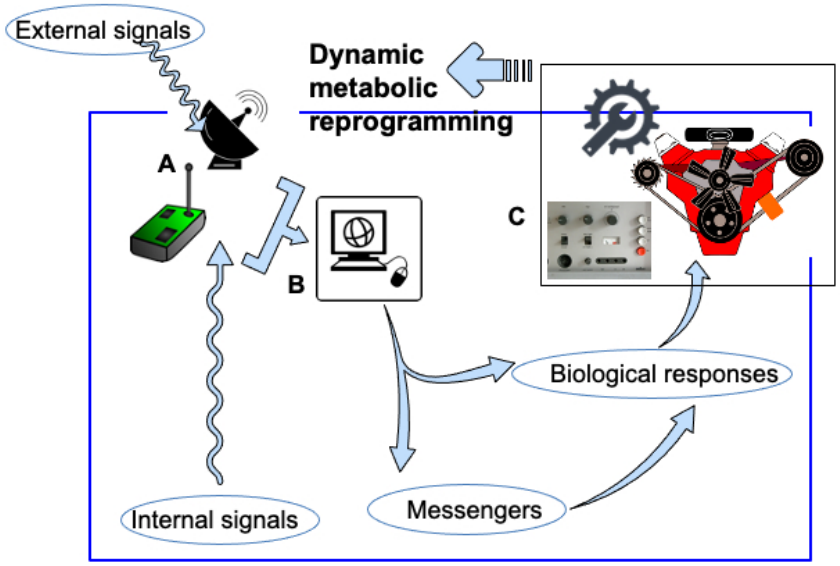

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