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GPCRs, at the Crossroad of Distortions in Extracellular Microenvironment and Intracellular Energetics Homeostasis, a New Model for 21st Century Cancer Therapeutics

Running Title: GPCRs and Cancer Cellular Network Energy Distortions

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Abstract

G-protein coupled receptors (GPCRs) have evolved in complexity and are most widely used by metazoan for essential physiological functions. They are involved in mechanisms that allow cells to receive signals from their environment and react to them. Nearly 20% of human tumors harbor mutations in GPCRs and aberrant expression and activity of G proteins and G-protein-coupled receptors are frequently associated with tumorigenesis. In this article, we review and discuss the roles of GPCRs in normal and neoplastic transformation. This could be looked upon the crossroad of distortions in extracellular microenvironment and intracellular energetics landscape homeostasis. We hypothesize that GPCRs have taken over the role of sensing cellular energetics status and are involved in regulation of signal transduction and gene expression. We also present evolutionary biology perspectives lending further support to the above mentioned notions. We propose that however complex and intricate these pathways and interactions seem, they are all guided by one elegant and simple law, namely keeping the network entropy of the cell at the minimum possible level which correlates inversely with its free energy. Cancer cells are in abnormal state(s) characterized by dysregulated energetics. Based on this view of malignant transformation, further studies and measurements of cellular energetics landscape in both normal cell and its malignant counterpart and mathematical modeling could open the way for future cancer therapeutics strategies. We propose that our future cancer treatment strategies should target conversion rather than destruction of the malignant cell which is the current dominant theme of cancer therapy that has faced insurmountable barriers as evidenced by the short and limited survivorship of patients diagnosed with advanced malignant disorders.

Keywords: G-protein coupled receptors, evolution, cancer, multicellular unit, environment, network entropy, free energy

Abbreviations: GPCRs, G-protein coupled receptors

1. Introduction

G protein-coupled receptors (GPCRs) are the oldest and the most fundamental cellular machineries that have persisted at all levels of life evolving over hundreds of millions of years following their birth and booming in multicellular era. GPCRs are a large superfamily of proteins found on the plasma membrane of cells, characterized by a signature seven-trans-membrane configuration that are encoded by over 800 genes in human genome, and essential components of the mechanism that allows cells to receive signals from their environment and react to them. Hence the central roles of GPCRs have been found in neural, endocrine and paracrine signaling. They respond to a broad spectrum of chemical and physical entities ranging from photons, protons and calcium ions, and small organic molecules (including odorants and neurotransmitters), to peptides and glycoproteins (B. Kobilka, 2013; Pierce, Premont, & Lefkowitz, 2002).

GPCRs have evolved in complexity and are most widely used by metazoan (Perez, 2003). Metazoan cell

membranes are at the interface between intracellular and extracellular microenvironments. In plants and fungi, however cell wall shields cell membranes from direct interaction with their extracellular microenvironments. Hence even through hundreds of millions of years of evolution in parallel with metazoan, only a few GPCRs are found in plants and fungi, with their roles limited to the control of cellular proliferation, development, and nutrient sensing (Brown et al., 2015; Chakraborty et al., 2015; Chen, 2008; Chen et al., 2003; Jones & Assmann, 2004; Taddese et al., 2014). In plants GPCRs control the dynamics of the function of the ionic channels in stomatal aperture responsible for plant biomass acquisition and draught tolerance (Fan et al., 2008). Hence the evolutionary success of GPCRs in metazoan is consistent with the diversified, specialized, and fine-tuned communication between cells, tissues and organs. They are the most involved protein family in animal physiological and pathophysiological functions (Lagerstrom & Schioth, 2008). Therefore, GPCRs constitute the target of the majority of marketed drugs.

In this article, we discuss the roles of GPCRs in neoplastic transformation that could be looked upon at the crossroad of distortions in extracellular microenvironment and intracellular energetics homeostasis. We look at normal state of life and its evolution from the second law of thermodynamics view point. This testifies to the evolutionary success of cell membrane receptors versatility, most notoriously GPCRs, to redirect the intracellular communication network accordingly to maintain cellular energetics homeostasis and balanced replication while maintaining maximum allowable free energy. Such controls in cellular energetics homeostasis and energy efficiency are broken down in malignancy, causing low-energy efficient aerobic glycolysis as respiration machinery known as Warburg effect (Warburg, 1956), in contrast to high-energy efficient oxidative phosphorylation. Cancer is, in principle, a disease of cell losing boundary control, a disease of signal transduction and a consequence of aberrant transmission of environmental cues to intracellular network of signaling in a multi-faceted fashion. As the communicators of cells to extracellular microenvironment, GPCRs are potential culprit in neoplastic transformation (Dorsam & Gutkind, 2007). GPCR crystallography is now in full blossom (Costanzi, 2013), opening the way to structure-based drug discovery that may help in developing new cancer therapeutics.

2. GPCRs – Guardians of Cellular Network Energy Efficiency

GPCRs have successfully evolved during the multi-cellular era which is the most puzzling period in the evolution of higher level of complexity and organization of the living cell. GPCRs therefore probably participated in evolution to expand, specialize and fine-tune communication between cells, tissues and organs. The critical significance of this era is best characterized by a transition from eukaryote organism dependent on anaerobic glycolysis (a-mitochondrial living cell) to oxidative phosphorylation by acquiring mitochondrion through endosymbiosis. In this sense the cell becomes much more efficient by consuming much less of the nutrients in the environment for generating similar amount of energy. This demands a more complex connection loop with the surrounding environment containing oxygen and nutrients as well as a more sophisticated intracellular communication network. Thus the more fuel efficient cell not only decreases its own network entropy through acquisition of much more refined and efficient energy generating machinery which enables it to have a much higher level of free energy but also would significantly decrease the speed of rise of entropy of its outside environment through conversion of its disorganized elements and molecules with significantly lower free energy into highly organized living macromolecules with significantly lower entropy (R. Liu et al., 2012). The generation of two separate entities, namely the multicellular unit and its environment or the niche demands interconnectivity and respect of barriers. These barriers are broken down in malignancy.

Exactly during this era GPCRs came into existence as the largest protein family which through their seven trans-membrane domains act as physical sensors and effectors of variations in their immediate environment which extends from the cell membrane to the intracellular micro and extracellular macro environment (Bohn, Lohse, Nitabach, Taghert, & Smit, 2015; Deupi & Kobilka, 2010; Ghanemi, 2015). Such variations range from temperature which affects the energetics of their intramolecular chemical bonds, to pressure, angulation and torque which could create distortion in orchestration of the seven trans membrane domains which could affect the very dynamics of their relationship with respect to one another and their layout in the membrane which could clearly affect the signal transduction function in a fundamental way. For the evolution of a more energy efficient biological system, it is reasonable to look at GPCRs as energy sensors in multicellular organisms, to allow complex intra- and intercellular signaling pathway to emerge.

Transition from anaerobic glycolysis of the unicellular era to the oxidative phosphorylation of the multicellular era demands meticulous sensing of the amount of available intracellular free energy. Let us take ratios of ATP/ADP or GTP/GDP as cellular free energy index. This ratio could enable us to envision mitochondria respiration and the Warburg effect dynamics (Maldonado & Lemasters, 2014), and their corollary of cellular

network entropy. GPCRs connect themselves to the intra cellular compartment in a multi-faceted fashion via agonists of GPCRs and G proteins, which function as a GTPase-activating protein and also activate adenylyl cyclase (Markby, Onrust, & Bourne, 1993; Oldham & Hamm, 2008; Pierce et al., 2002). Indeed evolution of GPCRs represent a unique and perfect design. In this sense at one end they perceive the most fundamental cues of the macro and micro-environment and at the other end they gauge the available intracellular free energy (B. K. Kobilka & Deupi, 2007). Thus GPCRs may have evolved to take on the function of sensing cellular energetics homeostasis and regulation of signal transduction that are coupled with GPCRs. Thus GPCRs are in a critical position of this loop by serving as energy sensor and signal transducer.

The spectrum of functions of the GPCRs is unsurpassed by any other family of proteins studied so far. This includes perception of macro cosmos through the highly specialized photoreceptor rhodopsin (Bhattacharya, Hall, & Vaidehi, 2008; Manglik & Kobilka, 2014). The landscape energetics of rhodopsin has been elegantly defined by Kobilka et al and is best exemplified as deep energy wells with low free energy which upon excitation of 11 cis-retinoic acid by photon and generation of its intermediary molecules, namely Lumi- Retinoic acids and finally high free energy molecule all trans-retinoic acid is pulled up to the hill of the energetics landscape which then activates downstream intracellular pathways culminating in vision. GPCRs for gustatory and olfactory cues represent the level of perception related to other vital surrounding environmental cues (Ihara, Yoshikawa, & Touhara, 2013). The perception and modulation of function by GPCRs extends to the intra organismic vital cues represented by hormones, chemokines and cytokines with their associated complex intracellular communication network, which brings the GPCRs at the cross road of immune regulatory, pain sensation, organogenesis, and cell population control network (Bodine & Komm, 2006; Doze & Perez, 2012; Krumm & Grisshammer, 2015; Z. Liu et al., 2013; Ma et al., 1998; Manglik et al., 2015; Neumann, Khawaja, & Muller-Ladner, 2014; Rogers, 2012; Zou, Kottmann, Kuroda, Taniuchi, & Littman, 1998).

Another example is the parallel evolution of organisms in the kingdom of plant, which are characterized by organelles to carry photosynthesis, called plastids in algae or chloroplasts in plants, that are evolved from endosymbiosis of cyanobacteria (Zhou & Ragan, 1993). Different from metazoan cells, the pace of cellular proliferation in plants shall be fine-tuned to the amount of free energy that becomes available via photosynthesis. Thus the lowest amount of plant cell network entropy would be maintained all the time as per the limits of the second law of thermodynamics. In other words generation of more ATP molecules through photosynthesis could exceed the upper limits of the second law in the plant cell which could increase the cellular network entropy in the same way that persistent decrease in free energy does. GPCRs through their intricate intracellular communication network connection loops, may come to rescue and orchestrate another round of mitosis. That is to say plant cell mitosis is acting as a decoy in maintaining the balance of cellular energetics and keeping the plant cell network entropy at its minimum possible level set by the limits of the second law. Connection of GPCRs to the plant cell apoptotic machinery could act as an additional decoy mechanism in this regard when further mitosis is not possible in either extremes of free energy status of the cell. Hence biomass of trees and their (seasonal) long-life span on earth are unreachable by any species of animals.

3. GPCRs Downstream Pathways Involved in Cellular Energetics Homeostasis

The two major downstream pathways of modulation of GPCR function are cAMP and PI3 kinase pathways (Godinho, Duarte, & Pacini, 2015). Interestingly enough adenylyl cyclase which converts ATP to cAMP is comprised of twelve transmembrane subunits embedded in the cellular membrane which enables it to be in direct contact with the membrane physical and chemical properties such as fluidity, tension, temperature and status of ion channels. Perhaps other cues are also transmitted by the seven-transmembrane subunit of GPCR to adenylyl cyclase (Maldonado & Lemasters, 2014). Without doubt the location of this enzyme in the cell membrane is of critical significance to its functionality in so far as its role in modulation of downstream pathways following activation of GPCR is concerned. The intramembrane events activating adenylyl cyclase are probably affected by excess ATP or high ATP/ADP ratio, i.e.: excess free energy, just like activation of its upstream GPCR which is associated with conversion of GDP to GTP. This reaction is promoted by excess GTP, probably beyond its normal 10/1 cytoplasmic ratio of GTP/GDP which could originate from conversion of excess ATP to GTP. The availability of excess phosphate moieties which are needed for the synthesis of GTP from GDP and activation of GPCR as well as phosphorylation and activation of numerous kinases needed for further activation of pertinent downstream pathways originate from blockade of ATP synthesis pathways. Such mechanisms include inhibition of electron transport system in the inner membrane of mitochondrion (Maldonado & Lemasters, 2014; Yap, Bjerke, Clarke, & Workman, 2015) in the presence of excess ATP molecules beyond the maximum allowable amount as per the limits of the second law in the living cell. Such limits could not be obviated under normal condition. The most immediate effect of activation of adenylyl cyclase is conversion of another molecule of ATP

to cAMP which serves the purpose of decreasing the ATP pool (Valsecchi, Konrad, & Manfredi, 2014). The downstream pathways of cAMP also aim at decreasing the synthesis of ATP which could happen at any or a combination of any reactions or steps involved in this regard. This could extend from epigenetic regulatory circuits to microRNA networks involved in activation of inhibition, degradation, or decreased synthesis of the responsible molecules, proteins or enzymes or inhibition of their activating pathways. However complex and intricate these pathways and interactions seem, they are all guided by one elegant and simple law, namely keeping the network entropy of the cell at the minimum possible level which correlates inversely with its free energy. This is clearly broken down in malignant cell.

Protein kinase A which is allosterically activated by cAMP, phosphorylates downstream enzymes dedicated to activation of pathways that inhibit ATP synthesis and this could happen through multiple loops including Krebs cycle and electron transport system and at all levels of their regulatory network ranging from microRNA to epigenome. By the same token the inhibitors of ATP synthesis are activated by phosphorylation in a parallel manner (Grahame Hardie, 2014). Interestingly enough the phosphate moiety used for phosphorylation originates from excess phosphate pool which has piled up because of inability to interact with ADP to generate ATP. So the delicate cellular bio economy achieves multiple goals at the same time and the excess free intracellular phosphate moieties which could prove harmful to the integrity of the cell are taken away.

The second major GPCR downstream pathway is PI3 kinase (Yap et al., 2015). Following interaction of ligand with the G protein GQ, activation of phospholipase C ensues both of which are located in the plasma membrane and affected by shared cues and share similar activation mechanisms of their energetics landscape. Phospholipase C converts PIP2 (phosphatidyl inositol 4, 5 biphosphate) to IP3 (inositol 1, 4, 5 triphosphate) and DAG (diacyl glycerol). IP3 helps open the calcium channel through its receptors in the endoplasmic reticulum and mitochondrion and DAG helps activate protein kinase C (PKC). Calcium activates calmodulin kinase and PKC phosphorylates many other proteins (Kania, Pajak, & Orzechowski, 2015). IP3 and DAG additionally converge through calcium calmodulin (Marshall, Nishikawa, Osawa, Stathopulos, & Ikura, 2015). PI3 kinase phosphorylates IP3 into PIP3 which activates protein kinase B (PKB) also known as AKT which stimulates cell survival, growth, proliferation, and metabolism; and negatively regulates autophagy (Heras-Sandoval, Perez-Rojas, Hernandez-Damian, & Pedraza-Chaverri, 2014). This happens through activation of activating loops and suppression of the suppressive signals and paths.

4. At the Crossroad of Mutation Induced Distortions in Cellular Network Energy Landscape

Nearly 20% of human tumors harbor mutations in GPCRs and aberrant expression and activity of G proteins and G-protein-coupled receptors (GPCRs) are frequently associated with tumorigenesis (O'Hayre et al., 2013). Activation and inactivation of GPCR downstream pathways are best definable under the premises of inflationary versus deflationary energetics concept, which is meant to be production of excess or inadequate amount of free energy. Persistence of either of these two conditions would take the cell outside of the border or firewall set by the second law in a similar fashion. Short lived oscillations happen all the time under normal condition (**Figure 1A**). These oscillations are perceived by the master sensor, i.e.: GPCRs, which in turn activate or inactivate downstream pathways in favor of restoration of balance of cellular energetics. Mutations and dysregulations could happen at virtually any point or a combination thereof in the network of cellular energetics regulatory pathways extending from GPCRs to cAMP and PI3Kinase pathways and beyond (Tsvetanova, Irannejad, & von Zastrow, 2015), leading to persistent deflationary (**Figure 1B**), or inflationary (**Figure 1C**) cellular energetics states. Such mutations and dysregulations could also happen at or extend to other critical nodes of intracellular communication network such as p53 (Meek, 2015), Rb (Indovina, Pentimalli, Casini, Vocca, & Giordano, 2015), Ras (Dibble & Cantley, 2015), BCL2 (Hata, Engelman, & Faber, 2015) family and their related loops, as well as BRAF (Lavoie & Therrien, 2015), JAK2 (Skoda, Duek, & Grisouard, 2015), and Wnt (Li, Ji, Chen, Zhang, & Ye, 2015) further complicating preceding derangements and minimizing the possibility of any reversibility.

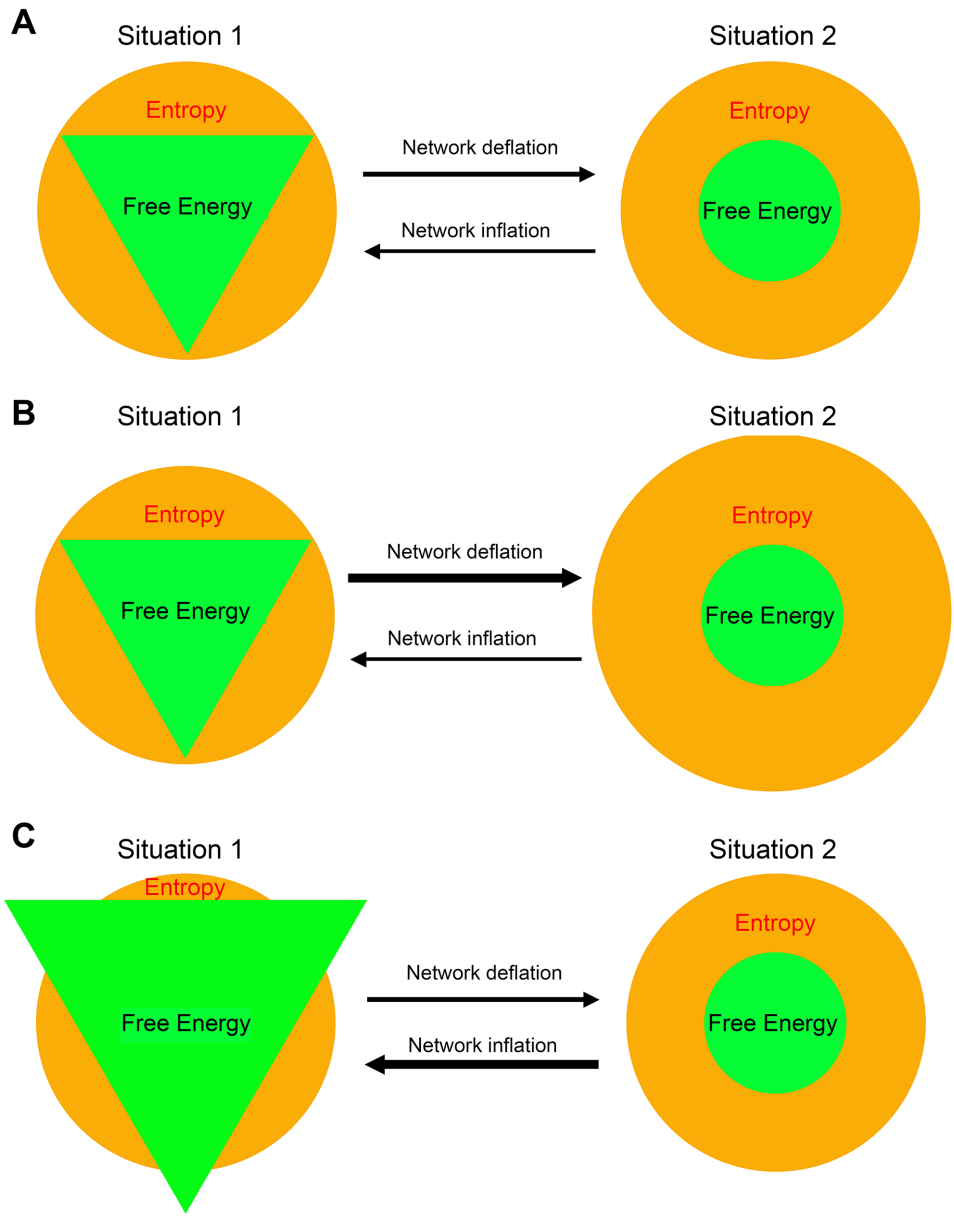

Figure 1. Inflationary and deflationary energetics model

A, balanced oscillation in cellular energetics landscape network creates a quantum fluctuation between situations 1 and 2 which defines normal cellular energetics landscape. **B**, deflationary drag to situation 2 as a result of deflationary mutations and dysregulations in cellular energetics landscape network locks the cell in high network entropy leading to landscape fracture. This leads to malignant transformation. **C**, inflationary drag to situation 1 as a result of inflationary mutations and dysregulations in cellular energetics landscape network characterized by excess ATP formation with high ATP/ADP ratio ignores limits set by the second law of thermodynamics. This leads to landscape fracture with ensuing persistent increase in cellular network entropy and malignant transformation.

4.1 PI3 Kinase in Inflationary and Deflationary Energetics Model

The most frequently mutated gene in human cancers positively regulates cell survival, growth, proliferation and glucose metabolism and negatively regulates autophagy and apoptosis (Xia & Xu, 2015). This happens through key player protein kinase B also called AKT which connects itself to numerous intermediary proteins to achieve these goals. This demands activation of activators and suppression of deactivator loops in an orchestrated fashion. When GPCR senses excess free energy, it could act through G-proteins or at times independently, and under normal condition the downstream pathways activate PI3 kinase (Robinson & Pitcher, 2013). This way the

available excess free energy gets spent towards growth and proliferation. This is an attempt to keep the cellular landscape energetics in balance. However when the free energy of the cell drops below this critical threshold, PI3 kinase gets inhibited and ATP generating pathways become active. In the meantime, autophagy and apoptosis become the dominant theme and cell proliferation ceases.

Activating mutations of PI3kinase or lack of function mutations of PTEN which are among the most common mutations in malignant disorders(Milella et al., 2015) disregard lack of availability of adequate amount of free energy and push for proliferation and growth as well as suppression of autophagy and apoptosis, endorsed by lack of function mutations of p53 commonly found in cancers (Gu et al., 2014; Meek, 2015). This creates a crisis in the energetics landscape of the cell. Activating mutation or dysregulation of downstream members of PI3 kinase suppressor network or loss of function mutations of the PI3 kinase downstream activating members could take place as the initial mechanism to handle the cellular energetics landscape crisis. As first line mutations fail to achieve this goal, more and more collateral pathways get mutated and dysregulated to contain the crisis. Further extension to a broader range of network of pathways ensues which leads to destabilization of intracellular communication network and finally fracture of the cellular energetics landscape into malignant phenotype.

By now the malignant cell has employed Warburg phenomenon to satisfy its fuel needs. Diverging into Glycine as nucleoside building block and Methionine addiction as described by some soon ensues (Booher, Lin, Borrego, & Kaiser, 2012). At this juncture the fracture of the cellular energetics landscape has reached a point of no return and the aberrancies scope and horizon has massively widened. The biochemical and biophysical derangements generate a reverberating vicious cycle reinforcing each other at an ever increasing pace. Through this chain reaction and sequence of events the malignant cell acquires the capability to survive extreme conditions such as hypoxia, and generate its own blood supply through activation of angiogenic loops and paving its way to foreign organs through activation of metalloproteinase and creating its niche in metastasized organs by activating autocrine and paracrine loops, endorsed by chromosome instability (Cimini, 2008; Holland & Cleveland, 2009; Kops, Weaver, & Cleveland, 2005; Rajagopalan & Lengauer, 2004; Ried et al., 2012). The above mentioned scenario represents the consequences of the deflationary mutations and dysregulations in PI3Kinase pathway. This scenario is best exemplified by triple negative carcinoma of breast. Interestingly enough ballooning of the distorted fine cytoskeleton in this condition which represents an increase in cellular volume and decrease in available free energy per cellular unit volume is a physical representation of increased cellular energetics landscape entropy.

Theoretically one could achieve malignant transformation by: 1) Inflationary mutations and dysregulations of PI3kinase pathway, which lead to pile up of excess ATP molecules. 2) Deflationary mutations and dysregulations in PI3kinase pathway, which deplete the cellular free energy pool. 3) Inflationary mutation and dysregulation of cAMP pathway, reflected by decrease in intracellular cAMP level. 4) Deflationary mutations and dysregulations in cAMP pathway, reflected by an increase in intracellular cAMP level. 5) Combination of PI3kinase inflationary and cAMP inflationary mutations. 6) Combination of deflationary mutations of both pathways. 7&8) Reverse combinations of both pathways.

Inflationary mutations in either PI3kinase and cAMP pathways or their combinations that lead to malignant transformation as a result of pile up of excess free energy could lead to downregulation of GPCR downstream pathways via irreversible GDP bound G-protein alpha subunit (Ga), or GTP bound G-protein inhibitor (Gi). This could also spread to other pathways and ultimately lead to fracture of energetics landscape network. Thus excess free energy also increases the cellular network entropy culminating in malignant transformation, associated with chromosome instability resulting functional distortion of mitochondria (Donthamsetty et al., 2014). In contradistinction, deflationary mutations in cAMP and PI3 kinase pathways could preferably lead to ante grade mutations and dysregulations of other collateral pathways further feeding into a deeper malignant phenotype. Thus the inflationary and deflationary model could act as a new blueprint that could also arm us with the power of prediction of ensuing mutations and dysregulations which could make preemptive intervention a real possibility.

4.2 TP53 Mutation

Analysis and measurement of cellular network energetics landscape in TP53 mutated cancers which comprise fifty percent of all malignant disorders (Gurpinar & Vousden, 2015) could open the door on future cancer therapeutics for a big majority of our patients. A TP53 mutated cancer cell is not able to activate apoptotic machinery when the master free energy sensor GPCR directly or through one of its delegates identifies the deflationary crisis and pushing for senescence and apoptosis. Thus proliferative and growth pathways are left

unopposed.

4.3 The JAK2^{V617F} Mutation

Mutations that allow hematopoietic progenitors to differentiate and expand in the absence of growth factors result in hematologic malignancies. In 2005 a single Gain of function mutation in the Janus kinase 2 (JAK2) gene was identified in the majority of patients with Philadelphia-negative myeloproliferative neoplasms (Baxter et al., 2005; James et al., 2005; Kralovics et al., 2005; Levine et al., 2005; Zhao et al., 2005). JAK2^{V617F} is a somatic mutation acquired in the hematopoietic stem cell compartment (Jamieson et al., 2006) which results in constitutive activation of the JAK2 signaling pathway, leading to unrestrained production of mature myeloid cells. JAK2 is a cytoplasmic tyrosine kinase which is critical in intracellular signaling by cytokine receptors such as erythropoietin (Epo), Thrombopoietin (Tpo), interleukin-3 (IL-3), granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (G-MCF).

This common theme follows mutations or dysregulations in other major pathways such as Ras, Rb, V600E BRaf, and Jak2 mutations which in different ways impose incessant growth and proliferation pressure on a cell with limited energy supply. The same vicious cycle of employment of Warburg phenomenon with its ensuing cellular energetics network dysregulation and finally network fracture will follow. Again delicate cellular energetics network measurements as mentioned previously would offer exceptional opportunities for cure of cancer.

4.4 Warburg Effect

As mentioned above this incessant proliferation ignores lack of adequate free energy supply and employs Warburg effect (Warburg, 1956) for its energy supply. Warburg shift takes place as a pathological energetics means of support for continuation of cellular growth and proliferation in the face of physiological decreased energy supply (Vander Heiden, Cantley, & Thompson, 2009). Glycine gets used as a building block for purine nucleoside synthesis and methionine addiction ensues. Collateral pathways that suppress cellular growth and proliferation could also get suppressed through mutation or network dysregulation and the spectrum of cellular energetics catastrophe widens and takes the cell to the point of fracture of cellular energetics landscape. At this juncture the malignant cell has reached the point of no return.

In case of mutations and dysregulations that directly affect the stem cell compartment such as Wnt, population sensor disruption is the dominant theme. In case of colon adenocarcinoma this leads to crypt overpopulation which culminates in energy demand far beyond the available supply. Again Warburg effect is employed with its ensuing vicious cycle leading to full blown malignancy. Activation of Warburg effect opens the door on other ill mutations and dysregulations leading to chromosomal instability the distinguishing hall mark of neoplastic disorders.

5. Future Cancer Therapy Strategies Based on Dealing with Cancer as a Distortion in Cellular Network Energy Landscape

Analysis of normal and cancer cells would reveal distorted oscillation in cellular network energetics landscape. Breakthrough in cancer therapy strategists would follow this type of understanding. Clearly one needs to do a detailed energetics analysis of each individual mutation or dysregulation corresponding to a specific malignant disorder before designing bioenergetics based treatment strategies. By doing so, one could decipher the net effect of major mutations and dysregulations identified in different malignant disorders on the cellular energetics landscape network. Achieving the capability to make such measurements could prepare the grounds and create the opportunity for conversion to normal energetics landscape as future cancer therapeutics strategy. One potential measurement methodology is liquid NMR spectroscopy. Flux analysis of cellular bioenergetics by Seahorse Extracellular Flux Analyzer could offer an original though critical perspective on energetics distortions. Together with advances in crystallography, GPCR structure-based drug discovery may help in developing new cancer therapeutics that target the fundamental issues of cancer energetics distortion.

6. Discussion

The biggest puzzle in biology is evolution of the delicate and goal oriented activation and inhibition of the complex regulatory network of proteins involved in signal transduction and their orchestration in targeting homeostasis and balanced replication which is clearly broken down in malignancy. This puzzle seems to have its roots in the interplay of the second law of thermodynamics with the living cell simply because keeping the balanced oscillation in cellular landscape network energetics is its main goal. Thus the true definition of cancer cell is the breakdown of this balance.

In a nutshell when the GPCR system as the proposed master sensor senses excess free energy released by ATP hydrolysis and determined by ratios of ATP and ADP, all the downstream pathways of ATP formation or

accumulation get inhibited and excess phosphate moieties which pile up as a result of blockade of reaction with ADP are used as transducers through phosphorylation of kinases, leading to activation of survival, growth and proliferation pathways and consumption of the excess free energy, and vice versa.

The complexity of the regulatory network of GPCR is governed by homeostasis of cellular energetics rather than directionality (Mondal, Khelashvili, Johner, & Weinstein, 2014). For example both GPCRs and G proteins could function independent of each other as well. That is to say under certain conditions the canonical pathways are ignored in favor of homeostasis (Garcia-Marcos, Ghosh, & Farquhar, 2009). This is another attestation to the fact that hyper plasticity of the intracellular communication network rather than a peculiar path serves the purpose of maintenance of minimum allowable cellular network entropy in normal cell.

The concept of receptor activation by ligand also is not a discrete one. The truth about receptor- ligand interaction is dictated by the quantum state of the receptor and the sum over histories of all possible receptor configurations which allow interaction with ligand or lack thereof. That is to say that any type of receptor including the GPCR is in constant flux between and among innumerable configurations, and in the smallest fraction of a second, the meeting of a ligand with a receptor happens in the quantum universe and not the one that we conventionally observe and can measure. This is exactly why it is impossible to get a precise image of ligand and receptor interaction in real time. For that reason a methodology such as NMR spectroscopy could prove very helpful in delineation of receptor function and potential ligand receptor interaction. Thus the inherent necessity to maintain the cellular energetics homeostasis could ignore the need for ligand and one of the many possible and existing receptor configurations of GPCRs could lead to activation or inactivation of the downstream pathways to achieve this goal. Kobilka et al have delicately done measurements of landscape energetics of the GPCRs using NMR spectroscopy. Thus under certain conditions activation of GPCRs downstream pathways happens independent of G proteins and vice versa again as dictated by homeostasis rather than directionality.

In the last seventy three years since the time nitrogen mustard was introduced as the first classic chemotherapeutic agent, we have witnessed discovery of a lot of cytotoxic and genotoxic agents. This long journey has taken us into incorporation of multi-agent chemotherapy protocols at times in combination with radiation therapy. In the last twenty or so years targeted therapy against new targets of cancer cell survival and proliferation has become the dominant theme in cancer medicine. Most recently a new generation of immunotherapy taking advantage of check point inhibition has significantly improved the outcome of certain malignancies such as metastatic melanoma. However if we look critically into all these developments, they have one thing in common, namely aiming at destruction of cancer cell. However successful we have been at improving the survival of cancer patients, cure is a far reaching goal. We are falling prey to lack of our understanding of the deeply seating laws that govern the very dynamics of the normal cell which is the essential prerequisite of understanding the truth about cancer cell and design of meaningful treatment strategies.

Deep understanding of fundamentals of cellular energetics down the line of evolution of living organisms and its breakdown in malignant cell could generate unique and unprecedented opportunities for designing a revolutionary generation of cancer therapeutics based on conversion rather than destruction. We believe that GPCRs play a fundamental role in the homeostasis of cellular energetics as witnessed by their birth in multi-cellular era and their persistence at all levels of living organisms ever since. For that reason they deserve the designation of master free energy sensor and harmonizer.

Our inflationary and deflationary model of cellular energetics offers the opportunity for a tailored and customized conversion based curative approach to each individual malignant disorder. The time has come to give an end to our misunderstanding of destruction as the curative measure for cancer and embrace conversion as the path leading to cure of this devastating disorder.

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Author Contribution

Kambiz Afrasiabi, created the concept, orchestrated, and wrote the manuscript. YiHong Zhou, incorporated evolutionary biology perspectives, generated all figures, did critical review of references and the whole article. Angela Fleischman, contributed the first paragraph of section 4.3 and references.