Can Micro Pathways Lead to Macro Healing?

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Abbreviations: AMPK: Adenosine Monophosphate activated Protein Kinase, HBOT: Hyperbaric Oxygen Therapy; SYNJ 2: Synaptojanin 2; BBB: Blood Brain Barrier; ROS: Reactive Oxygen Species; LPS: Lipopolysaccharide; TNF: Tumor Necrosis Factor; SHAs: Secondary Hyperalgesia Areas; SCI: Spinal Cord Injury; PDH: Pyruvate Dehydrogenase; EGFR: Epidermal Growth Factor Receptor

Introduction

What do I mean by micro pathways leading to macro healing? Are there avenues we can follow in the 'micro-verse', I mean within the microbiological genomic level, that can lead us to healing on our organ system level in which we live daily? The micro-verse is being discovered at a phenomenal rate and trying to sift through the vast amounts of new relevant data from recent studies on Hyperbaric Oxygen Therapy (HBOT), Adenosine Monophosphate activated Protein Kinase (AMPK), and cancer cell Invadopodia can be confusing and cumbersome because of the rapid progression of high powered studies due to incredible advancements in gene research and the integration of many data sets from many different research groups through 'Big Data and Powerful Analytics'. Yet, when one takes a broader view into the micro-verse of how and why cancer can easily spread throughout a human, we must consider not only the metabolic pathways of the cell's mitochondria (Because cancer hacks the cell's energy production in order to produce a symmetrical copy of itself and sometimes for invasion into sterile cells), but also cancer's ability to mine healthy cells through Invadopodia (Stopping cancer's invadopodia would advance cancer medicine tremendously). Is there a relationship between these seemingly different avenues of research? How do HBOT and AICAR (5-Aminoimidazole-4-carboxamide ribonucleotide, a tool used in the lab to activate AMPK) effect AMPK? We will discuss in what ways HBOT and AMPK activation effect invadopodia later in the text. AMPK putatively phosphorylates Fe65/Tip60 to facilitate the Fe65/Tip60/AICD, this then increases Synaptojanin 2 (SYNJ 2). SYNJ 2 is implicated in endocytosis, vesicle recycling, tau dephosphorylation, and Invadopodia.

In a recent study, SYNJ2 promoted cell migration and invasion in culture and lung metastasis of breast tumor xenografts in mice. When they knocked down SYNJ2, it impaired the endocytic recycling of EGFR (Epidermal Growth Factor Receptor) and the creation of lamellipodia and invadopodia. When they screened compound libraries associated with SYNJ2-specific inhibitors that prevented cell migration yet had no change on SYNJ1, which makes SYNJ2 an excellent candidate to create medications targeted to SYNJ2 that may be capable of slowing and/or halting cancer cell migration [1].

Lipopolysaccharide (LPS) is used in the laboratory to mimic an infection reaction. A recent study showed that LPS, which makes up most of the outer membrane of Gram-negative bacteria, disrupts the expression of tight-junction proteins in the blood brain barrier (BBB) through the production of ROS (Reactive Oxygen Species) which kick starts AMPK. The AMPK activation then helps to maintain the integrity of the BBB by suppression of NAD(P)H oxidase (nicotinamide adenine dinucleotide phosphate-oxidase). Therefore, AMPK is important in maintaining the integrity of the BBB in patients with sepsis and AMPK inhibition plays an important role in the start and progression of many neurological disorders [2].

Recent data supports AMPK in acute inflammatory reaction mitigation. AMPK is a serine/threonine protein kinase that is composed of three different subunits, a catalytic α subunit and two regulatory subunits β and γ, and they all exist as at least 2 different shapes. Why do we think that AMPK is involved in the inflammatory response? Recent In vitro studies have shown that the activation of AMPK is associated with the inhibition of LPS- or IL-1b (Interleukin-1 beta)-induced cytokine production. In vivo studies show that the activation of AMPK inhibits the production of pro-inflammatory mediators in serum and their expression in the central nervous system of rats injected with LPS. They also showed that enhanced activation of AMPK results in a diminished severity of LPS-induced acute lung injury in mice. They found that activators of AMPK can have a strong anti-inflammatory effect in vitro and in vivo [3].

HBOT effects AMPK which putatively phosphorylates Fe65/Tip60 to construct the F365/Tip60/AICD complex which increases SYNJ 2, which then increases endocytosis, vesicle recycling, Invadopodia, and tau dephosphorylation, which leads the invasion of cancer cells into sterile cells. How does HBOT effect AMPK? In a recent study on China's use of HBOT they have illustrated how HBOT can effect AMPK. HBOT is associated with decreased apoptotic cell death, reduced inflammation, a balance of oxygen free radicals, and the activation of stem cells and other mechanisms. Considering AMPKs role in inflammation HBOT, we should look deeper into how HBOT reduces inflammation. HBOT can reduce inflammation by reducing the release of inflammatory mediators such as lymphokine (IL) family and tumor necrosis factor (TNF). They have found that HBOT attenuates inflammation by reducing IL-1, IL-6, IL-8, and IL-10 expression. HBOT reduces

TNF-α. HBOT can also reduce the incidence of membrane cofactor protein-1(MCP-1), keratinocyte-derived chemokine (KC), and IFN-gamma-inducible protein 10 (IP-10) which all increase inflammation [4].

In 2013 the Chinese Medical Association released the new contraindications, absolute and relative for HBOT use. There is only one absolute contraindication instead of the previous four. The only absolute contraindication according to the CMA is an untreated tension pneumothorax. They list 6 relative contraindications now versus the previous 10. The six new relative contraindications for HBOT according to the CMA are

I. Intraventricular external drainage

II. Fracture of the skull base with cerebrospinal fluid leakage

III. Birth weight < 2000 g in premature and low birth weight infants

IV. Serious infection of the upper respiratory tract

V. High blood pressure (SBP > 180 mmHg, DBP > 110 mmHg)

VI. Patients with chronic obstructive pulmonary disease with C02 retention [4].

Usually we use HBOT for patients with ischemic hypoxic damage like patients with burns. HBOT has an antinociceptive effect or in other words it takes the sensation of pain away. A recent study on HBOT's ability to do this on humans has shown that the anti-nociception effect is due to changes in the secondary hyperalgesia areas (SHAs). [4,5] {They used 2.4 ATMs (Atmospheres) of pressure at 100% oxygen for 90 minutes at a time.} They found that HBOT induces an anti-inflammatory or antihyperalgesic effect of central origin. Interestingly they found an additional finding. They discovered a pre-conditioning sequence effect if a repeat thermal injury is preceded by a HBOT session 5 weeks later. SHA response attenuated compared to a control. The combined hyperbaric and Hyperoxic effect has already been shown in animal studies that HBOT protection mechanisms include the induction of complex cascades of antioxidant enzymes and anti-inflammatory proteins. A different rat study showed an antinociceptive response for up to 3 weeks. {This study used 3.5 ATM at 100% for 60 minutes each day} [5].

The results of a very recent optical imaging study on the response of irradiated and non-irradiated tumor cells of mice to HBOT showed that HBOT speed up the growth of non-irradiated tumors, while the mouse survival was improved. The tumor vascular leakiness and hypoxia were enhanced after HBOT. They found that squamous cell carcinoma responds to HBOT with respect to tumor growth, vascular permeability, and hypoxia, suggesting future HBOT use in cancer patients. They did however find some variability between their study and other animal and human studies. They attributed this to different pressures, durations, and frequencies of HBOT across different studies. I support their belief that a standardized protocol for HBOT in the research setting needs to be formed in order for there to be homogeneity across studies which are rapidly increasing [6].

Geng CK et al. [7] published a study this year which also states the need for standards in HBOT. They found that the majority of scientific studies with HBOT in the treatment of spinal cord injury (SCI) had good results [7]. Yet, there was no protocol to follow or mimic. How long should HBOT last? At what pressure and for how many times per week should HBOT be given? Creating a standard HBOT protocol for research will take away these questions that frustrate us and restrict our knowledge of the true treatment mechanism of HBOT. Their research yielded four main discoveries:

a. HBOT transplantation favored the development of M2 phenotype, while preventing the development of a population of M1 phenotype.

b. HBOT was associated with a decrease in IFN-gamma and TNF-alpha, and an increase in IL-4 and IL-13.

c. HBOT resulted in increased axonal growth and myelin sparing.

d. These morphological findings correlated with improved locomotor function in the HBOT group compared to with the NBA group [7].

The use of HBOT is a well-established treatment for decompression sickness including cerebral and spinal cord ischemia. But, there are only a few experimental studies with animal models, and very few studies exploring the utilization of HBOT in the treatment of SCI in humans. In Geng CK et al. [7] study they found that more frequent exposures to HBOT could help sustain its positive effects on the metabolism of the spinal cord and regeneration of the neuronal structure [7].

It is no wonder why Israël M [8], found that preserving methylation decreases cancer's ability to thrive [8]. Cancer is able to remove or disrupt the serine-threonine phosphatase (PP2A) 'brake' methylation process which usually keeps the cell from mitosis. Israel M, then states that, "Glycolysis is then interrupted by the M2 PK (Pyruvate Kinase M2) and PDH (Pyruvate Dehydrogenase) bottlenecks resulting from the phosphorylation of these enzymes, probably related to the PP2A methylation failure. Above the neck, glycolysis operates in association to muscle proteolysis; alanine transamination feeds lactate dehydrogenase, generating NAD+ necessary for glycolysis, and the lactate released. Below the neck, citrate, condensation operates at the expense of lipolysis (No wonder fatty stores of some cancer patients is so low). Triglycerides increase, ketone bodies decrease. Epigenetic effects turn off genes and up-regulates other genes. In parallel GH –IGF- IGFBP pathways are supposed to control the distribution of the IGF receptors in the mitotic daughter cells, the cell inheriting receptors is a stem cell the other normally differentiates, a low IGFBP level perturbs the system leading to two cells with a mitotic potential." He is then able to show a remarkable similarity in pathways of Alzheimer's disease lesions [8].

Cancer hacks the metabolic processes of the cell and starts flipping on energy switches (by using AMPK which pre-cancer fought tumor genesis) but that makes sense because it must. There is the great need for some reason to not only make a copy of itself, but it must be a symmetrical copy or it takes one step forward and one step backwards in its ultimate goal of taking over its micro-verse AND at the same time (in some cancers) invade sterile cells around it. Of course, it needs anaerobic metabolism and fatty acid synthesis, it needs all the energy production it can get in order to fulfill some cancer's central dogma of growth, symmetrical

division, and invasion. Some of the more aggressive cancers show an increased fatty acid synthesis. Therefore, invadopodia formation is emerging as a promising road of further research right not. Scott KEN, et al., showed in their study that "ACC1 (acetyl-CoA carboxylase 1) is required for invadopodia formation and the invasive ability of tumor cells" [9]. Their data showed that AMPK activation is associated with the loss of invadopodia because of reduced F-actin polymerization. They showed that the effect correlates with a reduced fatty acid synthesis and invadopodia are reformed by the addition of more fatty acid. Given that fatty acid metabolism is required for membrane-cytoskeleton interactions, their study also suggests that "decreased fatty acid synthesis and changes in membrane lipid compositions could be the mechanism that links AMPK activity to the effects on actin cytoskeleton dynamics in other systems" [9].

Invadopodia and AMPK activation now appear to be instrumental for cancer's more aggressive behaviors, accelerated growth, division, and invasion capabilities through mitochondrial hacks produced through methylation disruption, bottlenecks, and energy multiplying [1-9]. Therefore, since Invadopodia formation seems to be so important let us take a short time to review our current understanding of these motility and invasive cancerous structures to bring us all up to speed Table 1.

Table 1: 25 years of Podosome and Invadopodia research (by Murphy and Courtneidge).

1985	Actin- and phosphotyrosine-rich ventral protrusions are recognized as cell attachment points to the ECM (extracellular matrix), and called podosomes.
1985	Src (Sarcoma gene or 'Sarc') is localized to the sites of cell contact to ECM, and it is shown that ECM degradation occurs at these sites.
1988	Podosomes are found in osteoclasts adhering to bone laminae.
1989	The Src-enriched sites of degradation are shown to be identical to the actin-rich protrusions known as podosomes – the new name invadopodia is coined.
1990	Bone resorption by osteoclasts is shown to require the podosome belt - the first physiologic process shown to require podosomes.
1994	First description of invadopodia-dependent proteolytic activity in human cancer cells.
1997	MT1-MMP is located in podosomes and invadopodia and is required for cancer cell invasion.
1999	First demonstration of a podosome-associated disease - Wiskott-Aldrich syndrome49.
2000	Microtubules are required for podosome formation.
2005	The adaptor protein Tks5 is shown to promote invadopodia formation, and be required for invasive behavior of human cancer cells.
2006-2008	In vivo studies demonstrate that invadopodia-associated proteins are required for both tumor growth and metastasis.
2008	ECM rigidity promotes invadopodia activity.
2009	Reactive oxygen species are necessary for podosome and invadopodia formation.
2009–2010	First demonstration that vascular pathophysiology involves podosome formation and that podosomes exist in vivo.
2010	Detailed visualization of invadopodia elongation as cells traverse basement membrane.
2010	First description of podosome structure and invasion in 3D, demonstrating that podosomes invade into the ECM using a mechanism similar to invadopodia [10].

Murphy and Courtneidge also summarized that Podosomes and Invadopodia are actin based protrusions that change shape in order to degrade the extracellular matrix. They contain Cortactin and (N)-WASP, which are actin regulators. They are able to adapt with help from adaptor proteins, Tks4, Tks5 and several pericellular proteases. Invadopodia are found in invasive human cancer cells. They found that in 2D cultures, their presence correlates with invasive behavior. Yet in 3D culture and in vivo, invadopodia proteins are required for cell growth. Small molecule regulation of podosomes and invadopodia might represent a novel therapeutic strategy to treat several diseases. They also highlight a few of the main components that are needed to regulate podosome and invadopodia formation. Actin Regulatory Proteins: Polymerization Activators (Cortactin, (N)- WASP, WIP), Filament Cross linkers (alpha actinin, Caldesomon, Fascin), Actin Nucleators (Arp2/3, Formin, and Actin Binders (Troposmysin, Coronin, and Cofilin). Extracellular Stimuli: TGFβ, PMA, EGF, ROS, PDGF. Proteases: MMP-2, MMP-9, MT1-MMP, Seprase, uPAR, Cathepsins, and ADAMs. Microtubules Associated Proteins: Kinesins and Myosin. Ca2+ Regulated: TRPM7 and S100A4. Adaptor Proteins: AFAP-110, p130 Cas, Tks4, Tks5, and Paxillin. GTPases: Rho, Cdc42, Dynamin, p190 RhoGAP, AMAP1, and ARF6. Kinases: Src, Abl, Pyk2, ERK, PAK, LIMK, PKC, and FAK. Integrins: Beta3 and Beta1. Adhesion Molecules: Vinculin, Zyxin, and Talin. Lipds like PI (3,4)P2 and microRNAs [10].

There are three main steps to the formation of invadopodia, Initiation, Assembly, and Maturation. In the initiation stage, the cells establish focal adhesions with the ECM through interaction of integrins, Src, and FAK (Focal Adhesion Kinase). Release of Src allows it to bind with TKS5 and localize the regions containing PI (3,4)P2. EGF, PDGF, and TGFβ initiate these intracellular changes. The Assembly stage: Formation of invadopodia happens when recruitment and activation of actin regulatory proteins (Arp2/3, WIP), phosphorylation of cortactin, TKS5, fascin, AFAP110, and the production of ROS. The final Maturation stage: Invadopodia promote degradation of ECM by coordinating secretion of MMP-2 and MMP-9, and enabling delivery (potentially through microtubules) and presentation of MT1-MMP to the tip of the protruding structure through the interaction with cortactin, TKS4, and β1 integrin [10,11].

There are five basic questions that need further research in the formation of invadopodia. If we are able to add to our understanding these questions of invadopodia formation and function, we will be better able to provide clinical applications specifically targeted to invadopodial proteins [10]. Question one. How is the early invadopodium precursor assembled? The role for EGFR-Src-Vav1-Cdc42 has been identified, but what are the molecular mechanisms by which Cdc-42 induces precursor assembly? Question two. What determines where the invadopodia will attack? There is evidence that invadopodia and podosomes form at the proximal tips of focal adhesions in smooth muscle cells and MTLn3 cells. But, this doesn't happen in many other cell types. It is suggested that the formation of invadopodium precursors at the proximal tips of focal adhesions is due to the specific characteristics of this site. Decreased contractility versus their specific association with adhesion proteins. These generalities have to be confirmed in order to provide crucial insights into the mechanisms of invadopodia assembly. Question three. What proteins recruit RhoGTPase GEFs and GAPs to invadopodia? Normally p190RhoGEF and p190RhoGAP are recruited to focal adhesions through binding to FAK, but FAK does not localize to invadopodia. How are these proteins recruited then? Question four. How are matrix degradation, adhesion, protrusion and translocation through degraded ECM coordinated in a 3D matrix setting? Question five. Do invadopodia play a role in extravasation and colonization of secondary organs? [11]

What can we specifically target then, considering our approach to a cancer cell invasion denial technique? Synaptojanin 2 is a phosphoinositide phosphatase that is an effector of Rac1. Rac1 is a small GTPase that we believe is important in cell migration and invasion. Depletion of Rac1 or Synaptojanin 2 has been shown to inhibit invasion of glioblastoma cells. Depletion of Rac1 or Synaptojanin 2 also inhibits the formation of lamellipodia and invadopodia. Studies suggest that Synaptojanin 2 contributes to the role of Rac1 in cell invasion and migration by regulating the formation of invadopodia and lamellipodia. Synaptojanin 2 may be a target for therapeutic interventions of malignant tumors [12].

Therefore, taking all of this into consideration we have gleaned valuable insights into how we might actually heal a person's disease instead of chasing after a patient's symptoms. We do this by studying the actual micro mechanical pathways of inflammation initiation, response, and mitigation. This avenue of evidenced based research has lead us to near solutions to not just a specific cancer, but many cancer's, not just one disease, but many similar disease processes. We are on the cusp of unlocking the door to true cellular healing. We have known about comorbidity ever since Feinstein defined it as "any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study". The patient's main singular disease is central to other diseases within the same patient, which are then treated secondary to this central disease. The integration of genetic, proteomic and metabolic datasets related to comorbidities improves our knowledge of disease etiology and phenotype – biomarker – genotype associations and builds a bridge between medical disciplines. What is 'Inverse Comorbidity'? Inverse comorbidity happens when one disease gives a certain patient a very low probability of developing the inverse comorbidity disease. Inverse Comorbidity is a paradoxical concept. Inverse Comorbidity is based on biological and non-biological factors that make it very highly unlikely for given groups of people against certain diseases. Neuro-protective factors in Central Nervous System disease process and anti-proliferative factors in cancer. Also, Alzheimer's disease seems able to protect against some cancers. There is a tradeoff between the risk of one disease and the protection from another with this 'Inverse Comorbidity' model. PARK2 is a putative tumor suppressor gene that might be down regulated in glioblastoma, colon cancer and lung cancer and it is over expressed in Parkinson's disease patient's brains. Down's syndrome is implicated in protecting against most solid tumors. Cancer protection in patients with Down's syndrome may be a result of the fluctuation of some basic aspect of tumor progression or growth. The evidence for this intriguing association and possible underlying mechanisms are an incalculably valuable chance to glean understanding into the pathogenesis of these diseases and learning why certain people with Central Nervous System diseases are protected against many different types of cancer and may help us develop new improved treatments, with a higher level of accuracy and precision. There are links with Alzheimer's disease and cancer. Certain signaling pathways in AD (Alzheimer's disease) and their connections to the cell cycle regulate the function of certain proteins which are also very important in cell cycle regulation and cancer formation. "p53 is a tumor suppressor diversified in both neuro developmental processes and neuro developmental disorders. 'Polymorphisms may lead to an increased susceptibility to cancer or schizophrenia. This tumor suppressor gene (p53) regulates the transcription of phosphatase and tensin homologue (PTEN), which negatively regulates AK1 Kinase, leading to a decrease in cell growth and a reversal of the cancer phenotype.' Never the less, we have just started to distinguish the specific molecular and cellular processes that the brain modulates multiple aspects of tumor genesis and progression, more research is desperately needed. When we glean insight into comorbidity of diseases we vastly improve the quality of life for all of us aging humans. We can accomplish this by studying the disease to disease relationships and their specific mechanisms of action. This is the main theme of understanding the relationship between the genome and the observable changes that arise from the interaction with the genotype and the environment. Studying inverse comorbidities gives us an excellent chance to find out the biological connections between the development of CNS diseases while protecting against cancer and vice versa. These knew views of disease interactions

not only help us with CNS and cancer diseases but may lead to the expansion in the knowledge of different inverse comorbidities with other specific diseases such as, obesity, hypertension and diabetes. These biological processes have a direct application in other research fields like nosology, genomics and systems medicine. A real benefit of investigating comorbidities and inverse comorbidities will be the development of a series of scientific and medical procedures that apply computational techniques to biological experimental studies. Inverse cancer comorbidities with CNS disorders are of great interest to us all. Increased research into these comorbidities and inverse comorbidities can improve medical practice and may allow us to create new clinical guidelines and recommendations for national health survey items, the reorganization of health services and the setting up of early medical comorbidities detection units [13].

In a review article Israël uses the inverse comorbidity of Alzheimer's disease and cancer, he shows us that we should 'preserve the methylation capabilities of cells, for avoiding cancer and Alzheimer's disease.' He found that if the methylation fails with a normal anti-oxidative defense, there is a cancer risk. Also, if the methylation deficit is associated to a poor oxidative defense. Then the Alzheimer's disease rather than cancer becomes possible. In this case, anti-oxidative treatments should be associated to the treatment of the methylation deficit and its consequences: if not, you will restore the cancer risk without healing the neurodegenerative disease [14].

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