ENERGY HOMEOSTASIS AND THE TUMOR/HOST INTERACTION: THE ROLE OF THE BRAIN pdf

1: Frontiers | Gut Microbiota: An Integral Moderator in Health and Disease | Microbiology

The defensive regulation of energy homeostasis by neural and endocrine systems is examined to evaluate the role of the brain in macroenvironmental metabolic control systems that help counterattack the aggressive tumor. Brain homeostatic mechanisms (neural and hormonal) discussed are those linked to metabolic rhythms, food intake and adiposity.

Energy homeostasis Save In biology, energy homeostasis, or the homeostatic control of energy balance, is a biological process that involves the coordinated homeostatic regulation of food intake energy inflow and energy expenditure energy outflow. Definition In the US, biological energy is expressed using the energy unit Calorie with a capital C i. But energy can be converted from one form of energy to another. So, when a calorie of food energy is consumed, one of three particular effects occur within the body: The internal heat produced is, in turn, mainly a sum of basal metabolic rate BMR and the thermic effect of food. External work may be estimated by measuring the physical activity level PAL. Imbalance Positive balance A positive balance is a result of energy intake being higher than what is consumed in external work and other bodily means of energy expenditure. The main preventable causes are: In time, overweight and obesity may develop, with resultant complications. Negative balance A negative balance is a result of energy intake being less than what is consumed in external work and other bodily means of energy expenditure. The main cause is undereating due to a medical condition such as decreased appetite , anorexia nervosa , digestive disease , or due to some circumstance such as fasting or lack of access to food. Hyperthyroidism can also be a cause. Requirement Normal energy requirement, and therefore normal energy intake, depends mainly on age, sex and physical activity level PAL. Human energy requirements Rome, 17â€”24 October An older but commonly used and fairly accurate method is the Harris-Benedict equation. Yet, there are currently ongoing studies to show if calorie restriction to below normal values have beneficial effects, and even though they are showing positive indications in primates[11][12] it is still not certain if calorie restriction has a positive effect on longevity for primates and humans. Society and culture There has been controversy over energy-balance messages that downplay energy intake being promoted by food industry groups. Energy Balance and Body Weight Regulation". A Human Perspective 3rd ed. Retrieved 9 January Sydor A, Brown RY, ed. A Foundation for Clinical Neuroscience 2nd ed. Orexin neurons are regulated by peripheral mediators that carry information about energy balance, including glucose, leptin, and ghrelin. Accordingly, orexin plays a role in the regulation of energy homeostasis, reward, and perhaps more generally in emotion. The regulation of energy balance involves the exquisite coordination of food intake and energy expenditure. Experiments in the s and s showed that lesions of the lateral hypothalamus LH reduced food intake; hence, the normal role of this brain area is to stimulate feeding and decrease energy utilization. In contrast, lesions of the medial hypothalamus, especially the ventromedial nucleus VMH but also the PVN and dorsomedial hypothalamic nucleus DMH , increased food intake; hence, the normal role of these regions is to suppress feeding and increase energy utilization. Yet discovery of the complex networks of neuropeptides and other neurotransmitters acting within the hypothalamus and other brain regions to regulate food intake and energy expenditure began in earnest in with the cloning of the leptin ob, for obesity gene. Indeed, there is now explosive interest in basic feeding mechanisms given the epidemic proportions of obesity in our society, and the increased toll of the eating disorders, anorexia nervosa and bulimia. Unfortunately, despite dramatic advances in the basic neurobiology of feeding, our understanding of the etiology of these conditions and our ability to intervene clinically remain limited. The energy homeostasis system comprises neurons in the mediobasal hypothalamus and other brain areas4 that are a part of a neurocircuit that regulates food intake in response to input from humoral signals that circulate at concentrations proportionate to body fat content An emerging concept in the neurobiology of food intake is that neurocircuits exist that are normally inhibited, but when activated in response to emergent or stressful stimuli they can override the homeostatic control of energy balance. Understanding how these circuits

interact with the energy homeostasis system is fundamental to understanding the control of food intake and may bear on the pathogenesis of disorders at both ends of the body weight spectrum. Insights from human brain imaging". Bloom December 14,

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2: Dissecting brain tumor growth and metastasis in vitro and ex vivo

The defensive regulation of energy homeostasis by neural and endocrine systems is examined to evaluate the role of the brain in macroenvironmental metabolic control systems that help counterattack.

Metabolic resilience promotes brain health and has the potential to prevent or reverse brain disease. A renewed and increasing interest in the relationship between metabolism and homeostasis is evident across multiple disciplines and has the potential to spawn new insights and therapeutic targets. For this Research Topic authors were encouraged to submit basic research on homeostasis and excitability as well as metabolic mechanisms associated with neurological diseases and novel treatment approaches based on metabolic and homeostatic interventions. This special issue features several papers examining molecular mechanisms involved in neural network homeostasis and higher brain function. Not surprisingly, dysregulation of those key metabolites is implicated in virtually every neurological condition, whereas therapeutic reconstruction of biochemical homeostasis has potential for disease prevention and cure Boison. A molecular link to basic biochemical mechanisms is further provided in an original research article that ascribes a specific role of the methionine cycle-associated enzyme enolase phosphatase 1 in apoptotic response mechanisms triggered by oxidative stress Zhang et al. The link between metabolic homeostasis and neuronal activity is evident in the relationship between ion homeostasis and energy demand of fast neuronal network oscillations associated with higher brain functionsâ€”including sensory perception, attentional selection, and memory formation and requiring timed synaptic excitation and inhibition with glutamate and GABA, respectively Kann et al. Fast neuronal network oscillations are characterized by high oxygen consumption and significant changes in the cellular redox state, indicating rapid adaptations in glycolysis and oxidative phosphorylation. A second review article highlights the complex role of glycogen and its role in brain energy and particularly synaptic plasticity Waitt et al. Exquisite sensitivity to metabolic stress is essential for adaptation and plasticity and confers vulnerability of higher brain functions to injury and disease. Advances in sequencing technologies led to the discovery of amino acid-recoding RNA editing in many gene transcripts. This mechanism points to the systemic relevance of the neurotransmitter receptor for glycine GlyR and possible clues to disease mechanisms. C-to-U RNA editing of GlyR-coding transcripts is increased in the hippocampus of patients with intractable temporal lobe epilepsy and can provoke completely different symptoms depending on the neuron type that is affected Winkelmann et al. APP seems to serve as a rheostat where too much or too little causes hyperexcitabilityâ€”suggesting that normalizing APP levels can address aspects of this pathophysiology. An analysis of post-traumatic brain injury cerebrospinal fluid finds that mortality at 6 months can be predicted by levels of cortisol and BDNF, particularly in younger people, and suggests a regulatory role for cortisol Munoz et al. Several articles look at changes mobilized by a metabolic therapy used to treat epileptic seizures for nearly years: In an original research paper, anxiolytic behavioral effects of ketone-based metabolismâ€”mobilized by administering a ketone ester to induce nutritional ketosisâ€”are reported in two rat strains Ari et al. A second original paper compared ketosis induced by exogenous ketones vs. Laboratory and clinical evidence is reviewed regarding the prevalence of dysfunctional mitochondria and altered metabolism in ASD alongside current limited but positive data on the role of ketogenic diets and metabolic therapy in reducing ASD symptoms and common comorbiditiesâ€”potentially via adenosine or other mechanisms Cheng et al. An original research article demonstrates that enhancing adenosine in brain through pharmacological blockade of the enzyme adenosine kinase prevents radiation-induced cognitive impairment in rats Acharya et al. This study shows that hASH1 suppresses neuronal differentiation by inhibiting transcription at the retinoic acid receptor element, highlighting hASH1 as a key determinant of neuroblastoma resistance to differentiation therapy Kasim et al. Metabolic therapy with a ketogenic diet is highlighted as a multifaceted therapy for glioma, particularly glioblastoma, and clinical and basic research is reviewed indicating that a metabolic approach may both limit tumor growth and augment the efficacy of chemotherapy

and radiation Woolf et al. Taken together, this research topic provides a cross-cutting perspective of the relationship between metabolism and homeostasis and showcases novel metabolic therapies to restore molecular and biochemical networks. The direct and potentially imminent clinical implications of several of these articles will be exciting to follow as the field moves forward. While a range of topics and mechanisms is featured herein, there is room for much more. Author Contributions All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication. Conflict of Interest Statement The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Identification of parvalbumin interneurons as cellular substrate of fear memory persistence.

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3: Gut Microbiota: The Brain Peacekeeper

In: Springer eBooks Summary: The present multi-volume Book Series, CANCER GROWTH AND PROGRESSION, encompasses the widest possible framework of cutting edge research in the field of neoplastic pathology and other integrated fields.

The gut microbiota interacts with various organs and systems in the body, including brain, lung, liver, bone, cardiovascular system, and others. Microbiota-derived metabolites such as the short chain fatty acid SCFA butyrate are primary signals, which link the gut microbiota and physiology. Moreover, several microRNAs participate in signaling networks through the intervention of the gut microbiota. The interaction between the gut microbiota and miRNAs plays a crucial role in vascular dysfunction and hepatocellular carcinoma HCC. In this review, we will report and discuss recent findings about the crosstalk between the gut microbiota and physical organs and how the gut microbiota and miRNAs regulate each other while influencing the host via genes, proteins, or metabolites. Introduction Growing investigations on hostâ€"microbe interactions have revealed that the gut microbiota is a critical mediator in maintaining health Holmes et al. The composition of gut microbiome is similar at the phylum level mainly Bacteroidetes and Firmicutes , but diversity and richness of species is variable between individuals Tremaroli and Backhed, Host genetics, environmental factors, diet, disease, stress, and some other factors decide the structure of the gut microbiota Shukla et al. Physiological energy homeostasis could be regulated by microbiota. For example, Donohoe et al. In addition, physiological homeostasis may be disrupted by the microbiota, resulting in disruption of host metabolism, immune dysregulation, neurological and cognitive dysfunction and others Roy and Trinchieri, This disrupted status would cause a series of disorders, including obesity, diabetes, autoimmunity, allergy, inflammatory bowel disease IBD and cancer Holmes et al. Emerging data of the gut microbiota reveal that the microbiota is involved in diverse diseases via gutâ€"brain axis Baruch and Schwartz, ; Mu et al. It has been found that microbiota-produced butyrate regulated hepatic cell apoptosis and proliferation by inducing miR expression Pant et al. The research about gut microbiotaâ€"miRNA interaction has revealed that the gut microbiota could be regulated by host-secreted miRNAs and the gut microbiota may affect the host via inducing miRNAs Liu et al. The gut microbiotaâ€"miRNAs-diseases axis could serve as a new direction for future investigation. In this review, we summarize the physiological and pathological functions of the gut microbiota including signals from gut to other organs. Specifically, we highlight the new functions about the gut microbiota in diseases and how the gut microbiota monitors the host status by governing special miRNAs. Microbeâ€"Host Communication in Disease Since the gut microbiota settles in gastrointestinal tract, it is unsurprising that microbiota contributes to regulating intestinal diseases Holmes et al. However, emerging evidence indicates that the microbiota is implicated in extraintestinal organs due to the difference of microbiota composition. More substantially, communication pathways between the gut and other organs are mediated by direct neuronal contact, enteroendocrine cells, immune cells and microbial metabolites Schroeder and Backhed, Part of cell signaling pathways in the process has been presented in Table 1. It is pivotal to explore how the microbiota communicates with host and develops disease. These relevant investigations will be revealed as follows. Gut microbiota influences cell signaling pathways in diseases. Gut Microbiota and Intestinal Disease The gastrointestinal tract is an extremely complex organ system. De Filippo et al. In parallel, Enterobacteriaceae Shigella and Escherichia were higher in European children than that in Africa children De Filippo et al. Nucleotide-binding oligomerization domain-containing protein 2 one of the genes associated with IBD risk allele count increases with Enterobacteriaceae relative abundance, which may well explain the higher occurrence of IBD in Europe than that in Africa Farrokhyar et al. Intestinal microbial composition is also a common factor in CRC. Members of Fusobacteria has been identified as pro-inflammatory via recruiting myeloid-derived tumor-infiltrating immune cells such as tumor-associated macrophages TAMs , dendritic cells DCs , and myeloid-derived suppressor cells MDSCs Kostic et al. In addition, the gut microbiota

affects the host via the immune system or metabolites. However, LTA-deficient Lactobacillus acidophilus inhibited inflammation and could prevent against colon cancer, colitis and polyposis Yang et al. Overall, paying attention to the roles that the gut microbiota plays in regulating immune responses and tumorigenesis in the gastrointestinal tract will be necessary for disease prevention. Microbiotaâ€"Gutâ€"Brain Axis in CNS Adaptive immunity especially T cells and innate immune system contribute to gutâ€"brain communications via regulation of immune activity and the production of proinflammatory cytokines in IBD, irritable bowel syndrome IBS and functional dyspepsia Leue et al. The microbiota composition changes due to aging and environmental factors, while function of the intestinal mucosal barrier reduces, and bacterial amyloids and lipopolysaccharides LPSs systemically leak with increasing age. These toxins are translocated to the CNS due to the increase of bloodâ€"brain barrier permeability associated with aging. At the same time, gut dysbiosis affects amyloid beta peptide physiology possibly by changing energy metabolism and insulin resistance. Microbial metabolites produced by an imbalanced microbiota aggravated and participated in the pathogenesis of certain neurologic conditions. Accurate identification of relevant flora and metabolites may benefit from the discovery of new drug targets. Currently, very limited data about the interactions of the microbiotaâ€"gutâ€"brain from human studies exist. The roles of the microbiotaâ€"gutâ€"brain axis in CNS are highly plausible. New animal and clinical studies may provide novel approaches for prevention and treatment of mental illness Fung et al. NAFLD has been the extremely frequent origin of chronic liver disease with growing obesity. Hepatic gluconeogenesis could be controlled by the gut microbiota. Probiotics induced hepatic gluconeogenesis while caecal microbiota from obesity reduced markers of hepatic gluconeogenesis Nicolas et al. Recent report showed the mechanistic link between microbiota and hepatocellular carcinogenesis Xie et al. The report revealed that sex-based disparity in liver carcinogenesis is associated with the gut microbiota, bile acids, and tumor-suppressive microRNAs miRa, miRa-1, miR, miR, miR, and miRb in male and female mice treated with the streptozotocin-high fat diet STZ-HFD. Microbiota regulated bile acids and microRNAs promoting the hepatocellular carcinoma HCC in a male mouse model, however, the regulatory mechanism is unclear. Elevated levels of farnesoid X receptor FXR , a bile acid nuclear receptor, in female mice may increase expression of miRa, miRa-1, and miR, as the suppressors in liver cancer, possibly resulting in a lower risk of developing liver cancer in female mice Xie et al. Additionally, butyrate from microbiota induces apoptosis through up-regulation of miR expression and repression of sirtuin1 Sirt-1 expression in hepatic cells Pant et al. FXR plays a pivotal role in host liver metabolism, including liver regeneration, hepatoprotection, prevention of NAFLD and hepatocarcinogenesis Wang et al. Microbiota and Gutâ€"Lung Axis The study about gutâ€"lung axis is in the initial stage, but it may potentially serve as a new direction for lung disease treatment Budden et al. Asthma is a relatively stubborn bronchial disease. In childhood asthma, it may be closely related to decreasing relative abundance of the genus Faecalibacterium, Lachnospira, Veillonella, and Rothia and altered metabolites Arrieta et al. Microbiota-accessible carbohydrates particularly dietary fermentable fiber can shape the lung immunity via changes in the microbiota and increase in SCFAs Gray L. Propionate is capable of improving the bone marrow hematopoiesis of DC precursors. Furthermore, these DCs were in a position to stimulate T helper type 2 effector cells in the lung. The propionate-mediated mechanism may well protect lung from allergic airway inflammation and this process depends on GPR41 Trompette et al. In summary, T cell receptor signaling may be the primary pathway in the communication between gut and lung. Gut Microbiotaâ€"Bone Axis The gut microbiota is responsible for bone physiology, and it can regulate bone mass via the immune system and promote bone resorption and formation via SCFA production Ohlsson and Sjogren, ; Yan et al. In detail, the increased bone mass in germ-free animals was associated with a reduction in inflammatory cytokine expression in bone and less osteoclastogenesis. The change of the gut microbiota composition caused by dietary changes, antibiotic treatments or pathogens induces the imbalance in metabolic and immune regulatory networks, affecting bone mass Ohlsson and Sjogren, Probiotics and prebiotics, especially Lactobacillus and galactooligosaccharide, regulate bone metabolism and promote bone growth by altering the gut microbiota composition and

maintaining or increasing mass Britton et al. Galactooligosaccharide may improve calcium absorption and increase the relative proportion of bifidobacteria in the gut microbiota, possibly resulting in increasing bone mass Whisner et al. The mechanisms involved the gut microbiota regulation of bone should be further investigated, since it might be a promising therapeutic theory for bone disease such as osteoporosis, osteoclastic bone resorption and rheumatoid arthritis. Both microbiota and miRNAs play key roles in health and disease. The gut microbiota-miRNA interactions comprise two processes: These physiological processes are linked to host health. They play essential roles in nutrient absorption and hormone production, maintaining intestinal homeostasis Peck et al. Moreover, when the microbiota communicates with other tissues, the intestinal epithelium is the first transmission channel for gut microbial signals Schroeder and Backhed, A recent report showed that miRNAs could possibly enter the bacteria within endocytosis in in vitro experiments Zhao et al. Therefore, it could be believed that these intestinal miRNAs from IEC or other tissues might shape the gut microbiota and then induce dysbiosis. Quantified miRNA analysis among germ-free, conventionalized and conventionally raised chow-fed animals was achieved by miRquant. It was found that expression of some miRNAs are different among IEC subtypes and the difference depends on microbial status. Similarly, Nakata et al. However, there is no direct evidence showing how the microbiota regulates miRNAs. Possible mechanisms are based on the regulation of bacterial endotoxins and some metabolites or immune or mesenchymal cells signaling. A Gut microbiotaâ€”miRNAs interactions in intestinal epithelial. B Postulated pathway through which the gut microbiota governs vascular endothelial dysfunction via altertion of miR C The gut microbiota regulates macrophage cholesterol efflux and atherosclerotic lesion via down regulation miRb. E SCFA butyrate from microbiota induced apoptosis and inhibited proliferation through up-regulation of miR and repressing Sirt-1 expression in hepatic cells. Gut Microbiotaâ€”miRNA Interactions and Liver Disease The gut microbiota promotes or suppresses liver disease, where, part of the alterations were attributed to the interaction between microbiotaâ€”miRNAs. Differential expression of bile acid synthesis, transport genes, and differential accumulation of hepatic bile acid between female and male mice resulted in a sex-dependent incidence of liver carcinogenesis Xie et al. Also, these altered miRNAs could possibly interfere with other signaling pathways affecting homeostasis. Further studies are needed to explore the signaling molecules from the gut microbiota to miRNAs and bile acid, and may provide a novel perspective to treat HCC with sex-based disparity. Butyrate produced by the microbiota in vivo is involved in numerous functions of host physiology, including tumor suppression. The mechanisms by which butyrate suppresses tumor progression are different depending on the type of cancer cells Stilling et al. They found that butyrate upregulated miR expression, followed by SIRT-1 downregulation, resulting in hepatic cell apoptosis. Although the proposed mechanism needs to be confirmed in vivo, it supplied valuable information for HCC treatment. Altered gut microbiota has been linked to various diseases. For example, further in vivo studies need to be performed to confirm the function of the gut microbiota-mediated miR expression in liver cancer. Insight into the mechanisms of CNS diseases based on the microbiota gutâ€”brain axis will provided a new research direction for studying CNS diseases. In addition, the gut microbiota, directly or indirectly, maintains homeostasis in many organ systems, but the mechanisms remain to be studied in detail. To conclude, the gut microbiota has physiological and pathological functions. Further investigation of the physiological function of the gut microbiota may supply promising and effective treatments in complex diseases. Author Contributions QF wrote the manuscript. Conflict of Interest Statement The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Acknowledgments We apologize to colleagues whose work could not be cited due to space limitations.

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4: Faculty | UIC Physiology

Host genetics, environmental factors, diet, disease, stress, and some other factors decide the structure of the gut microbiota (Shukla et al.,) while the microbiota dictates host's health and diseases via genes, proteins or metabolites (Van de Wiele et al.,). Physiological energy homeostasis could be regulated by microbiota.

Received Nov 15; Accepted Mar 4. The use, distribution or reproduction in other forums is permitted, provided the original author s or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms. This article has been cited by other articles in PMC. Abstract Gut microbiota regulates intestinal and extraintestinal homeostasis. Accumulating evidence suggests that the gut microbiota may also regulate brain function and behavior. Here, we review recent discoveries on the role of the gut microbiota in central nervous system-related diseases. We also discuss the emerging concept of the bidirectional regulation by the circadian rhythm and gut microbiota, and the potential role of the epigenetic regulation in neuronal cell function. Microbiome studies are also highlighted as crucial in the development of targeted therapies for neurodevelopmental disorders. Gut microbiota is functionally diverse and participates in carbohydrate metabolism, fiber degradation, and immune maintenance. In addition, gut microbiota has also been implicated in regulating neurophysiological-governed behaviors, such as stress, autism, pain, and multiple sclerosis Cryan and Dinan, Gut microbiota is found to regulate the neurophysiological behaviors through immune, endocrine and neural pathways Collins et al. It is now clear that the gutâ€"brain communication is bidirectional. On one hand, changes in the microbial community affect behavior. On the other hand, perturbations in behavior alter the composition of the gut microbiota Collins and Bercik, However, the microbial community is affected by many environmental factors and host-related factors physiological status; Lozupone et al. Since changes in the composition of the gut microbiota are associated with the behavioral and cognitive alterations Cryan and Dinan, , a healthy microbiota community is essential for a normal regulation of the microbiotaâ€"gutâ€"brain axis. Among the potential factors regulating the axis, microbial metabolites may be the major mediators Cryan and Dinan, Gut Microbiota and Factors that Drive Variations in Microbiota Composition The gut contains more than 1, bacterial species, as being identified by culture-independent approaches Rajilic-Stojanovic and de Vos, Firmicutes and Bacteroidetes are the predominant phyla Collins et al. The distribution of the gut microbiota shows the spatial and temporal variation in both humans Eckburg et al. The complexity of the microbial community, together with its diversity, stability, and resilience, enables the gut microbiota to adapt readily to the gut environment Lozupone et al. A typical mutualism interaction is the degradation of fiber in the gut. Fiber degradation occurs through a mutualism interaction with the host, whose digestion system itself does not have this function Velasquez-Manoff, To complement the deficiency, intestinal microbes use glycoside hydrolases and polysaccharide lyases to degrade the fiber into short-chain fatty acids while these acids benefit the host El Kaoutari et al. The resilience ability is also an important property of the gut microbiota. The ability of certain microbiota members which dephosphorylate lipopolysaccharide LPS is important for the microbiota resilience during inflammation-induced disturbance Cullen et al. Within the gut microbiota, some members, such as Lactobacillus and Bifidobacterium species, are widely used as probiotics to promote intestinal homeostasis Bron et al. Others, such as Akkermansia muciniphila Derrien et al. Clearly, the gut microbiota adapts well in the gut with varying functions. Identification and clarification of these functions provide the basis for manipulating microbiota in order to maintain homeostasis and contribute to setting the targets for developing the therapy against disorders. Take the genotype as an example, the inbred mice with different genetic backgrounds own different composition of the gut microbiota in the cecal lumen Campbell et al. Diet is known to affect the composition of the gut microbiota. We find that a high-protein diet alters the colonic microbiota in rats Mu et al. In pig models, the pig breed Yang et al. Other studies which use a pig model, the composition

of the gut microbiota from different sites, such as the lumen and epithelial wall, varies, as well as their ability to utilize amino acids Dai et al. Pathogen infection also changes the microbial community. Citrobacter rodentium infection increases the abundance of Enterobacteriaceae in the colon of mice Lupp et al. A recent research shows that feeding patterns alter the daily cyclical composition of the gut microbiota in mice Zarrinpar et al. These facts indicate that multiple variables affect the composition of the gut microbiota. Additionally, the aforementioned factors can also affect the intestinal function, enteric nervous system ENS function, and central nervous system CNS function.

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5: Energy homeostasis | Revolvy

These commensal microbes are important for the normal development of the host immune system and alteration of the microbiota of gastrointestinal system has been found to play an important role in the development of obesity, metabolic syndromes such as type 2 diabetes, and cardiovascular diseases.

How to cite this article: Dissecting brain tumor growth and metastasis in vitro and ex vivo. J Cancer Metastasis Treat ;2: Abstract Local infiltration and distal dissemination of tumor cells hamper efficacy of current treatments against central nervous system CNS tumors and greatly influence mortality and therapy-induced long-term morbidity in survivors. A number of in vitro and ex vivo assay systems have been established to better understand the infiltration and metastatic processes, to search for molecules that specifically block tumor cell infiltration and metastatic dissemination and to pre-clinically evaluate their efficaciousness. These systems allow analytical testing of tumor cell viability and motile and invasive capabilities in simplified and well-controlled environments. However, the urgent need for novel anti-metastatic therapies has provided an incentive for the further development of not only classical in vitro methods but also of novel, physiologically more relevant assay systems including organotypic brain slice culture. In this review, using publicly available peer-reviewed primary research and review articles, we provide an overview of a selection of in vitro and ex vivo techniques widely used to study growth and dissemination of primary metastatic brain tumors. Furthermore, we discuss how our steadily increasing knowledge of tumor biology and the tumor microenvironment could be integrated to improve current research methods for metastatic brain tumors. We believe that such rationally improved methods will ultimately increase our understanding of the biology of brain tumors and facilitate the development of more efficacious anti-metastatic treatments. Primary brain tumor; metastasis; in vitro model system; cell migration; organotypic brain slice culture Introduction Impressive achievements in genomic and epigenomic analyses of tumor tissues and individual tumor cells have revolutionized our understanding of primary brain tumors. Alterations detected on the genome or transcriptome level in large patient cohorts in combination with our increasing understanding of epigenetic gene regulation have disentangled apparently identical brain tumors as related but functionally different tumor entities. However, in order to translate this still growing knowledge into clinical applications targeting the tumor phenotype, sophisticated model systems are necessary to explore and validate potential interference strategies under physiologically relevant conditions. In addition, functional genomics and cell-based molecular analyses are indispensable in many cases to clarify whether mutated or amplified genes are necessarily contributory to an altered proteome and causative for the cancerous phenotype. Moreover, the current wealth of genomic and transcriptomic data is insufficient on its own to isolate specific signaling networks driving tumor progression from a benign lesion to a disseminated cancer. Hence, to tackle the complexity of the metastatic process it is necessary to dissect it into individual steps that can be addressed with rationally adapted model systems. In this review we focus on in vitro and ex vivo primary brain tumor model systems and discuss how they can be improved and used to develop the molecular understanding necessary for designing novel anti-metastatic therapies. While none of these model systems on its own will suffice to tackle such a complex disease as cancer, they can effectively guide our search for efficacious and less toxic therapies and instruct the design of appropriate in vivo studies. It is triggered by the transient or permanent induction of motility and invasiveness in the tumor cells. An essential prerequisite for primary brain tumor cell migration and invasion is the remodeling of the actin and tubulin cytoskeletons,[ ] which not only provide force, traction and rigidity but also scaffold signaling complexes in a spatially controlled manner. In a seminal review by Giese et al. Consequently, the authors concluded that an approach to influence the underlying mechanisms could be the basis of novel anti-invasive therapy strategies. A computational modeling study predicts that even a small increase in the motile capability of tumor cells, and the consequent short-range dissemination, increases net tumor growth and resistance to targeted therapy[14] [Figure 1]. Indeed, targeting

tumor cell motility and invasiveness as a strategy against metastasis is an emerging theme in cancer research,[ ] and the pro-migratory phenotype in tumor cells has been addressed in the past by a number of approaches that impair cell autonomous migration, cell-cell communication, cell-cell or cell-matrix interaction [15] and references therein. This research led to the development of a number of clinical trial studies for solid tumors with approaches inhibiting various components of the aforementioned pro-migratory determinants. Model of growth, progression and dissemination of primary brain tumors. The progression of primary brain tumors from a small neoplastic lesion to a metastasizing tumor through growth and dissemination of tumor cells is schematically visualized. The mode of tumor cell growth and dissemination varies between different tumors and involves random or guided, single or collective dissemination of tumor cells. The model depicting low range dissemination at early stages and the consequent increased net tumor growth is according Waclaw et al. This lack of adequate anti-dissemination therapies is due in part to the complexity of the cell migration process itself and the redundancy of the signaling that controls its mechanics. Additionally, tumor cells exploit mechanisms that normally direct physiological movements. However, the addiction of tumor cells to druggable pathways and our increasing understanding of cell mechanics and its control offer room for therapeutic interventions targeting tumor cell dissemination specifically. The following paragraph will briefly discuss some relevant aspects of the still poorly understood interaction between the cells of primary brain tumors and their cellular host environment. Biophysical properties of the brain microenvironment Mammalian cells are sensitive to biophysical and chemical signals emanating from the surrounding matrix environment, the extracellular matrix ECM , which can influence their behavior. It depends on the elastic modulus or compliance of its constituting material e. Thus, the stiffness of the ECM depends on its components and their elastic modulus. As the parenchyma of the brain is mostly devoid of fibers with a high elastic modulus such as collagen or fibronectin fibrils, its stiffness is very low compared to the ECMs in other tissues of the human body. The basic constituents of the brain ECM are glycosaminoglycans with their most prominent member hyaluronan Hyaluronic acid, HA , link proteins, lecticans and tenascins. The distribution and composition of these ECM components in the developing rodent brain is changing during embryonal and postnatal phases and reaches a mature stage at postnatal day Relatively little change in the expression levels of a small set of proteins in normal brain tissue and in brain tissue surrounding invasive glioblastoma was observed in a recent study,[29] except for Tenascin-R and CD, which were both up-regulated. Matrix stiffness regulates proliferation and motility of Glioblastoma multiforme GBM cells[30] and the increase of ECM stiffness through fiber crosslinking by the product of the LOX gene causes their enhanced integrin-dependent invasion. Hence, the impact of matrix stiffness on the migratory behavior should always be investigated in the context of the cognate receptors. Whether matrix stiffness could exert a selective pressure on brain tumor cells contributing to the altered genetic landscapes is still poorly understood. One potential sensor and transducer of matrix stiffness in brain tumors is the HA receptor CD44, which was identified in GBM to facilitate invasiveness in stiff matrices. Microglia are involved in first-line innate immunity in response to brain injury, when they convert to an active proliferating, migrating and phagocytic phenotype. Microglia are outnumbered by astrocytes, which account for nearly half of all cells resident in the brain. Astrocytes respond to brain injury and tumor growth in a process named reactive gliosis. On the one hand, reactive gliosis and the associated secretion of growth factors and cytokines help repairing injury in the CNS. Current in vivo model systems to address functions of metastatic primary brain tumors Preclinical evaluation of novel anti-metastatic therapy strategies in animal models will remain an essential step towards the development of novel therapeutics. However, cell culture models are instrumental for deciphering essential morphological and functional aspects of the biology that drives neoplastic lesions into disseminated diseases. They also provide essential insights for designing appropriate animal models and help elucidating the causes that may underlie controversial outcomes of in vivo studies. Although a general trend towards 3D model systems can be noted, a majority of experiments in tumor-related research are still conducted in 2D settings. For a general, in depth description and comparison of 2D versus 3D culture systems, the reader is referred to Zimmermann et al. A series of

excellent reviews have recently described in depth the use of 3D tissue culture model systems in pathophysiology[49] and high-throughput drug candidate toxicity analysis,[50] to identify tumor-specific signaling pathways and biomarkers,[51] and to determine growth determinants for drug target discovery. To understand the causes and consequences during pathophysiological progression from a primary neoplastic lesion in the brain towards a metastatic cancer and to pre-clinically test potential intervention strategies, we thus require model systems that mimic not only the proteomic heterogeneity of the tumor cell itself but also the reciprocal interactions between the tumor and the receiving brain tissue [Figure 2]. The following paragraph provides an overview over some recent approaches in primary brain tumor research. It highlights the difficulty to design an optimal, tumor-adapted system and emphasizes the need to further improve currently used systems. Tumor cell growth, survival and dissemination are governed by extrinsic and intrinsic parameters. Tumor cells are under the spheres of influence of intrinsic and extrinsic parameters. Colored ovals represent various degrees and manifestation patterns of such parameters, which dramatically increase in number and complexity in the organotypic environment Click here to view 2D and 3D model systems in primary brain tumor research A number of articles have been published in the last few years that used in vitro model systems to evaluate effects of novel potential treatment strategies on growth, viability or motile behavior of primary brain tumors [Table 1]. A general consensus has been reached in that 3D cell culture model systems reflect the specifics of the in vivo situation better compared to 2D model systems. On the down side of this was the lack of high-throughput capability of 3D methods that hampered until a few years ago their broader use in combination with in screening approaches. A milestone in this context was the generation of spheroid cultures in 96 or even well format from primary brain tumors that allowed the parallel testing or large sample sizes. A general protocol describing the reproducible establishment and microscopy-based analysis of spheroid cultures using fluorescent protein quantification in high throughput was described recently. Using different combination of dyes to separate subpopulation of cells grown in co-culture combined with diagnostic flow cytometry and two-photon microscopy allowed to further refine the selective output of 3D methods. Studies using 3D primary brain tumor model systems Click here to view The impact of the embedding matrix on the behavior of the tumor cell The choice of the embedding matrix is of outmost importance for 3D cultures, in particularly for primary brain tumors that encounter in vivo mostly brain parenchyma and collagen-rich surfaces and structures in the subarachnoid space. In this context, Fernandez-Fuente et al. They found that GSCs grown in collagen-based 3D conditions were markedly less susceptible to receptor tyrosine kinase inhibition by currently available inhibitors, suggesting that oncogene addiction of tumor cells could also be bypassed by adhesion signaling. Primary cells from glioma patient tumor material exposed to increasing concentrations of HA responded with rounded morphology and reduced migration, suggesting that HA concentrations may affect glioma cell behavior. However, the finding that increasing matrix stiffness - by adding agarose to a collagen I matrix - blocks glioma invasiveness,[19] suggested that stiffness alone and independent of ligand binding acted as a critical determinant for primary brain tumor cell function. An improved in vitro environment for brain tumor research would consist of neuronal and brain-resident interstitial cells that secrete the brain-specific ECM components into which the brain tumor cells can then be implanted. Such an environment was established from brain tissue extracts on micro filters Hi-spots on which GBM cell sensitivity to anti-proliferative compounds was tested. A while ago, a simple but intriguing co-culture model of medulloblastoma and leptomeningeal cells was published, and it indicated paracrine, growth-promoting effects of latter that might be instrumental for studying the notoriously difficult to grow primary tumor cells in vitro. An interesting approach to evaluate the effect of metabolic activity on cytotoxicity of compounds and chemotherapeutics in vitro was tested by Ma and colleagues using a 3D micro-tissue perfusion system. Analogous experimental follow-ups are a number of organ on a chip technologies that are currently developed for assaying different disease states[69] and testing drug effects and metabolization. Rho-family GTPase-FRET fusion protein-expressing glioma cells were orthotopically implanted in rat brains and later analyzed inside brain slice cultures derived of these brains using two-photo

microscopy. This study revealed higher Rac1 and Cdc42 and lower RhoA activities in glioblastoma cells penetrating the brain parenchyma than those advancing in the perivascular regions, and suggested that different driver mechanisms could exist for single cell dispersion in glioma. Together, these studies highlight the need for adapting the model system to the specifics of the biological context, with the consequent inclusion of biophysical or chemical components that best reflect the in vivo situation. Besides high-throughput screening platforms for the identification of novel pro-metastatic key players or alternative interference strategies against metastatic dissemination, we also need improved phenotype-based single cell analysis to decipher clonal differences and micro environmental impact on tumor behavior at the single cell level. Organotypic brain slice culture OBSC in primary brain tumor research A number of causal gene s and associated genetic mutations, molecular changes, probable targets and treatments for a variety of primary brain tumors have been identified. Despite of this, the process of dissemination, metastasis of the tumor cells from the primary site, and tumor recurrence, which is the leading cause for brain tumor related mortality in patients, remain obscure. Total removal of the primary tumor is on many occasions impossible at the microscopic level due to the insidious infiltration of the tumor cells into the surrounding brain tissue. Standard 3D in vitro invasion assays use ECM macromolecules that mimic the basement membrane e. These assays described above and in table 1 although quick, reliable, commercially available and easy to perform, have several limitations. This is further emphasized by the fact that distinct types of brain tumors localize within specific regions of the brain, highlighting the need for different microenvironments for modeling tumor growth and invasiveness. To circumvent this, mouse models have been generated for studying tumor propagation via orthotopic or subcutaneous xenografting of tumor cells. These experiments, however, are ethically controversial if inappropriately conducted, costly, labor intensive and need lengthy time periods for animal surgery and subsequent tumor development especially for low grade tumors. These challenges and limitations highlight the need for developing a novel system wherein living brain tissue can be used as an ideal matrix for studying tumor cell growth and invasion. An excellent overview of 3D organotypic cultures has recently been provided,[73] which describes their potentials as experimental systems to visualize cellular mechanisms that drive tissue development, to study the genetic regulation of cell behaviors in tissues and to evaluate the role of micro environmental factors in normal development and disease. One hallmark of organotypic cultures is the tissue environment mimicking the structural and functional specifics of the organ of origin. This turns them into attractive models for cancer research to explore tumor host tissue interactions and to advance therapeutic approaches. Organotypic brain slice culture for visualization and quantification of brain tumor cell dissemination OBSCs allow culture, maintenance and long-term survival of sections from any tissue of the CNS. OBSCs have been widely used in the field of neurobiology for synaptogenesis, neurogenesis, myelin formation, as models for studying neurodegeneration, for neuroprotective and neurotoxic assays, etc. Indeed, Jung et al. After 24 h, control human astrocytoma cells stably expressing enhanced GFP or GFP-RHAMM receptor for hyaluronan-mediated motility transfected astrocytoma cells were placed in a small centrally punched-out hole in the slice. The infiltration and migratory behavior of the GFP-expressing astrocytoma cells could be easily studied using confocal laser scanning microscopy CF-LSM up to 30 days post implantation. The authors were able to demonstrate that different astrocytoma cell lines display different degrees of invasion and that the migration of the human astrocytoma cells could be stimulated or, using antisense targeting strategies, specifically blocked. They offer several advantages: The slices were then co-cultured with C6 glioma cells labeled with PKH2 fluorescent dye.

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6: Blood-Brain Barrier Integrity and Breast Cancer Metastasis to the Brain

In humans, the brain accounts for ~2% of the body weight, but it consumes ~20% of glucose-derived energy making it the main consumer of glucose (~ mg glucose per g human brain tissue per minute). Glucose metabolism provides the fuel for physiological brain function through the generation of ATP, the foundation for neuronal and non-neuronal cellular maintenance, as well as the generation of neurotransmitters.

 A key event of brain metastasis is the migration of cancer cells through the blood-brain barrier BBB. Although preventing brain metastasis is immensely important for survival, very little is known about the early stage of transmigration and the molecular mechanisms of breast tumor cells penetrating the BBB. The brain endothelium plays an important role in brain metastasis, although the mechanisms are not clear. BMECs are joined together by intercellular tight junctions TJs that are responsible for acquisition of highly selective permeability. Failure of the BBB is a critical event in the development and progression of several diseases that affect the CNS, including brain tumor metastasis development. Here, we have delineated the mechanisms of BBB impairment and breast cancer metastasis to the brain. Understanding the molecular mediators that cause changes in the BBB should lead to better strategies for effective treatment modalities targeted to inhibition of brain tumors. Introduction Breast cancer patients often develop metastatic lesions in the brain [1 , 2]. The development of CNS metastasis in patients with solid malignancies represents a turning point in the disease process. The prevalence of CNS metastasis from breast cancer may be increasing due to improved systemic therapy for stage IV breast cancer. The standard treatment for multiple brain lesions remains whole-brain radiation for symptom control, with no improvement in survival. The therapy for a single brain metastasis remains either surgery or radiosurgery, with conflicting information as to the benefit of prior whole-brain radiation. To metastasize to the brain, breast cancer cells must attach to microvessel endothelial cells and then invade the blood-brain barrier BBB , which constitutes the endothelium and the surrounding cells. The BBB is a unique anatomical structure that is mainly defined by tight junctions and adherens junctions between the brain endothelial cells, that strictly regulate the flow of ions, nutrients, and cells into the brain [3 , 4]. Compared with endothelial cells from other vascular beds, brain microvascular endothelial cells BMECs characteristically have very low permeability to solutes, high electrical resistance, complex tight junctions, and an array of transport systems that both supply the brain with nutrients and eliminates byproducts of brain metabolism. The low permeability is also important in protecting the brain from toxins circulating in the blood and restricting the migration of leukocytes and monocytes. The BMECs form an active permeability barrier and transport system known as the BBB, which is instrumental in the control of the brain fluid milieu. A widely supported hypothesis is that tumor cell adhesion to endothelium induces a retraction of the endothelium, which exposes the vascular basement membrane to the tumor cells. Numerous studies have shown that tumor cells recognize and bind to components in the vascular membrane, thereby initiating extravasation and the beginning of new growth at secondary organ sites. The impairment of the BBB was observed recently in breast cancer patients who developed metastasis to the brain [5]. The BBB is a highly selective diffusion barrier at the level of the cerebral microvascular endothelium, characterized by the presence of mainly tight cell-cell junctions, adherens junctions and lack of fenestrations Figure 2. The BBB regulates bidirectional control over the passage of a large diversity of regulatory proteins, nutrients and electrolytes, as well as potential neurotoxins [7 , 8]. Figure 1 Figure 2: Increased BBB permeability can be either a consequence of the pathology or a precipitating event [7 , 8]. Impairment of the BBB leads to an increase in permeability and formation of edema. Inflammatory mediators such as histamine, bradykinin, and Substance P cause increase in permeability of BBB in vivo, which results from the rapid formation of endothelial gaps [7 , 8]. The interendothelial space of the cerebral microvasculature is characterized by the presence of a junctional

complex that includes adherens junctions AJs , tight junctions TJs and Gap junctions [8] see Figure 3. Whereas gap junctions mediate intercellular communication, both AJs and TJs act to restrict the permeability across the endothelium. AJs are ubiquitous in the vasculature and mediate the adhesion of endothelial cells to each other, contact inhibition during vascular growth and remodeling, initiation of cell polarity and partly the regulation of paracellular permeability. The primary component of AJs is VE-cadherin. The TJs are the main components that confer the low paracellular permeability and high electrical resistance. TJs are elaborate structures that span the apical region of the intercellular cleft of endothelial barrier tissues. The TJs are composed of a complex of belt-like zonula occludin, which is localized close to the lumen of the capillary. Interestingly, brain microvascular endothelial cells do not express ZO-3 [8]. Proposed molecular organization of blood-brain Barrier tight junctions [9]. The ZO proteins are involved in the coordination and clustering of protein complexes to the cell membrane and in the establishment of specialized domains within the membrane [3]. ZO-1 links transmembrane proteins of the TJ to the actin cytoskeleton. The primary cytoskeletal protein, actin, has known binding sites on all ZO proteins and on claudins and occludin. Actin filaments serve both structural and dynamic roles in the cell. ZO-1 binds to actin filaments and to the C-terminus of occludin and claudins, which couples the structural and dynamic properties of perijunctional actin to the paracellular barrier. The numerous pathways by which specific TJ proteins are regulated and the specific effects of certain pathologies on tight junction TJ proteins strongly suggest that therapies targeted to components of the TJ complex and its modulators for the treatment and prevention of breast metastasis to the brain and development of brain tumors are a promising avenue that needs to be explored. Genes That Mediate Breast Cancer Metastasis to the Brain The molecular mediators that influence metastasis in distant sites appear to vary by organ Figure 4. In malignancies of the breast, cancer cells enter a prolonged period of latency before they gain competence to colonize and produce organ-specific metastases [10 â€” 12]. During this period of time, disseminated cancer cells may acquire distinct sets of metastasis functions depending on the target organ [13 , 14]. Despite the various infiltration and colonization functions, the general process of metastasis can be broken down into local invasion, intravasation, survival in the circulation, extravasation and colonization [15] Figure 5. After intravasation the cancer cells need to survive in the circulation, travel to specific target organs and extravasate into a microenvironment where they can colonize as secondary tumors [15]. Searches for genetic determinants of metastasis have led to identification of gene signatures that selectively mediate breast cancer cell metastasis to bones, the lungs, and the brain [13 â€” 15]. The barriers to metastasis are distinct in organs. To colonize the brain parenchyma, invading tumor cells must penetrate the blood-brain barrier BBB. Brain capillary walls are more difficult to penetrate due to a tight layer of endothelial cells, tight junctions, and astrocyte foot processes [10 , 16]. Functional validation of these genes provided clues as to how cancer cells can penetrate the BBB and initiate tumor growth in brain vasculature. A brain metastasis signature BrMS consisting of 17 genes was created using genomic profiling and univariate analysis. Comparison of the BrMS with the lung metastasis signature LMS showed an overlap of genes between signatures, but not in the bones or liver. Pathogenesis of cancer metastasis: The outcome of each step is influenced by the interaction of metastatic cells with homeostatic factors. Each step of the metastatic process is considered rate limiting in that failure of a tumor cell to complete any step effectively terminates the process. Therefore, the formation of clinically relevant metastases represents the survival and growth of unique subpopulations of cells that preexist in primary tumors. Schematic presentation of tumor cell penetration across the BBB. The time point of interest, referencing current knowledge of metastatic progression, lies in the events between extravasation into distant tissue and any subsequent neoangiogenesis-driven growth Figure 4 [19]. It is important to emphasize at this time that the current discussion will focus on the breast-brain relationship. The genetic heterogeneity of migrating tumor cells is well documented and undoubtedly contributes to profound differences in interaction involving other tissues and organs [20 , 21]. It is this lack of convincing proof that prompted the study of breast cancer cell migration to the brain with a greater focus on the specific steps that lead to successful colonization. In their paper, direct observation of early tumor colonization revealed a

predisposition for growth around existing brain vasculature. This is not to deny the possibility that cytokines and chemokines are responsible for drawing tumor cells to certain areas as they traverse the systemic circulation. Upon arrival, tumor cells preferentially attach to existing blood vessels [22] rather than the chemoattractant releasing neural tissue as expected from the Piagetian viewpoint. Thus, from current knowledge it can be inferred that trophic signaling could play a role in the macroscopic targeting of breast primary tumor cells to the brain, but that the same factors may have a diminished role once access to brain tissue has been attained. All cell lines tested exhibited behaviors consistent with vascular cooption. The underlying similarity between all conditions and tests is the brain host tissue, its vascular basement membrane and HBMECs. The tight junctions and associated pericytes of the blood brain barrier are a difficult challenge for any invader to penetrate. The slower rate of extravasation in brain is well noted in comparison to the fenestrated capillaries of other tissues such as bone and liver [25]. The question becomes whether or not this difficulty in extravasation directly promotes the viability of vascular cooption over direct attachment and growth on neural tissue. It is important to note that these recent findings on vascular cooption within the brain do not diminish the substantial effect of neoangiogenesis on subsequent growth in tumor size and scope. Successful migration and initial attachment are steps that must be conceptually separated from the unregulated macroscopic growth that commonly defines cancer. Thus, vascular cooption [22] is the most reliable method by which breast primary tumor cells are able to procure the necessary nutrients and physical scaffolding for initial implantation and growth within the brain. Colonization of Tumor Cells around the Blood Vessels The importance of vascular cooption as a means for tumor cells to survive is highlighted in a study by Gevertz and Torquato [27]. They explain that neoplastic growth is possible even with angiogenesis inhibited as long as vascular cooption is an alternative [27]. Nonetheless, they also report that neoangiogenesis and vascular remodeling is necessary if tumor masses are to grow beyond mm in diameter. Clearly, it is the proximity to, as well as early and ongoing interaction with blood vessels in the brain, that contributes significantly to tumor cell fate. They find a pattern of vascular cooption, vessel regression, and robust angiogenesis that requires tight regulation of these factors [27]. The possibility of regulation at the gene level warrants further study. Such a mechanism supports data on the genetic heterogeneity of primary tumor cells and the Darwinian selection of those tumor cells with the capability for metastasis [28]. It is known that primary tumors can shed more than a million cells per gram of the tumor mass a day [19]. Despite this constant dispersal of tumor cells, and despite public fear and opinion, metastasis is relatively difficult and inefficient. Thus, the study of physiological changes due to changes at the gene level is a promising direction for cancer research. In light of the importance of vascular cooption and blood vessel colonization to invading tumor cells, a look at gene-regulated factors influencing vascular cooption and colonization could provide a clue to the prevention of secondary growths. The steps preceding angiogenesis, according to Lorger and Felding-Habermann contribute to the lower success rate of brain metastasis compared with other tissues [25]. They report that tumor cells extravasating into brain parenchyma were found to be arrested in G0 of the cell cycle. These findings suggest an amount of stress and energy expenditure consistent with a greater effort needed in penetrating the intercellular junctions already discussed in this paper. It is well known that loss of cell attachment proteins and mechanisms leads to the shedding of material from primary tumors [20]. We have revealed here that the process for metastasis could very well complete the circle, at least in regards to breast-brain metastasis. Just as loss of adhesion is a necessary first step for tumor cells to leave their primary tissue site, prompt adhesion to the vascular basement membrane of brain endothelial cells is required and sufficient for initiation of secondary growth. From evidence collected thus far, it is a possibility that attachment proteins and their constituents largely assume control of primary tumor cell fate as soon as extravasation into brain tissue is complete; wresting control away from any trophic factors. There is evidence that the presence of the blood brain barrier would make such a shift in cellular interaction necessary. Reactive Astrocytes and Glia on Tumor Growth The brain provides a unique microenvironment due to its distinctive structure of extracellular matrix Table 1 and the blood brain barrier BBB [29]. It is known that interactions of

the host microenvironment and metastatic cells affect the outcome of metastatic progression and tumor survival [30]. Lorger and Felding-Habermann provided in depth in vivo analyses of early changes in brain microenvironment upon arrival of breast cancer cells [31]. After cell injection into left carotid artery of mice, astrocyte activation was detected in the left hemisphere in brain, showing consistent upregulation in the vicinity of intravascular arrested cancer cells. Reactive astrocytes surrounded and infiltrated brain metastases.

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7: Frontiers | Editorial: Metabolic Control of Brain Homeostasis | Frontiers in Molecular Neuroscience

In this review, we discuss recent studies on the microbial regulation of the brain health and the potential of the host-microbiota interaction in regulating various neurophysiological behaviors, highlighting the role of the gut microbiota as a "peacekeeper" in regulating the brain-controlled function and behavior.

This relationship is protected and promoted by numerous elements of the diet. In terms of the interactions between these three metabolic systems, one need only recognize a select few: Immune modulation of brain activity elements such as body temperature and sleep and feeding behavior. The role of the major histocompatibility complex - not only directing T cells to immunogenic molecules held in its cleft, but also modulating neuronal connection development. Memory sharing between the nervous and immune systems. Further examples illustrate how the nervous, immune, and endocrine systems interact: The immune system is compromised during depression. Under adverse conditions, this Syndrome led to the enlargement of the adrenal gland and atrophy of the thymus, spleen, and other lymphoid tissue. Sustained malnutrition then becomes a major risk factor for morbidity and mortality. Critical Nutrients It is not difficult to point out that the intake of a proper balance of nutrients for maintaining optimal energy metabolism and building materials extends to neurotransmitters, neuroplasticity, and integrity of the neuron itself. Studies of animal and human behavior and cognition have added to the clinical domain of evidence in support of the neuroprotective role of nutrition, while advances in cell and molecular biology have contributed greatly to conceptualizing the constructive roles of proper nutrition in promoting neural structure and function. There are specific examples of critical nutrients supporting the neuro-immuno-endocrine triad: Docosahexaenoic acid DHA is the most abundant omega-3 fatty acid in the brain, facilitating membrane activation of phosphatidylinositol 3-kinase Akt signaling. This signaling increases the level of phosphatidyl serine, the major phospholipid in cell membranes. Vitamin A is needed for generating the antibody response to specific antigens. As a coenzyme which mediates the transfer of one-carbon units, folate participates in multiple reactions critical to the endogenous synthesis and metabolism of DNA, RNA, and amino acids. Coenzyme Q10 is known for its ubiquitous presence, and it is involved in every process that requires energy, including enzyme synthesis, hormone action, and the synthesis and reuptake of neurotransmitters. Elaborate interactions between the immune and nervous systems. Nature Immunology ; 5: Depression, the immune system, and health and illness. Findings in search of meaning. Archives in General Psychiatry ; A longitudinal study of age-related loss of noradrenergic nerves and lymphoid cells in the rat spleen. Experimental Neurology ; Telling the brain about pain. From inflammation to sickness and depression: When the immune system subjugates the brain. Nature Reviews, Neuroscience ; 9: A step further Brown TM, Fee E. Pioneer physiologist of human emotions. American Journal of Public Health ; 92 Hans Selye and the field of stress research. Journal of Neuropsychiatry and Clinical Neuroscience ; Katona P, Katona-Apte J. The interaction between nutrition and infection. Clinical Infectious Disease ; 46 PLoS Medicine ; 4 5: Nutritional disorders in the elderly. Medical Clinics of North America ; 90 5: Proceedings of the National Academy of Sciences ; The biochemistry of n-3 polyunsaturated fatty acids. Journal of Biological Chemistry ; Diet and Immune Function. The effect of ascorbic acid supplementation on some parameters of the human immunological defence system. International Journal of Vitamins and Nutritional Research ; 47 3: The effects of increasing weekly doses of ascorbate on certain cellular and humoral immune function in normal volunteers. American Journal of Clinical Nutrition ; 33 1: Periconceptional use of multivitamins and the occurrence of neural tube defects. Journal of the American Medical Association ; Present Knowledge in Nutrition, 9th Edition. Folate metabolism and requirements. Journal of Nutrition ; 4: Ernster L, Dallner G. Biochemical, physiological, and medical aspects of ubiquinone function. Biochem et Biophysica Acta ; 1: Coenzyme Q10 in health and disease. European Journal of Clinical Nutrition ; 53 Functional Neurology ; 9 3 ; Neuropsychobiology ; 36 2: In vitro and in vivo immunomodulating and immunorestorative effects of Astralagus membranaceus. Journal of

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Ethnopharmacology ; 1: Mechanisms of probiotic actions: International Journal of Medial Microbiology. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Systematic Review ; 5: Implications for therapeutic applications in inflammatory bowel disease. Inflammatory Bowel Disease ; 14 About The Author WholisticMatters We are dedicated to advancing the latest insights and information available in nutrition therapy and clinical nutrition through this site and present only the most balanced, credible and reliable clinical nutrition and science available. A Nutritional Epigenetic Perspective video.

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Thus, OBSC is an excellent technology to address a wide range of topics in primary brain tumor research, ranging from growth- and dissemination-promoting signaling, to the intricate interrelations between the tumor and its surrounding host tissue to the evaluation of efficaciousness of novel targeting strategies.

Figure 1 Change in the microbiome fermentation profile changes gut permeability and energy homeostasis which causes endotoxemia, low-grade inflammation, and obesity. Poor energy homeostasis leads to hyperglycemia and hyperlipidemia which may lead to obesity and ultimately insulin resistance. Short-chain fatty acids have significant effects on the GIT wall health as, for example, a source of energy, anti-inflammation agents, angiogenics and vasodilators, promotility agents, and wound healing agents [20]. Microbial fermentation products also affect the muscles, liver, brain, and adipose tissue metabolism. The liver metabolic profile of gnotobiotic mice is different from that of conventionally raised mice, probably because of an over influx of SCFAs into the liver. Both hepatocytes and enterocytes are reported as energy deprived and have an overexpression of AMP-activated protein kinase AMPK , which determines cellular energy status in gnotobiotic germ-free mice [21 , 22]. Butyrate is principally used as an energy source for enterocytes, whereas acetate and propionate are flushed to the liver for lipogenesis and gluconeogenesis. Butyrate supplementation to obese, prediabetic mice significantly improved the intestinal epithelial barrier and insulin secretion from beta cells and decreased body adiposity as well as weight gain, insulin resistance, hyperinsulinemia, and hyperglycemia [23]. In the last few decades, Lactobacillus has gained much importance as probiotic, live microbes that augment the microbial profile. Notably, certain bacterial clades, for example, Bacteroidetes and Firmicutes, enhance ATP-binding cassette transporter expression in enterocytes and glucagon-like peptide 1 and 2 secretion. Similarly, family Desulfovibrionaceae is associated with dyslipidemia and obesity [27]. In a broader sense, a microbiome shift, delineated by a rise in Firmicutes and a decline in Bacteroidetes populations, is implicated in obesity. The underlying mechanisms for these interactions are not yet fully understood. Although the aforementioned literature enhances our understanding of the role of the microbiome in host metabolism and energy homeostasis, the identification of better molecular markers of metabolism regulation is of greater significance. GIT Microbiome and Metabolic Disorders as Precursors to Diabetes The gastrointestinal tract microbiome interacts with host nutrition, the environment, and host genetics for the development of obesity-related metabolic disorders. Various studies have reported that GIT microbial dysbiosis enhances energy harvest and expression of obese phenotype. The microbiomes of obese persons differ from those of lean individuals and, generally, are characterized by a lower prevalence of phylum Bacteroidetes and a higher prevalence of phylum Firmicutes [28]. The higher energy harvest promotes lipogenesis and increases the number and size of lipid droplets in the extraintestinal tissues Figure 2. Most patients suffering from this metabolic syndrome have excessive fat accumulation which suggests that the dyslipidemia is an important etiological factor of the syndrome [30]. Figure 2 A schematic diagram describing the role of the gastrointestinal tract microbiome in the development of the metabolic syndrome that leads to diabetes mellitus pathogenesis. Microbial dysbiosis impairs intestinal wall integrity and allows translocation of toxins from the gut lumen to the systemic circulation. This endotoxemia leads to low-grade inflammation, autoimmunity, and oxidative stress that may lead to beta cell destruction or insulin resistance. Autoimmunity, insulin resistance, and hypertension are a few potentially lethal consequences of obesity. Transient changes in the microbiome can disrupt the microbiome and host-immune axis. There is an increasing amount of evidence that suggests that intestinal commensals directly influence the development of autoimmunity and low-grade inflammation [31]. In general, the inadequately functional immune system of gnotobiotic mice or neonates suggests that its maturation is compelled by the resident microbiome. However, cellular and molecular processes by which GIT microbes promote autoimmune responses are poorly understood. Different studies propose more than one method of immune disruption in systemic and local

immune systems in response to changes in microbial ecology. Candidatus savagella , a normal commensal bacterium, is associated with the development of autoimmune arthritis and encephalomyelitis. In contrast, the same bacterium is involved in protection against autoimmune T1DM [32]. In the previously mentioned experiments, excessive production of T helper 17 Th by Candidatus savagella has a causal role in autoimmune diseases. In other studies, commensal Bacteroides fragilis has been associated with systemic Th1 cells and local interleukin IL producing regulatory T cells [33]. In addition, SCFAs, through G protein-coupled receptors, have been associated with inflammatory bowel disease, colitis, arthritis, diabetes, and asthma [34]. Microbiome-triggered chronic low-grade inflammation is another important causal factor for obesity and related metabolic syndromes. These endotoxins can cross the GIT mucosal barrier through mucosal tight junctions or by infiltrating chylomicrons [36]. Once in the extraintestinal tissue, endotoxins trigger innate immune responses by activating CD14, nucleotide oligomerization domain NOD , and toll-like receptor 4 TLR4 at the surface of dendritic cells and macrophages.

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