Chapter 14

Energy Homeostasis and the Tumor/Host Interaction: The role of the Brain

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Abstract: 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. Homeostasis is discussed in terms of rheostasis, the low probability of dysregulation, and the potential risks for the defense. The perspective of this review is that many of the metabolic alterations observed in tumor progression may be due to appropriate central homeostatic regulation. Clear deficits in homeostatic regulation during tumor growth have not been unequivocally demonstrated. Yet the brain of the host is clearly under duress due to the tumor. Clarification of homeostatic macroenvironmental regulatory responses may be useful in developing strategies that collaborate with these brain mechanisms. Further analysis of these regulatory systems may identify key changes that ultimately subserve the lethal failure of all host responses. Strategies that protect the brain from the pathological consequences of tumor growth (glucoprivation, oxidative stress, ketogenic diets) and thereby enable a stronger defense are discussed.

Key words: Anorexia, cachexia, circadian rhythms, glucoprivation, ketogenic diet, leptin, melatonin, neuropeptide Y, oxidative stress, suprachiasmatic nucleus

1. ENERGY HOMEOSTASIS

Considerable attention has been focused in recent years on the microenvironmental interaction between the host and tumor, yet relatively little attention has been focused on the macroenvironmental interaction between the host and tumor, particularly with the role of the brain. This is curious because the brain is the site of potent metabolic homeostatic defense systems. Much of what occurs locally is monitored and adjusted centrally. Indeed, disparity in outcomes between *in vitro* and *in vivo* analyses is often due to interactive contributions by the brain.

Homeostasis is regulated through dynamic control mechanisms that defend the host from perturbations that threaten the miliu intérieur (1-4). These energy-related phenotypes are central to the evolved organization of the higher organism that may host a tumorous neoplasm. The macroenvironmental management of homeostasis occurs in the brain where there are regulatory mechanisms for the complex control of food intake (5-11), adiposity (6-12), glucose (13-14), and metabolic rhythms (14-22) that rely in part on peripheral information derived from hormonal and neural input and in part on the local environment within the brain (e.g., glucose sensing). During the progression of aggressive tumor growth these defended parameters in the host are often altered to manifest a metabolic syndrome that features unusual rhythms (23-26), glucose intolerance (27-28), insulin

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resistance (27-28), increased gluconeogenesis (29), increased free fatty acid turnover, oxidation and clearance (30), cachexia (31-32) and anorexia (31-32).

The perspective of this review is that many of the metabolic alterations observed in tumor progression may be due to central homeostatic regulation that is often appropriate, sometimes disturbed, but seldom dysregulated. Whether the response is appropriate or disturbed has been difficult to establish. For example, food restriction inhibits tumor growth and the host response to the tumor is to inhibit food intake (anorexia/cachexia) (33-36). If food restriction is additionally reduced by fasting the tumor grows faster[37]. Thus the brain seems to have achieved just the right balance of food intake and food restriction to minimize the growth potential of the tumor. Yet there are risks for this strategy due to the dire long-term consequences of anorexia/cachexia. Similarly, the brain and the tumor compete for glucose and the brain can enhance gluconeogenesis to meet its glucose needs.

Clarification of homeostatic macroenvironmental regulatory responses may be useful in developing strategies that collaborate with these brain mechanisms. Moreover, further analysis of these regulatory systems may identify the key events that ultimately subserve the lethal failure of all host responses. For example, homeostatic systems may be misled by or blind to the re-activated embryogenic systems often observed in malignant tumors (e.g., proteolysis-inducing factor (31)). Thus the etiology of lethality in cancer pathology may plausibly be due to tumor factors that disturb, foil, or overwhelm homeostatic regulation, even when that regulation is working appropriately.

Progress has been made in the last decade that furthers our understanding of some key neural circuits utilized for energy homeostasis, in particular the integrated hypothalamic and brainstem circuits for metabolic rhythms, feeding, fuel, adiposity. Key hormonal metabolic signals to the brain (e.g., leptin) have been identified and extensively examined. Cross-talk between the research fields of energy homeostasis and cancer may be fruitful for both disciplines.

Evidence on the role of macroenvironmental regulatory mechanisms residing in the brain for energy homeostasis as an adaptive and/or maladaptive response by the host to tumor progression will be briefly reviewed in this chapter.

2. HOMEOSTASIS, RHEOSTASIS AND DYSREGULATION

Much of medicine is assisted homeostasis. But parsing malignant metabolism and parceling out the contribution of the host and the tumor can be difficult. The tumor perturbs, the host responds. Most of the metabolic characteristics of malignant metabolism probably reflect the interaction of host and tumor.

The metabolic syndrome that occurs during cancer malignancy has some features of starvation, infection and late term pregnancy[33] as well as some features of another metabolic syndrome, diabetes. In each analogy however there are significant differences and in the final analysis cancer appears to induce its own metabolic syndrome[38]. As with diabetes the contribution of host homeostatic mechanisms to each of these metabolic alterations has been difficult to assess. And certainly there are significant differences in etiology for each metabolic syndrome. But just as certainly there are common features and a limited set of control system weapons to work with in the defense of energy homeostasis. To understand that set of control systems is one aim of those who study energy homeostasis.

Altered homeostatic parameters alone do not constitute dysregulatory pathology. Indeed it may be more appropriate to reconsider homeostasis as rheostasis where the defended level changes, but the defense of the level remains intact. For example, as Mrosovsky (4) has eloquently articulated, hibernation, starvation, infection, and pregnancy are physiological conditions where appropriate regulatory changes occur. The organism might run a fever, not eat, conserve energy and/or reduce activity. Each of these adaptations may become pathological but each represents a risk that favors survival. Obesity, for example, derived as a phenotype from adaptive selection that favored survival during sustained food deprivation (39). The fat survived. Hypertension may be required to adequately provide circulation especially when there

is about a mile of additional capillary length for each pound of fat. Hyperglycemia may assure glucose delivery during insulin insufficiency (40). Fever fights infection but may itself become pathological. These examples suggest that pathology does not require dysregulation.

Indeed true dysregulation is probably rare and would best be characterized by no defense at all. The host seldom misinterprets or is blind to the homeostatic insult, especially in chronic conditions. One important example may help clarify this point. Hypoglycemia is an acute risk in insulin treated diabetes and can be fatal. The phenomenon is called hypoglycaemia-associated autonomic failure (HAAF) and is often referred to as hypoglycemia unawareness (41). In HAAF the regulatory responses transduced in the medullary brainstem (e.g., glucoprivic feeding, stimulation of epinephrine, glucocorticoid and glucagon secretion, enhanced gluconeogenesis) do not occur (42). When studied in rats HAAF was produced by an acute prior induction of hypoglycemia during which the normal regulatory responses occurred, followed in a few hours by a second bout of hypoglycemia. During the second bout the normal regulatory responses did not occur. Hypoglycemia unawareness in these rats, however, did not occur when glucocorticoids were removed by prior adrenalectomy (42). Thus we see that hypoglycemia unawareness may reflect either 1. homeostatic unawareness; 2. a regulated, yet adverse, reaction to a competition between homeostatic responses (acquisition of glucose versus stress induced glucocorticoids); or 3. a regulated, yet adverse, reaction to components of the same homeostatic response (acquisition of glucose) in which glucocorticoids may play a direct role.

The lesson then is that dysregulation can not be assumed to occur. A demonstration of a changed response, or even an inappropriate non-response, is not necessarily a demonstration of dysregulation. In addition, integrated responses to complex challenges can create competition between regulatory subsystems, which may result in a lack of metabolic stability[4]. When not extreme such a competition is usually resolved with metabolic stability. For example, rats will leave a warm environment to acquire food in a cold environment (-15º C) but they will eat that food as quickly as possible (43). The suggestion from this perspective on homeostasis during cancer is that the identification, and experimental manipulation, of environmental impediments (e.g., glucoprivation, cyclic AMP deficits, and oxidative stress) on function is teleologically necessary in order to understand the brain-derived defense of the energy realm. In addition, experiments on the direct impact of tumor-derived molecules (e.g., proteolysis-inducing factor and Zn-alpha (2)-glycoprotein (31) on brain outcomes are needed, as are further analysis of brain energy systems under the influence of a malignant tumor.

Clearly, without further study, the complex perturbations caused by cancer that render the host inadequately defended will continue to a lethal outcome. Assisted homeostasis through a better understanding of the role of the brain in cancer may be critical in tipping the counterbalance of this defense in favor of the host.

3. ENERGY HOMEOSTASIS CIRCUITS IN THE BRAIN

Neural and neuroendocrine mechanisms for the defense of energy homeostasis have been extensively elaborated on during the last decade (5-12, 14-22, 44-48). These reviews have identified the regulatory signal to the brain from adipose tissue as the cytokine leptin, a hormone derived primarily from adipose tissue. Leptin levels in the circulation reflect the level of adiposity. The administration of exogenous leptin to rodents potently reduces body weight (49-55). This reduction in body weight is almost entirely due to loss of stored lipid fuels and is not due to loss of protein (56-58). This pattern differs from starvation, during which both lipid and protein are lost (59-60).

Leptin's central actions are critical for its effects on feeding and body weight. First, hypophagia can be produced by central administration of leptin at doses several fold lower than equally-effective systemic doses, and this effect is achieved without any increase in the circulating levels of leptin (56, 61), either by efflux from the cerebral spinal fluid into venous blood or by enhancing peripheral leptin

secretion. Second, central administration of leptin is sufficient to reverse the obesity of ob/ob ($Lepr^{ob}$/$Lepr^{ob}$) mice lacking the gene for leptin (50). Although peripheral administration of leptin also causes anorexia and weight loss, these actions of leptin may be mediated centrally since leptin is able to gain access to the brain from the circulation. Finally, selective deletion of neuronal leptin receptors abolished leptin's anorexic effect and resulted in obesity in mice (62); and epigenetic expression of leptin receptors only in the brain reversed the obese phenotype of the db/db mouse ($Lepr^{db}$/$Lepr^{db}$), which is without leptin receptors due to an autosomal recessive mutation (63).

The related cytokines ciliary neurotrophic factor (CNTF), interleukin-6 (IL-6) and leukemia inhibitory factor (LIF), which signal through the highly related glycoprotein-130 (gp-130) JAK/STAT receptor circuitry, also dramatically decrease fat pads to a similar degree when chronically given centrally into the ventricles (64-68). These members of the interleukin (IL)-6-receptor family of cytokines appear to redundantly activate a brain system that controls fat mass to the extent that rodent models live in good health without adipose tissue for most of their adult life (68). Redundancy in signalling is a common feature of this system (69-71).

Yet these cytokines that employ the gp-130 signal transducing subunit also interact with specificity (69). Oncostatin M (OSM) regulated IL-6 expression in glia, but LIF did not (72). OSM did not produce anorexia, but LIF and interleukin-11 (IL-11) did produce anorexia in short-term feeding tests (68).

Numerous neuropeptide effectors in the brain that are implicated in the control of feeding occur downstream of leptin and have been extensively studied (5-12, 14-22, 45-48, 73, 74). Orexigenic neuropeptides inhibited by leptin include neuropeptide Y (NPY) (75-76), galanin (77), melanin concentrating hormone (MCH) (75) and agouti-related peptide (AGRP) (75-76). Anorexigenic neuropeptides stimulated by leptin include corticotropin releasing hormone (77-78), glucagon-like peptide 1 (GLP-1)79, alpha-melanocyte stimulating hormone (80), neurotensin (75, 81) and cocaine- and amphetamine-regulated transcript (CART) (82). Neurotrophins such as brain-derived neurotropin factor (BDNF) (83, 84), CNTF (85-88) and the neurotropin regulated VGF (90-91) have emerged as important in this matrix of neural signals necessary for energy homeostasis, as has leukemia inhibitory factor (LIF) (85, 89). The specific role of each signalling agent is beginning to be clarified (83). Thus there is an extensive brain circuitry that subserves the control of food intake (e.g., anorexia, hypogeusia, hyposmia, nausea, satiation, aversion, and appetite), metabolism (e.g., gluconeogenesis, free fatty acid release, compartmentalization of fuels), adiposity (fat cachexia) and perhaps muscle mass (muscle cachexia).

4. WHY IS BRAIN CIRCUITRY FOR ENERGY HOMEOSTASIS OF INTEREST IN CANCER?

In the sections that follow six particular topics will be briefly considered with each section providing only a partial, and necessarily incomplete, suggested answer to this question. More complex brain functions that affect the host/tumor interaction but involve external events and behaviors that transcend energy homeostasis (e.g., biopsychosocial oncology (93) or psychoneuroimmunology (94), such as social stress (95), social defeat (96) or social dominance (97) will not be discussed because these topics are beyond the scope of this review.

4.1 Regulatory feeding responses appear intact during tumor progression

Although anorexia, cachexia and numerous metabolic disturbances are manifest in many cancer models, the normal controls of feeding are still substantially intact (33-34). That is, the anorexia can be returned to normophagia under some experimental conditions. In a classic review Seoras Morrison asked his version of the central question of cachexia/anorexia: “Why the host does not respond to change in need with change in intake?” (33). Why doesn’t the energy-depleted host simply invoke hyperphagia? For example, cold exposure (5º C vs.

24º C) for two days normalized food intake in rats with tumor-induced anorexia (98). And the hyperphagia induced by insulin-induced glucoprivation was intact in Walker 256 carcinoma-bearing Sprague-Dawley rats (34). Interestingly, obese mice maintained on a food for which they had developed a conditioned taste aversion lived longer with B16 melanoma than those maintained on a food that was not aversive (99). These examples indicate that the metabolic changes observed during tumor progression may be due to a regulatory response to the tumor and are not due to incapacity of the regulatory system.

Moreover cachexia and anorexia do not require the presence of the tumor (34). As with parabiosis (100), direct transfer of blood from a cancer-bearing host to a non-cancer-bearing host results in cachexia/anorexia without a tumor (101). And, indeed, removal of the tumor, except in the late stages of cachexia, reverses both the anorexia and cachexia (34, 102). Thus the cachectic/anorectic response interaction by the host to the tumor does not require the tumor and does not require structural alterations to the host that can not be rapidly adjusted.

The answer to Seoras Morrison's central question, therefore, may be that the host has already responded appropriately to the tumor with just the right amount of food restriction.

4.2 There is an altered energy environment within the brain during tumor progression

Alteration in homeostatic function may occur because of alterations in the metabolic environment within the brain, as a distant function of tumor growth. Tumor growth involves vascular leakiness within the tumor induced by a unique tumor angiogenesis that produces a necrotic condition characterized by hypoxia, elevated glycolysis even under aerobic conditions, high glucose turnover, glucose deprivation, adverse acidity and increased interstitial fluid pressure (103-104). These elements of tumor growth alter the brain environment by reducing glucose availability and increasing oxidative stress.

The high glucose turnover of the aggressive tumor reduced glucose utilization by the brain and increased utilization of lactate and 3-hydroxybutyrate (ketones) (105). Indeed it is probable that the proximal cause of death with rapidly growing non-metastasizing tumors is often acute hypoglycemia (106). Survival for sarcoma-bearing hypoglycemic mice was not enhanced by administration of glucagon, but drinking of glucose by food-deprived mice did enhance survival. And adrenalectomy shortened survival time (106).

The homeostatic responses to glucoprivation are transduced in the ventrolateral medulla of the brainstem (107-108) and include hyperphagia, gluconeogenesis and thus the sympathoadrenal stimulation of epinephrine, glucagon and glucocorticoids. The need to provide nutrients to the brain quickly is paramount during acute hypoglycemia.

One way to reduce the brain's need for glucose, and the adverse consequences of oxidative stress, is to substitute ketones for glucose as fuel for the brain (109). Several reports (110-116) have examined the mostly positive effects of a ketogenic diet based on medium-chain triglycerides on non-brain tumor cachexia and tumor growth but not on survival rates or brain function. Glycerol supplementation may also be helpful (117). And recently a direct role for glucose supplementation has been beneficial (118). Additional studies with diets that may support brain function during cancer are warranted. From the perspective of this review the support of brain function should be considered a different objective than ameliorating anorexia/cachexia.

Oxidative stress was increased within the brain, with highest levels of increased stress observed in the hypothalamus, during the growth of the Walker-256 tumor, due to the elevated rate of oxygen consumption, the high level of endogenous polyunsaturated fats (119) and iron (120). TNFα has been implicated in this increased stress (122). Specific sites within the hypothalamus are rich in TNF-α receptors, especially the paraventricular nucleus, the supraoptic nucleus and the arcuate nucleus (123). Central catecholamines are particularly susceptible to oxidative stress (123) and critical participants in energy homeostasis and especially in glucose regulation (107-108).

Oxidative injury to catecholamines has been reported in the locus coeruleus (124) and ventrolateral medulla (VLM) (125). The VLM is a critical site for transduction of numerous homeostatic responses, including those stimulated by hypoxia and glucoprivation. Melatonin functions as a neuroprotectant during oxidative stress to catecholamines in part due to upregulation of glial derived neurotrophic factor (GDNF) (124). Oxidative stress induced by the tumor stimulated glycose-6-phosphate dehydrogenase activity, pentose phosphate pathway activity and elevated flux of substrates, while brain mitochondrial activity was inhibited (119).

Thus in these two ways, and probably others (e.g., the aberrant presence in the brain of tumor-derived molecules), the brain environment is altered by the presence of the tumor.

4.3 Altered expression of neuropeptides and monoamines in brain circuitry for energy homeostasis during tumor malignancy

The hypothalamus is an important site for integrating metabolic information and regulating energy homeostasis and metabolism (5-9, 12, 14-15, 20, 73-78, 80, 82-83). Alterations in signalling within the hypothalamus during tumor progression have usually been reviewed in the context of cancer anorexia (31, 126-137). For example, there are reportedly decreased NPY fibers in anorectic tumor-bearing rats in the parvocellular region of the paraventricular nucleus, as well as in the supraoptic, suprachiasmatic and arcuate nuclei (138). Most of the NPY fibers in the hypothalamus are located in these nuclei. This decrease in NPY fibers tends to support these authors' hypothesis that the anorexia induced by the tumor alters the structure of the neuronal signalling pathway for food intake, of which NPY is one important part. Indeed, when NPY was acutely delivered directly into the perifornical hypothalamus in MCA sarcoma-bearing rats before the expression of anorexia hyperphagia in a four-hour food intake test was at first induced comparable to non-tumor bearing controls (139). While elevated food intake in tumor-bearing rats who received acute hypothalamic injections of NPY continued to occur during the ongoing experiment over the next two weeks and five injections, the elevation was greatly attenuated in tumor bearing rats compared to controls without the MCA sarcoma that received hypothalamic injections of NPY. A similar refractory response to perifornical NPY was observed with chronic minipump infusion (139). This refractory feeding response induced by perifornical NPY in tumor-bearing rats may reflect refractory adenylate cyclase AMP formation (131).

The effect of a tumor on NPY expression and signalling in the hypothalamus is far from clear, which may reflect differences between tumors, in the brain site examined, experimental designs, rodent strains, multiple roles for NPY and/or other factors. Some studies report decreased expression of NPY (137, 141-143), other studies report increased expression (144-148) and yet other studies report normal expression (149-150). A more complete critical review of the NPY feeding system and its alteration by a malignant tumor is overdue but beyond the scope of this review. However, further exploration of the NPY feeding system, and related systems within the prevue of brain regulated energy homeostasis, seems warranted. Indeed, the direct examination in tumor bearing rodents of the effects of infusion into the brain of either energy related molecules such as this orexigenic neuropeptide NPY, or of tumor-related molecules into non-tumor bearing hosts, seems to be a neglected area of cancer research with only a few examples (139, 151-152), even when experiments with proinflammatory cytokines (66, 67, 126, 131) are included. Perhaps to refocus research on brain pathology engendered by a malignant tumor and on brain responses to that tumor would reenergize research in this neglected area.

In addition to NPY, there are expression changes that occur for other neuropeptides and monoamines critical to neural communication in the circuitry for energy homeostasis during the progression of malignant tumors. Alterations in brain serotonin (141, 143), dopamine (141, 143), MCH (145), orexin (145) and interleukin-1 beta (150) have been reported.

Which subset of homeostatic controls these changes reflect (anorexia, cachexia, the regulation of

adiposity or muscle, metabolites) is unclear. But clearly the brain is reacting to the presence of the tumor with alterations in this critical neural network that serves energy homeostasis.

4.4 Destruction of the medial basal hypothalamus with gold thioglucose, or agouti blockade of the melanocortin-4 receptor, accelerates lipid wasting and demise in mice

In 1971 Liebelt and co-workers induced hyperphagia and obesity in two strains of mice by destruction of the medial basal hypothalamus with gold thioglucose (GTG) (153). They predicted that the hyperphagia induced by this treatment would override the hypophagia induced by either of two strains of tumor, the CBA 2663 stomach tumor or the C57Bl sarcoma. To their surprise a profound anorexia and cachexia were accelerated in these obese mice, who died by day twenty of tumor growth. The lean mice lived until the end of the experiment, at day thirty of tumor growth, and never expressed anorexia or cachexia. Tumor growth was not accelerated in the obese mice and the tumors remained small but lethal. Carcass weight loss was primarily lipid in the GTG tumor-bearing mice. A parallel experiment utilized the agouti yellow (Ay/a) obese mice, which have a dominant mutation of the agouti gene so that there is a blockade of the melanocortin-4 receptor and insensitivity to αMSH (154), produced the same pattern to tumor bearing.

There are several factors in common to these two mouse models of obesity. The ability of central leptin to reduce body weight, adiposity and food intake is attenuated in both the GTG mouse and the agouti yellow obese mouse (155-156). In both models there is insensitivity to POMC and αMSH157. And both obesity models require the neurotropin-induced polypeptide VGF (158), which is also important in energy homeostasis. Thus the circuitry of energy homeostasis in the hypothalamus is blocked with catastrophic consequence in tumor bearing mice. Further work in cancer with these models is warranted, but clearly both the circuitry and the site of action are important in the host defense against tumor lethality.

4.5 Suprachiasmatic nucleus-induced rhythms inhibit tumor growth

Time-keeping is important for energy homeostasis. Metabolism is processed with rhythm (14-22). Food is anticipated with activity (22). Insulin is secreted in anticipation of food (20). There are circadian rhythms for metabolites such as glucose (14), and metabolic hormones such as ghrelin and leptin (159). Food (21), or glucose, but not lipid, reset the biological clock (160). Disrupted sleep also disrupts these rhythms (161).

The suprachiasmatic nucleus (SCN) in the hypothalamus serves as a site for photic transduction of the light/dark cycle; as an entrainer for its endogenous clock; and, as a site for rhythm synchronization with non-photic stimuli (14, 17-20, 162, 163). Ablation of the SCN in rodents removes photic entrained rhythms and accelerates tumor growth (164, 165). In a recent experiment, Filipski and co-workers demonstrated that a simple advance of the light/dark cycle by eight hours every two days accelerated Glasgow osteosarcoma tumor growth (166).

Circadian rhythms are often disrupted in cancer and chronotherapies are currently under investigation for improved management of cancer (24, 26). Sleep disorders are a common feature of cancer (23). Brain derived rhythms inhibit tumor growth and sustain normal sleep. And the tumor may disrupt those rhythms. Thus there is a need for further investigation of the role of circadian rhythms in tumor growth and malignancy.

4.6 The pineal gland and melatonin

The pineal gland is located within the brain and is the source of the hormone melatonin (167-168). Both the pineal gland and melatonin are involved in energy homeostasis (169-170). And both melatonin and the pineal can interact with tumor growth, which has stimulated an interest in the antitumor properties of this hormonal system (171-176).

In one study the removal of the pineal gland stimulated the growth of melanoma (177). And in another study administration of melatonin shortened the survival rate of mice with the Ehrlich ascites

tumor (178). And overexpression of the melatonin MT1 receptor suppressed mammary tumor formation (179).

These examples, supported by correlational studies (171-176), have generated a recent surge of interest in the role of the pineal axis in the treatment of malignant tumors.

5. SUMMARY

The brain is the ultimate defender of energy homeostasis and cancer is the ultimate aggressor. The metabolic syndrome expressed in this terrible struggle is due in part to both a stout defense and a violent aggression. Disentangling this interaction requires further experiment but may prove to be important in the management of malignancy. Fundamental components of the defense are apparent and suggest that the brain is responding appropriately, with roles for particular sites (e.g., the medial basal hypothalamus, the suprachiasmatic nucleus, the pineal gland), that mediate the control of rhythms, food intake, and adiposity. The environment within the brain is altered by the tumor, which may compromise the defense. Analysis of the altered environment (e.g., glucoprivation, oxidative stress, tumor-derived molecules, alterations in neuropeptides and monomines) may lead to an improved defense. And, finally, analysis of the antitumor strategies of this brain-derived defense may lead to assisted homeostasis: interventions that serve to tip the counterbalance in favour of the host.

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