Thaker, Sood & colleagues provided empirical evidence that psychological stress can facilitate tumor growth in multiple animal models via its promotion of glucocorticoid and adrenergic signaling[12,93]. These studies demonstrated that multiple ovarian cancer tumor cell lines (e.g., EG, SKOV3, 222, HeyA8…) enhance invasiveness when exposed to norepinephrine and/or glucocorticoids (in part) via the upregulation of matrix metalloproteinases (MMPs), critical regulators of angiogenesis and tissue remodeling. Blockade of adrenergic signaling or inhibition of MMPs prevented elevations in cell invasiveness. *In vivo* experiments demonstrated that chronic behavioral stress (restraint) increased tissue catecholamines, tumor growth, vascularization, and invasiveness in an orthotopic mouse model of ovarian cancer. These effects were driven by adrenergic signaling (through the b2-adrenoceptor), resulting in downstream cAMP-protein kinase A (PKA) pathway activation. This subsequently promoted the transcription of vascular endothelial growth factor and the MMPs (-2 and -9). These findings highlight adrenergic-receptor signaling as a potential target for reducing tumor angiogenesis and growth. Indeed, perioperative cyclo-oxygenase 2 and beta-adrenergic blockade was shown to improve measures of metastasis in breast cancer patients, offering a safe and effective adjuvant treatment strategy[94].

Energy balance and feeding

Disrupted energy balance resulting in enhanced capacity to sustain proliferative growth is a hallmark of cancer[9]. Indeed, one of the first major breakthroughs in cancer research was the discovery that tumor cells are biased towards aerobic glycolysis rather than oxidative phosphorylation to produce energy (i.e., the Warburg effect[95-97]). Therefore, a common finding in malignant cancers is a strong upregulation of lactate and catalytic enzymes required for lactate production from pyruvate (e.g., lactate dehydrogenase)[98-101]. Lactate normally acts to aide in glucose sensing and food intake, where it is transported into the brain via monocarboxylate transporters present on endothelial cells lining the blood-brain barrier[102]. After entering the brain, lactate is able to interact with neurons that normally promote food intake, such as those that produce agouti-related peptide (AgRP) within the arcuate nucleus. Lactate's mechanism of action on orexigenic cells is via its effects on the adenosine monophosphate kinase/methylmalonyl CoA signaling pathway within the hypothalamus[103]. Lactate alone, however, does not seem to be responsible for cancer-associated anorexia (discussed below)[104].

Anorexia is a common phenomenon in cancer patients with weight loss, and even when patients attempt to eat enough to compensate, they frequently cannot maintain a healthy weight. Although significant evidence suggests that inflammatory signaling secondary to tumor growth or cancer-treatment associates with anorexia, a specific neural population and mechanism governing this common problem is lacking[99]. An attractive candidate neural population that may underlie these traits (in part) is the calcitonin-gene-related-peptide (CGRP) expressing population of cells in the parabrachial nucleus (PBN_{CGRP}). These cells powerfully suppress appetite and promote the termination of feeding behavior[105,106]. CGRP neurons are activated by upstream circuits that respond to cancer-associated signals, and are inhibited by those that promote feeding, including hypothalamic AgRP/neuropeptide Y neurons[107]. These neurons are also sensitive to peripheral noxious and painful stimuli, which are other aspects of cancer progression[108].

In a mouse model of Lewis lung carcinoma, Schwartz and colleagues investigated how peripheral tumors modulate CGRP neural activity and their role in cancer-associated anorexia/cachexia[109]. CGRP neurons were strongly activated in tumor-bearing mice compared with controls, a phenotype typically found after ingestion of a large meal. This suggests that tumors activate cells normally responsible for meal termination and cessation of feeding behavior. Using a cre-dependent tetanus toxin transgene, they demonstrated that inactivation of these cells prevented cancer-associated anorexia/cachexia. Additionally, this manipulation normalized the activity of neurons in circuits downstream from the PBN, namely the central amygdala (CeA) and oval subnucleus of the bed nucleus of the stria terminalis (ovBNST), which may play additional roles in cancer-associated behavioral phenotypes. To control the activity of PBN_{CGRP} neurons with better temporal precision, they used Gi-coupled DREADDs to transiently inhibit these neurons in anorexic/cachexic mice. This manipulation was able to recapitulate the effects seen with their previous approach using tetanus toxin.

Another research area that is rapidly growing in scope is that of brain-gut and gut-cancer interactions. Changes in systemic microbial diversity can influence brain function, alter immune phenotypes, and dictate subsequent cancer development or a tumor's response to immunotherapy[110,111]. In a proof-of-principle experiment, Lakritz *et al.*[112] demonstrated that *Helicobacter hepaticus*, a pathogenic gut microbe, promotes distal breast tumorigenesis in a neutrophil-dependent manner. Cancer-prone female mice (FVB-Tg(C3-1-TAg)cJeg/JegJ) were infected with *H. hepaticus* (via gastric gavage) at 3 months of age, and then assessed for subsequent mammary tumorigenesis. Mice infected with these bacteria developed significantly more tumors than their counterpart controls that were not infected. Additionally, mammary intraepithelial neoplasias were associated with strong neutrophil invasion (myeloperoxidase staining). Chronic depletion of neutrophils (via anti-Ly6-G antibodies) prevented *H. hepaticus*-induced cancer development. These data suggest that host-microbe interactions may drive cancer in distal tissues through an immune-mediated mechanism.

CONCLUSIONS AND IMPLICATIONS

Together, the studies discussed above aim to provide an understanding of the types of inputs the brain receives, the signals it propagates, and the effects of these messages on tumor growth and metastasis. Reciprocally, tumor-induced changes in physiology are relayed to the brain via endocrine, immune, or neural signals that ultimately change the activity of discrete neural populations important for maintaining homeostasis. Resolving the "conflict of interest" between cancer and the brain will undoubtedly lead to improvements in patient quality of life and unlock a novel means for cancer treatment. A summary of these findings from basic science are presented in Table 2.

In this vein, treatments targeting the circadian system (i.e., chronotherapy) have gained significant traction in recent years[113,114]. These approaches leverage natural circadian rhythms in metabolism and detoxification systems to schedule chemotherapy or radiotherapy to coincide with times of peak effectiveness with the lowest potential for side-effects. Animal models have further demonstrated that this approach can effectively limit hepatic toxicity and the inflammatory response to chemotherapeutics[115,116]. Artificially boosting circadian rhythms (e.g., with nobiletin) adds an additional prospective anti-cancer strategy[64].

Alternatively, targeted stimulation of specific brain areas deregulated in cancer may help overcome resistance to more traditional treatment strategies. As discussed above, stimulation of the dopaminergic ventral tegmental area promotes tumor suppression via the sympathetic nervous system[87]. If findings such as these translate to humans, deep brain stimulation protocols could be adapted for adjuvant cancer treatment. For example, deep brain stimulation of the subthalamic nuclei for Parkinson's disease promotes sympathetic activation in a safe and reversible manner[117,118], a procedure that could be repurposed in the context of advanced cancer. Alternatively, biobehavioral therapies can be designed to promote positive thinking and rewarding experiences (to activate the dopaminergic system) to aide in cancer suppression. Indeed, mindfulness meditation has been demonstrated to improve mood, reduce stress, and attenuate inflammation in patients with breast cancer[119].

As cancer drastically alters energy balance, influencing the activity of specific brain nuclei regulating metabolism and food intake (e.g., hypocretin, AgRP, POMC, CGRP neurons) represents a strategy to not only improve quality of life, but limit energy availability to the cancer. Indeed, inhibition of aberrant hypocretin/orexin signaling promotes sleep and attenuates tumor-induced metabolic abnormalities in a mouse model of breast cancer[6]. Repurposing drugs that modify food intake and energy balance (e.g., metformin) further provides additional avenues for adjuvant cancer therapy. However, significant more research is needed to understand both (1) how the brain influences cancer-associated immune populations and (2) how the tumor communicates with the brain to deregulate homeostasis and health. Only then can we begin to manipulate this cross-talk to facilitate cancer elimination.

Table 2. Non-exhaustive list of primary animal model evidence for brain-tumor interactions regulating cancer incidence, disease progression, morbidity and mortality (see Figure 2 for more details)

Cancer type/model	Main focus	Primary findings	Ref.
67NR/4T1/4T07 syngeneic breast cancer cells (female BalbC mice; subQ/orthotopic)	Effects of peripheral tumors on central regulation of sleep and metabolism	Tumors alter leptin/ghrelin signaling, disrupting central hypocretin/orexin activity to influence glucose metabolism and sleep via the sympathetic nervous system	[6]
LL2 Lewis Lung carcinoma/B6 (male C57bl6j mice; subQ)	Dopaminergic regulation of tumor growth	Activation of VTA-dopamine neurons blunts tumor growth via sympathetic modulation of bone-marrow myeloid derived suppressor cells	[87]
$p53^{R270H©/+}$WAP-Cre mutant model of Li-Fraumeni syndrome (mouse; transgenic)	Circadian disruption-induced cancer development	Chronic phase shifting accelerated spontaneous tumor growth and altered tumor phenotype	[60]
N-nitroso-*N*-methylurea (NMU)-induced mammary tumors (rat; chemically induced)	Effects of tumors on affective behaviors	Tumor growth is associated with central cytokine concentrations, altered glucocorticoid responses, and the development of depressive-like behavior	[141]
Colon-26 adenocarcinoma cells (mouse; SubQ)	Effects of tumors on fatigue, muscle physiology, and affective behaviors	Tumors promoted central proinflammatory cytokine production and depressive-like behavior prior to defects in muscle function, behavior rescued by SSRI	[142,143]
HeyA8, SKOV3ip1, MB-231 orthotopic human ovarian carcinoma cells (nude mice; IP)	Effects of stress on tumor development and angiogenesis	Stress-induced adrenergic signaling (cAMP->PKA) promotes tumor growth and angiogenesis	[12]
Non-metastatic methylcholanthrene-induced sarcoma (F344/NTacfBR male rats; SubQ)	Effects of inflammation on central hypocretin/orexin neurons and fatigue	Tumors reduced hypocretin/orexin transcript expression and promoted fatigue	[144]
LL2 or TC-1 lung epithelial cells (male C57Bl6 mice; subQ)	Role of sleep fragmentation (SF) on tumor growth and progression	SF accelerates tumor growth, likely through a TLR4 dependent mechanism	[13]
LL2 Lewis Lung carcinoma cells/Apc/min+ mice (male and female C57Bl6; subQ/transgenic)	Role of calcitonin-gene related peptide (CGRP) neurons in cancer-associated cachexia	Inactivation of parabrachial CGRP neurons prevents and reverses cancer-induced anorexia, fatigue, and changes in affective behavior	[109]
MADB106 breast cancer cells (outbred "hyperreactive" Wistar rats; subQ)	Role of dopaminergic system in tumor growth/metastasis	Smaller tumors, fewer metastases, and reduced angiogenesis in rats with a hyperreactive dopaminergic system	[84]
$K\text{-}ras^{LSL\text{-}G12D/+}$;$p53^{flox/flox}$ (KP) or $K\text{-}ras^{LSL\text{-}G12D/+}$ (K) lung cancer model 129SvJ x C57bl6 mice (cre-dependent p53 deletion)	Effects of circadian disruption (environmental and genetic) on lung tumor growth and progression	Both genetic and physiologic circadian disruption accelerate tumor growth and promote c-myc upregulation and metabolic reprogramming	[61]
diethylnitrosamine-induced hepatocarcinogenesis (male Sprague-Dawley rats)	Sympathetic nervous system effect on hepatocarcinogenesis	High density of SNS bundles associated with poor prognosis, SNS activation of Kupffer cells drives inflammation	[145]
Hepatocarcinoma Morris 7288CTC cells (male buffalo rats) or steroid receptor (SR)-1+ or SR-1- MCF-7 human breast cancer xenografts (female nude rats)	Role of light and melatonin in cancer progression	Melatonin depleted blood accelerates tumor growth and metabolism compared to melatonin-rich blood from healthy women; light accelerates tumor growth in dose-dependent manner	[79]
B16 melanoma cells (male nude mice/C57bl6 D_2 receptor-KO)	Role of peripheral dopaminergic signaling in tumor growth/angiogenesis/metastasis	6-OHDA ablation of dopaminergic nerves enhanced tumor angiogenesis and growth, likely through D_2-mediated mechanism	[146]
GOS Glasgow osteosarcoma and pancreatic adenocarcinoma (P03) xenographs (male $B6D2F_1$ mice; subQ into flank)	Effect of suprachiasmatic nucleus lesions on tumor growth	SCN lesions drastically increased tumor size in both cancer models examined	[147]
TC-1 mouse lung cancer cells and human lung adenocarcinoma cells (male C57bl6 mice and obstructive sleep apnea patients)	Effect of sleep fragmentation on plasma exosomes and tumor growth	Chronic sleep fragmentation alters the microRNA cargo of plasma exosomes to promote tumor cell proliferation	[148]
EG, SKOV3ip1, and 222 human ovarian cancer cells (nude male mice)	Effect of stress hormones on cancer invasiveness and growth	Adrenergic and glucocorticoid signaling promotes tumor invasiveness (in part) via upregulation of MMPs	[93]

VTA: ventral tegmental area; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; 6-OHDA: 6-hydroxydopamine; MMPs: matrix metalloproteinases

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Authors' contributions

Borniger JC contributed solely to this study.

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The author declared that there are no conflicts of interest.

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