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Cancer as a tool for preclinical psychoneuroimmunology

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ABSTRACT

Cancer represents a novel homeostatic challenge to the host system. How the brain senses and responds to changes in peripheral physiology elicited by tumor growth is a largely untapped area of research. This is especially relevant given the widespread prevalence of systemic problems that people with various types of cancer experience. These include disruptions in sleep/wake cycles, cognitive function, depression, and changes in appetite/food intake, among others. Critically, many of these problems are evident *prior* to diagnosis, indicating that their etiology is potentially distinct from the effects of cancer treatment or the stress of a cancer diagnosis. Psychoneuroimmunology (PNI) is well equipped to tackle these types of problems, as it uses approaches from multiple disciplines to understand how specific stimuli (endogenous and environmental) are transduced into neural, endocrine, and immune signals that ultimately regulate health and behavior. In this article, I first provide a brief historical perspective of cancer and PNI, introduce the idea of cancer as a systemic homeostatic challenge, and provide examples from preclinical literature supporting this hypothesis. Given the rise of advanced tools in neuroscience (e.g., calcium imaging), we can now monitor and manipulate genetically defined neural circuits over the extended time scales necessary to disentangle distal communication between peripheral tumors and the brain.

1. Introduction

Cancer research and psychoneuroimmunology (PNI; i.e., a scientific discipline focused on interactions among the mind, nervous system, and immune system) have been intertwined since PNI's inception. In 1975, for instance, Ader & Cohen (who coined the term 'psychoneuroimmunology') used cyclophosphamide, a widely prescribed and immunosuppressive chemotherapeutic agent, as an unconditioned stimulus (US) in their demonstration of behavioral conditioning of the immune response in rats (R and N, 1975). Conditioned immunosuppression was subsequently demonstrated in cancer patients undergoing chemotherapy, where blood samples taken several days before scheduled treatment showed greater lymphocyte proliferative capacity when compared to samples drawn just prior to treatment (Bovbjerg et al., 1990). Around the same time, Besedovsky & colleagues demonstrated that the presence of neoplastic cells, either transplanted or autochthonous, could induce diverse changes in rat plasma endocrine profiles, a process that occurred before the tumors became palpable and when rats had no overt signs of disease (Besedovsky et al., 1985). Importantly, these endocrine changes were not observed upon injection of syngeneic non-cancer cells (e.g., hepatocytes). Studies such as these highlight potential pathways by which the brain can maladaptively regulate peripheral physiology (e.g., via modulating the immune response to chemotherapy), and how cancer in the body can disrupt systemic (e.g., endocrine) signals sensed by the brain (Spiegel, 2012; Sloan and Walker, 2019; Gillis et al., 2021).

We now know that tumors must adjust the physiology of their local environment in order to evade immune destruction and meet metabolic demands for growth and proliferation. This positions the host system as a major selective factor in the evolution of cancer (Basanta and Anderson, 2017). Mutant cells that are unable to break free of local homeostatic control mechanisms will be unable to form tumors. Cells that break past these barriers to the point that they are clinically relevant undergo a process of clonal evolution (Greaves and Maley, 2012), where the initial cell adapts to its environment, remodels it, and diversifies in a process promoting intratumor heterogeneity (ITH) (Gay et al., 2016). Competition between cancer cells (clonal interference) and with cells in the microenvironment leads to highly diverse tumors that are exquisitely adapted to their local niche. During cancer progression, interactions at the local level likely propagate to the entire host system, potentially resulting in adverse outcomes and ultimately, death (Vasquez and Borniger, 2020; Mu et al., 2018; Lee et al., 2014). It follows that approaches aiming to adaptively bolster homeostatic defenses against an evolving tumor may augment anti-cancer therapies (Gatenby et al., 2009).

In recent years, an appreciation of the complex interplay between the host system and cancer development has expanded further into the realm of the entire organism, with specific emphasis on the liver (Masri et al.,

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2016), musculoskeletal tissue (Flint et al., 2016), and the brain (Egeblad et al., 2010; Borniger et al., 2018; Dieterich and Bikfalvi, 2020; Burfeind et al., 2020a; Olson and Marks, 2019). Here, I use sleep disruption as an exemplar of the types of systemic problems cancer patients endure. I discuss evidence from my prior work on systemic and neurological effects of cancer development and the potential mechanisms underlying these problems. I do this to highlight the brain's role in sensing, integrating, and regulating cancer-induced changes in physiology. I further emphasize the types of questions that cancer models can help to address in PNI research.

2. Behavioral co-morbidities in people with cancer

Patients with cancer frequently experience systemic problems that are likely secondary to the primary tumor formation itself. These include disorders of physiological and behavioral homeostasis, including disrupted sleep, fatigue, and changes in appetite and food intake resulting in reorganization of systemic metabolism (Vasquez and Borniger, 2020; Flint et al., 2016; Baracos et al., 2018). These problems can be debilitating. For example, sleep disruption is strongly predictive of subsequent breast cancer mortality and patient quality of life, even when controlling for covariates like cortisol concentrations, hormone receptor expression, age, depression, cancer treatment, and metastatic spread (Palesh et al., 2014; Trudel-Fitzgerald et al., 2017). Up to 90% of breast cancer patients will experience chronic sleep disruption and fatigue following a cancer diagnosis, continuing through surgery, treatment, recovery, and remission (Budhrani et al., 2015). This phenomenon is also evident in other cancer patient populations, including those with lung (Masri et al., 2016; Vena et al., 2006) and colorectal cancer (Innominato et al., 2015), (Mogavero et al., 2021), (Costa et al., 2014), (Spiegel, 2012), (Spiegel et al., 1989).

There are two fundamental reasons why we lack a deep mechanistic understanding of these problems. The first is that due to the large heterogeneity of cancer types, treatment regimens, patient populations, and lifestyle factors that influence the host system, unraveling bidirectional communication between tumors in the periphery and the brain has remained challenging. The second is due to the limited interactions that occur between neuroscientists, cancer researchers, and clinicians, each of whom use specialized language in their respective fields. In recent years, however, an appreciation of the impact co-morbid cancer symptoms (e.g., sleep disruption) have on patients has galvanized researchers to work at the intersection of these fields (Monje et al., 2020). This has yielded significant research on how psychological stress, circadian/sleep disruption, or stimulation of specific areas of the brain influences distal cancer processes in the periphery (Ben-Shaanan et al., 2018; Thaker et al., 2006; Filipski et al., 2003; Hakim et al., 2014). However, studies on how non-CNS tumors may reciprocally influence brain function are scarce (Mampay, Flint, Sheridan). I believe this represents a major opportunity for psychoneuroimmunology, a discipline comfortable with questions that span multiple organ systems and large temporal scales.

3. Cancer as a homeostatic challenge

The PNI perspective allows us to 'zoom out' and think about neoplastic growth as a threat to the entire host system (i.e., as a homeostatic challenge). For as long as we have recorded our thoughts and observations, humans have been fascinated by a seeming paradox in nature: that organisms, which are composed of primarily soft and delicate material, are able to survive and thrive in a dynamic and harsh environment. This observation led Walter Cannon to develop the concept of 'homeostasis' (in the early 1900s), which forms the foundation of our understanding of how we interact with the environment in the most literal sense. The French physiologist, Charles Richet, emphasized this critical observation in 1900 (Richet, 1900):

> *"The living being is stable, …It must be so in order not to be destroyed, dissolved or disintegrated by the colossal forces, often adverse, which surround it. By an apparent contradiction it maintains its stability only if it is excitable and capable of modifying itself according to external stimuli and adjusting its response to the stimulation. In a sense it is stable because it is modifiable—the slight instability is the necessary condition for the true stability of the organism."* - From Walter Cannon's "*Wisdom of the Body*", 1939 (Cannon, 1939)

We now know that the brain plays an essential role in maintaining homeostasis in physiology and behavior. In response to (or in anticipation of) endogenous or environmental stimulation, it integrates salient cues (e.g., change in blood glucose (Burdakov et al., 2006; Burdakov et al., 2013), bright lights (Rossi et al., 1996), loud sounds (Kayser et al., 2005)) and exerts influence on distal tissues via both humoral and neural pathways in an attempt to re-establish systemic stability (Kalsbeek et al., 2010; Dunn, 2007). Additionally, the brain also directs adaptive changes in behavior that function to putatively facilitate the return to homeostasis (e.g., shivering (Thornhill and Halvorson, 1994), food seeking (Carus-Cadavieco et al., 2017; Betley et al., 2013), sleeping (Kilduff, 2011; Morairty et al., 2013)). Importantly, failure to restore physiological processes to their homeostatic range of functioning for extended periods can have deleterious consequences for the entire organism, including the development of chronic disease and ultimately, death (Beutler et al., 2017; Tan et al., 2016; Vaccaro et al., 2020). Cannon emphasizes the role of internal factors in challenging homeostasis: "*External conditions, however, are not the only factors which affect the internal environment. The activity of the body itself may upset homeostasis; and, if not guarded against, profound disorders may result.*" (Cannon, 1939)

I emphasize these points as cancer disrupts numerous internal factors that the brain regulates to maintain homeostasis. For example, leptin, an adipokine hormone that is primarily produced by white adipose tissue, acts centrally within the hypothalamus to inhibit food intake and regulate energy balance (Li, 2011). Within the hypothalamus, arcuate pro-opiomelanocortin (POMC)-expressing neurons are major targets for leptin's action. They project to the dorsomedial nucleus, paraventricular nucleus, and lateral hypothalamus in a circuit that transduces the adipocyte-derived signal into a neural code (Millington, 2007). Numerous studies have found altered leptin signaling directly in tumors and (more broadly) in the systemic circulation of cancer patients. Overexpression of both leptin and its long-form receptor (LepRb) have been noted in multiple cancers, including breast, colorectal, liver, and thyroid cancer (Ishikawa et al., 2004; Han et al., 2005; Koda et al., 2007; Rajesh and Sarkar, 2021). These findings have led to the development of several candidate therapeutics targeting leptin receptor signaling in cancer (Otvos and Surmacz, 2011). It follows that in order for these therapies to be successful, we need to understand how dysregulated leptin signaling in cancer interacts with normal hypothalamic circuitry regulating its function throughout the body.

Another major class of molecules disrupted by cancer are messaging signals of the immune system: cytokines and chemokines. For example, interleukin-6, a pleiotropic cytokine that acts on many target tissues throughout the body and brain is frequently dysregulated in cancer (Knüpfer and Preiss, 2010; Salgado et al., 2003; Kumari et al., 2016). In 'triple-negative' breast cancer, tumor cells can secrete IL-6 directly or in tandem with stromal cells to promote cancer cell dissemination in a CCL5/CCR5 dependent manner (Lee et al., 2014). IL-6 can act via its classical signaling pathway or via the soluble IL-6 receptor (i.e., *trans*-signaling) to influence the activity of distal organs, including the brain (Eskilsson et al., 2014; Timper et al., 2017). How CNS-relevant IL-6 signaling becomes disrupted during cancer progression, and whether this relates to the development of maladaptive behavioral phenotypes (indicating a potential breakdown in homeostasis) remains undefined.

4. Preclinical approaches towards understanding cancer-brain crosstalk

I will use an example from my prior work on sleep in cancer to illustrate how tumors in the periphery may influence the function of the brain from a distance. There is an assumption that disrupted sleep in cancer is secondary to the stress of a cancer diagnosis or the result of chemotherapy-induced inflammation (Bower and Lamkin, 2013; Bower et al., 2011; Borniger et al., 2015). These factors likely play a role; however, this view neglects the role the cancer itself may play in regulating sleep. This is important, as patients frequently experience sleep problems *prior* to their cancer diagnosis (Phipps Amanda et al.). I emphasize this as the interactions I detail below are independent from the large literature surrounding the effect of sleep/circadian disruption on cancer progression (Filipski et al., 2003; Hakim et al., 2014; Khalyfa et al., 2016; Blask et al., 2005; Haus and Smolensky, 1016), an area which is too broad to address adequately here.

We were first to describe a mechanism for non-metastatic breast cancer-induced sleep and metabolic disruption (Borniger et al., 2018). We characterized how sleep changes in a model of non-metastatic breast cancer (67NR syngeneic mammary tumor cells) using electroencephalography/electromyography (EEG/EMG) biotelemetry. It was important to begin by using a non-metastatic model, as we didn't want the cancer cells themselves to travel to the brain, lungs, or other sites that may independently influence sleep. This restricted the role the cancer could have on the brain to direct interactions with local nerves, or via secreted factors produced by cells within the tumor (i.e., cancer cells + stroma). Throughout the course of cancer progression, tumor-bearing mice reduced their locomotor activity and spent more time asleep during their active phase, indicating fatigue. Further, sleep the mice were getting was fragmented and of low quality. The effect of cancer on sleep was the strongest in the last few days of cancer progression (i.e., before endpoint criteria reached), so we focused on this timeframe when searching for a causal mechanism. Importantly, these aspects of sleep disruption are similar to those observed in patients with breast cancer (Innominato et al., 2016).

The obvious next step was to identify the neuronal substrate(s) driving sleep disruption. The hypothalamus is essential for normal sleep and wakefulness (Saper and Lowell, 2014) and discrete populations of neurons have been delineated based on their unique gene expression signatures, projection patterns, and/or developmental trajectory (Mickelsen et al., 2019; Bonnavion et al., 2016). In 1998, two groups published their findings describing a new group of neuropeptides exclusively expressed in the hypothalamus. Because of its anatomical location and similarity to the gut hormone secretin, the first group named these neuropeptides the 'hypocretins' (Lecea et al., 1998). The other team identified (unknowingly) the same neuropeptides via ligand screening against a library of orphan G-protein coupled receptors (GPCRs). When they infused these neuropeptides into the rat brain, they observed increased feeding behavior, leading them to name them the 'orexins' after the Greek word for appetite (*orexis*) (Sakurai et al., 1998).

These hypothalamic neurons are essential for the stability of wakefulness. Genetic ablation of hypocretin/orexin neurons or their neurotransmitter content results in the debilitating disorder narcolepsy (Chemelli et al., 1999; Hara et al., 2001; Crocker et al., 2005), which is characterized by aberrant transitions between arousal states. As we observed sleep fragmentation in response to breast cancer, we examined whether different populations of hypothalamic neurons were differentially active in tumor-bearing mice. We systematically examined immediate early gene expression (cFos) across the entire hypothalamus and found selective increases in hypocretin/orexin neuronal activity in tumor-bearing mice, without similar changes in co-mingled neurons that express melanin-concentrating hormone (MCH). When we examined the hypothalamus as a whole, there was no net increased in cFos expression between groups, suggesting that there was a specific effect of cancer on hypocretin/orexin neurons.

How does breast cancer distally alter the activity of these neurons in the hypothalamus? Hypocretin/orexin neurons are positioned as major systemic integrators, adjusting arousal in response to changes in metabolic state (Adamantidis and de Lecea, 2009; Borniger and de Lecea, 2019; Tyree et al., 2018). They express receptors for many systemic cues disrupted during cancer progression, including glucose, leptin, ghrelin, and insulin, among others. Tumor-bearing mice were hyperglycemic, and this was further associated with an upregulation of liver glucose production and impairments in insulin signaling (Borniger et al., 2018). Simultaneously, tumor-bearing animals showed increased sensitivity to the 'hunger hormone' acyl-ghrelin and reduced circulating concentrations of the 'satiety' hormone leptin. These signals converge on hypocretin/orexin neurons to increase their net activity, putatively promoting arousal and disrupted sleep. To test this idea, we used an orally available dual hypocretin/orexin receptor antagonist, Almorexant (ALX). Repeated administrations of ALX promoted deep, restorative sleep in tumor-bearing mice. More interestingly, blocking hypocretin/orexin signaling also attenuated hyperglycemia and normalized the expression of several metabolic genes in the liver.

Why would blocking the activity of neurons in the hypothalamus alter systemic glucose metabolism? Pioneering studies demonstrated that hypocretin/orexin neurons innervate diverse sympathetic outflow nuclei in the brainstem (Geerling et al., 2003; Peyron et al., 1998). Additionally, these neurons promote liver glucose production and elevations in circulating glucose via the sympathetic nervous system (Yi et al., 2009). Therefore, we hypothesized that blocking brain-to-body communication (i.e., via sympathetic denervation) would prevent cancer-induced hyperglycemia and liver dysfunction. To test this idea, we administered the neurotoxin 6-OHDA, which selectively destroys sympathetic noradrenergic nerve terminals and does not cross the blood brain barrier, to mice with and without tumors. In support of our hypothesis, we found that sympathetic denervation completely attenuated liver dysfunction in tumor-bearing mice, which was further reflected in reduced circulating glucose concentrations. Together, these studies provide evidence supporting the idea that non-metastatic cancer indirectly alters the activity of hypothalamic neurons controlling arousal and systemic metabolism, the latter via the sympathetic nervous system. This suggests that deleterious consequences often associated with cancer (sleep disruption and metabolic dysregulation) may develop as a result of aberrant homeostatic responses to cancer-induced changes in physiology.

5. Future work and outstanding questions

Studies such as the one I described above provide hints to the potential breadth of cancer's influence on the brain. Going forward, I believe cancer can be applied as a 'bottom-up' tool to address outstanding questions in psychoneuroimmunology. The use of autochthonous, syngeneic, and xenograft models allows for elegant experimental designs that can control for tumor immunogenicity, host genotype, and local tissue interactions that may all differentially influence the brain. Additionally, these can be combined with behavioral assays over long time scales (weeks to months), which allow for the careful charting of cancer's influence on the brain throughout tumor initiation, progression, and metastatic spread. Further use of optical tools (e.g., genetically encoded calcium indicators; GECIs (Tian et al., 2012)) permits longitudinal monitoring or manipulation of discrete neuronal populations in freely moving mice with or without tumors. Neuroscientists are additionally familiar with tract tracing techniques to map neural circuitry, usually between different brain regions or nuclei. Several of these tools are amenable for mapping brain-to-body circuits, such as pseudorabies viral vectors, which travel polysynaptically in the retrograde direction from the injection site to label all neurons in a circuit chain (Arriaga et al., 2015; Smith et al., 2000). Techniques such as these can reveal multi-synaptic innervation patterns for tumors in the body and investigation of how these differ from normal, adjacent tissue. *In vitro* techniques are also critical for reducing the complexity of biological

interactions present *in vivo*. Direct monitoring and manipulation of neuron/cancer co-cultures are now possible while keeping each cell type in their own separated compartments, a technique that was recently used to reveal a role for sensory nerves in providing the amino acid serine to pancreatic tumors (Banh et al., 2020). Recent advances in immunophenotyping (e.g., mass cytometry (Spitzer and Nolan, 2016; Keren et al., 2019)), RNA-sequencing (Hwang et al., 2018), and imaging (e.g., Deep Learning-enabled Metastasis Analysis in Cleared Tissue; DeepMACT (Pan et al., 2019)) allow for causal relationships between tumor phenotype, host response, and brain activity to be distinguished.

These strategies can be used to address several outstanding questions regarding cancer-brain crosstalk:

- What brain areas sense and integrate cancer-derived signals?
- How do these dynamics change over the course of cancer progression?
- When and how do cancer-induced changes in physiology reach conscious awareness (e.g., nausea, pain, fatigue)?
- How do cancer treatments alter these pathways?

Further, collaborations with computational scientists will be invaluable in developing models of cancer-associated physiological/behavioral disruption which can then be empirically tested. Additionally, understanding how tumor-derived signals alter non-neuronal cells within the CNS (e.g., glia, endothelial cells) is an area that requires significant work (Burfeind et al., 2020b), although some progress has been made in the peripheral nervous system (Stierli et al., 2019). Together, our evolving concept of cancer as a unique challenge to the host system, combined with recent technological advances in experimental tools, yields a fertile research area for further work. I believe that this integrative approach will provide the greatest benefit to those suffering from cancer.

COI statement

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Jeremy C. Borniger, PhD. Dr. Borniger is an assistant professor at Cold Spring Harbor Laboratory in New York. Born in Washington, D.C., he received his B.A. in biological anthropology from Indiana University – Bloomington and then his Ph.D. in neuroscience from The Ohio State University. He then completed a BRAIN Initiative postdoctoral fellowship at Stanford University before starting his faculty position in early 2020. His group is focused on unraveling the complex interactions between the nervous system and cancer in the body. To accomplish this, his lab uses techniques from systems neuroscience, immunology, and molecular biology to interrogate neuronal-cancer interactions at multiple spatiotemporal scales. In his dissertation work, Dr. Borniger demonstrated that non-metastatic breast cancer could distally alter the activity of neurons in the hypothalamus controlling arousal and systemic energy balance. Blockade of this aberrant neuronal activity was sufficient to improve sleep and rescue systemic changes in metabolism. These findings provided a potential mechanism driving cancer-associated sleep disruption, which is a common complaint of patients with breast cancer. In his spare time, Dr. Borniger likes to play piano and scuba dive when he gets the chance.