Modulation of autonomic balance by tumors and viruses

Summary

Autonomic balance, a function generally under host control, is subject to modulation by other signalers. In some cases, modulation of host autonomic function through behavioral and physical stressors exerted by another individual may have negative consequences for the stress recipient by inducing sympathetic bias. Modulation of autonomic function may sometimes benefit one party at the expense of another. Tumors and HIV are examples of illegitimate signalers who may induce host sympathetic bias to promote their own growth and evade host immune surveillance. Paraneoplastic and paraviral syndromes such as hypertrophic osteoarthropathy, QTc prolongation, insomnia, and cachexia could be viewed as epiphenomena related to the tumoral and viral manipulation of host autonomic balance. In a more general framework, other paraneoplastic and paraviral syndromes may represent epiphenomena related to modulation of endocrine, cytokine, and autonomic functions by tumors and viruses to promote their own survival. Spatial distribution of cancers and viruses within the host may reflect affinity for strategic locations that facilitate manipulation of a variety of host functions including autonomic, endocrine, and cytokine regulation. A more general framework for understanding spatial distribution of diseases based on gradients of autonomic balance in the body are explored. Darwinian perspectives are discussed.

Introduction

In a series of hypotheses that are presented in this issue, we postulate that host response systems such as autonomic balance may be modulated by cancers and viruses to promote their own survival. Indeed, cancer cells have been shown to directly secrete Th2 cytokines and suppress host Th1 function. We postulate that the shift to Th2 bias is also mediated by tumor modulation of host autonomic balance to sympathetic bias.

Introduction

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The previously unexplained QTc prolongation seen in cancer patients suggests that tumors may induce systemic host sympathetic bias. Indeed autonomic dysfunction has been described as a rarely-occurring paraneoplastic syndrome [1]. We believe that many more paraneoplastic syndromes are unrecognized manifestations of sympathetic bias. For instance, in paper IX we hypothesize that hypertrophic osteoarthropathy (HOA), a condition of unknown origin associated with cancers and other chronic conditions, may also be mediated by sympathetic bias. Tumor induction of sympathetic bias may represent a phenomenon of “illegitimate signaling” in which an entity exploits host response systems for its own benefit.

If HOA and QTc prolongation in cancer patients represent epiphenomenon of adaptive functions of tumors, does the concept generalize to other par-
Paraneoplastic syndromes such as cachexia, fever, and pain may represent host consequences of the tumoral drive to grow and evade surveillance by inducing host sympathetic and Th2 bias. While host sympathetic bias in these conditions can be induced by mechanisms such as hypoxia, host Th2 bias may be promoted by cytokines such as TNF-alpha, interleukin-6, leukemia inhibitory factor, and others [4]. Another paraneoplastic syndrome, acanthosis nigricans, is associated with insulin resistance, hyperinsulinemia, insulin-like growth factor (IGF)-1, fibroblast growth factor (FGF), epidermal growth factor (EGF), and transforming growth factor (TGF)-α [5–9]. These growth factors are considered to be important drivers of tumor progression [10,11], suggesting that acanthosis nigricans may be a signature of tumor subversion of the host growth axis. Humoral hypercalcemia of malignancy (HHM), characterized by tumor production of parathyroid hormone-related protein (PTHrP), may reflect a tumor adaptation to divert host ionic resources such as Ca²⁺ and phosphate to phosphate is an important constituent for cancer intracellular signaling [12] and gene regulation [13], and phosphate is the backbone of signaling and ATP formation. Ca²⁺ signaling is important for growth of prostatic carcinoma cells and the increased expression of CaT1, a channel protein highly selective for Ca²⁺, has been implicated in prostate cancer progression [14]. Ca²⁺ signaling inhibition is an anti-tumor strategy in development [15].

Other paraneoplastic syndromes may reflect consequences of tumoral manipulation of the hypothalamic–pituitary–end organ axes. How does subverting these host systems benefit tumors? Through direct synthesis, secretion of pro-hormone converting enzymes, or production of hypothalamic–pituitary stimulating hormones (e.g. ACTH), a tumor can increase levels of hormones such as cortisol, HCG, and ADH. Cross talk of these hormones with cytokines can shift host immune balance to Th2 bias, a more favorable state for tumor evasion of immune surveillance [16–20]. Some tumors also interfere with circadian rhythms, resulting in suppression of protective pathways of dehydroepiandrosterone (DHEA) and melatonin while activating autonomic and endocrine stress pathways of the hypothalamus and induce shift to Th2 bias [4,21–26]. Tumor-induced shift of host immunity to Th2 may play a role in autoimmune-mediated paraneoplastic syndromes such as Sweet syndrome, arthropathy, Eaton–Lambert myasthenia syndrome, polymyositis, polyneuropathy, retinopathy, and lupus [27–31]. Precise understanding of the mechanisms underlying these conditions remains elusive, but there is data to support the notion that these conditions are favored in Th2 biased states with elevation of Il-4 [32,33]. The relationship between Th balance and autoimmune diseases remains a topic of hot debate: some studies report cytokine profiles consistent with Th2 inflammation while other studies measure the Th1 response to the Th2 inflammation [34,35]. That cancers induce immune dysregulation is uncontroversial, but the assertion that autoimmune paraneoplastic syndromes are manifestations of this immune dysregulation requires further investigations.

In the context of our framework, multiple endocrine neoplasia (MEN) may represent a special case of tumoral modulation of host function. Unlike other cancers which unilaterally commandeering host functions, MENs appear to take a multilateral approach. MEN-1 can manifest synchronous or asynchronous neoplasias of the parathyroid, pancreas, pituitary, adrenals and thyroid gland as well as carcinoid tumors. These neoplasias are associated with abnormal production of hormones that can be seen as tumoral subversion of host pathways for growth and immunity including insulin, parathyroid hormone, growth hormone, gastrin, and catecholamines [36]. MEN-2 can manifest parathyroid tumors, pheochromocytoma and medullary thyroid cancer. These tumors engender hypermetabolic and hypersympathetic states in the host through the secretion of factors such as catecholamines and parathyroid hormone, which may promote tumor survival by supporting growth functions and shifting Th balance to Th2 bias. Interestingly, MEN-1 and MEN-2 are associated with specific mutations: a mutation on band 11q13 on MEN-1 and the RET mutation on MEN-2 [37]. Whether one takes the view that MEN represents clustering of distinct
tumors or is a complex manifestation of a single entity, the collective autonomic and endocrine output can be seen as a sophisticated multilateral subversion of host functions.

Modulation of host function by HIV and other viruses

A parallel argument could be made in the case of viral modulation of host pathways. For instance, modulation of host immunity has been observed in human immunodeficiency virus (HIV) infections. HIV is believed to influence host immunity through a variety of mechanisms including direct effects on host T cell survival, indirect effects on cytokine profile through modulation of immune cells, and modulation of endocrine functions that affect immunity such as steroids. HIV, like cancers and other viruses, directly encode for cytokines that modulate immune balance in their favor [38]. Gp160, an envelope protein of HIV, induces production of Th2 cytokines such as IL-5, IL-6, and IL-10 by host CNS cells, further enhancing their immune shroud [39].

In article X, we argue that HIV infection may also alter host immunity through modulation of host sympatho-vagal balance. Specifically, HIV may drive autonomic balance towards sympathetic bias, which can contribute to a more virus-friendly Th2-biased immune environment. Many of the syndromes associated with HIV such as fever, cachexia, QTc prolongation, accelerated coronary disease, atopic dermatitis, asthma, and hyper-IgE syndromes may be attributable to HIV modulation of autonomic and immune balance to sympathetic and Th2 bias, respectively [40–43]. Interestingly, the biology of HIV disease has been compared to the biology of aging [44].

Although the exact mechanism by which HIV modulates host autonomic function remains an enigma, direct modulation of hypothalamic function by the HIV itself is possible. HIV has shown a predilection for the central nervous system (CNS) and localizes in high concentration in the hippocampus, basal ganglia, and other regions involved in hypothalamic regulation. The immune-privileged CNS is an ideal hideout for HIV since the blood-brain barrier protects the CNS from Th1 immunity and anti-viral therapy. That HIV thrives in these regions, and the observation that gp120 envelope protein can activate the hypothalamic-adrenal stress axis in an experimental animal model, may indicate a plausible mechanism by which HIV might also directly modulate autonomic balance while residing unguarded in the CNS. Moreover, intraventricular injection of gp120 in rats significantly impaired function in the suprachiasmatic nucleus (SCN) [45]. The SCN is an area of the hypothalamus involved in biologic rhythms and setting autonomic balance in the body and its deterioration has been associated with age-related systemic dysfunctions [46–48]. As with cancer, the shift to host Th2 dominance achieved in part by autonomic modulation can be viewed as a viral adaptation to promote its own survival.

Other common diseases may reflect viral affinity for locations in the body that enable host autonomic modulation. Frequent settlement of viruses in the CNS, traditionally attributed to intrinsic Th2 bias of the CNS [49], may also be related to accessibility of structures that enable viral modulation of host functions. For instance, the propensity of herpes simplex Type 1 virus (HSV-1) to cause encephalitis in limbic structures was previously attributed to proximity of those regions to the point entry such as olfactory and trigeminal pathways [50]. Alternatively, since limbic structures are important in pathways that regulate host stress response [51–54], the settlement of HSV-1 in these areas can be viewed as an adaptive affinity for locations that enable modulation of key host pathways. Activation of host stress response by the virus may enable shift of host immune balance to Th2. Indeed, herpes viruses and other viruses can be reactivated systemically during times of stress or intercurrent infections [55], which may shift systemic autonomic balance and immune balance to sympathetic bias and Th2 bias.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) may also reflect settlement in tissues that enable exploitative modulation of host functions. Unlike hepatitis A virus, which is enterically acquired and may take residence in the liver due to the first-pass effect of portal circulation, HBV and HCV are acquired through sexual and blood-borne transmission. Thus, their affinity for the liver cannot be explained by direct vascular drainage from the site of entry. We propose that hepatic settlement by HBV and HCV may reflect an adaptive advantage associated with their ability to modulate host immunity by disrupting the hepatic glutathione pathway. Chronic HCV and HBV infections are known to lower glutathione levels [56]. Glutathione has been shown to promote Th1 function [57,58], and glutathione depletion has been shown to shift immune balance towards Th2 bias [59]. Glutathione has also been potentially implicated in impairment of vagal activity through the loss of responsiveness to oxidative stress [60]. Vagal impairment could partially account for the systemic
sympathetic bias observed in patients with cirrhosis and other chronic liver diseases [61].

As with cancer, many viruses also disrupt host sleep [62], a period that normally is dominated by parasympathetic and Th1 bias. By interrupting sleep, viruses may shift the host to sympathetic and Th2 bias [63–68]. Sleep disruption may be achieved by direct modulation in the CNS, and indirect effect on sleep centers through endocrine modulation such as cortisol or melatonin [69]. Awakening the host by triggering nocturnal coughing episodes, a common trait of many respiratory viruses, could achieve the same effect.

Spatial variation of diseases and autonomic-immune balance

Several sites in the body such as the CNS and gonads are well-known immune sanctuaries for secondary involvement of viruses and tumors. Relative Th1 absence in these regions likely represents host adaptations. Perhaps Th1 intrusions into the CNS are disruptive to neural networks that underlie cognition and other core neural functions. Th1 intrusion into gonads might elicit attack on haploid gametes. The adrenal glands may also represent de facto immune sanctuaries by virtue of their high local concentration of catecholamines and cortisol, which could create local Th2 bias. This might explain why adrenals are disproportionately involved in secondary viral and neoplastic diseases.

These examples suggest that physiologic and anatomic factors may create gradients of autonomic and Th balance in the body. For instance, normal pulmonary physiologic gradients of ventilation/perfusion (V/Q) ratio exist with lower V/Q ratio at the caudal regions of the lung compared to cranial areas [70–72], a circumstance attributed to gravitational effects on blood as well as other factors [73]. In regions of lower relative ventilation and oxygenation, the peripheral autonomic reflex activates the hypoxic pulmonary vasoconstrictor (HPV) response to maintain optimal gas exchange by decreasing perfusion to hypoxic regions [74,75]. Indeed assessment of spatial heterogeneity of HPV in the lungs shows higher vasoconstriction in caudal and dorsal areas of the lung [74]. A radial gradient of ventilation has been noted with lower ventilation in the peripheral lung compared to the hilum [76], leading to the possibility that the HPV response may be more active in periphery. Higher activity of HPV in the peripheral and basilar regions of the lung may be associated with relatively higher sympathetic activity [77], and thus, higher Th2 activity, in these regions. This spatial variation of autonomic and Th balance may account for the unexplained pattern of spatial distributions in many pulmonary diseases. Examples include the upper lobe predominance [78] of Th1-mediated diseases such as sarcoid [79,80] and the lower lobe and peripheral predominance [81–83] of Th2-mediated diseases such as idiopathic pulmonary fibrosis [84–86].

Notably, the physiologic autonomic gradients in the lungs can be rendered maladaptive in the setting of systemic sympathetic bias. Abnormal sympathetic bias can create intrapulmonary shunts by changing the receptor sensitivity of autonomic reflexes and inducing V/Q dysfunction and mismatch. Indeed, sympathetic bias [87,88] may underlie intrapulmonary shunts seen in association with conditions such as hepatopulmonary syndrome [89], respiratory distress syndrome of prematurity [90], ARDS [91], and post-operative state [92,93]. Respiratory sinus arrhythmias may represent a surrogate for assessing the degree of sympathetic bias [94].

Other subtle autonomic gradients may exist in the body and play a role in the distribution patterns of disease. For instance, there may be a parasympathetic to sympathetic gradient from the center of the body to the periphery and from large vessels to small vessels. These gradients might perhaps occur as a result of thermal gradients in the body or gradual oxygen desaturation in arteries as blood travels away from the heart. Regardless of the underlying mechanisms, the autonomic gradients may explain why Th1-mediated vasculitides such as giant-cell arteritis and Takayasu’s arteritis occur in large vessels while Th2-mediated vasculitides such as microscopic polyangiitis and Churg–Strauss disease predominate in small vessels [95–98].

Darwinian perspective

Cancers and viruses may view the host as a heterogeneous ecologic landscape with niches of varying opportunity. On a smaller scale, viruses and cancers face the same Darwinian challenges in the host micro-environment that hosts face in their macro-environment. Nutritional availability and stressors such as host immunity are selection variables for cancers and viruses. Variation and natural selection enable these entities to fill niches within the body such as the CNS that pose a lesser immune threat to their survival. Furthermore, viruses and cancer may settle in host locations that enable them to remodel their own environment. In some cases,
cancers and viruses may have deciphered the codes of host regulation and may be subverting important host pathways such as the autonomic system to enhance their own survival.

Evolution has endowed organisms with response mechanisms such as the autonomic system to enable the body to respond effectively to internal and external cues. Host response mechanisms, particularly if they are primitive or less plastic, are subject to exploitation by “illegitimate signalers” who seek evolutionary advantage [99]. The phenomenon of “illegitimate signalling” among humans is as old as human history, with spam email being the latest incarnation. The phenomenon of “illegitimate signalling” among other species is also widespread in nature. A classic example in nature is the exploitation of mating signals belonging to fireflies in the genus Photinus by predatory fireflies of the Photuris genus [100]. Photuris females can “break the code” of the mating signals of Photinus fireflies and lure the males to their death and consume them. Intraspecies competition can also foster exploitative modulation of host responses within species that leads to fitness transfer between conspecifics. Examples include the false alarm call of the willow tit, Parus montanus, designed to hoard food [101,102]. Exploitative modulation of host regulatory pathways by other entities may not have been anticipated during the evolutionary formation of these mechanisms. Perhaps insufficient time has passed for the evolutionary arbitrage to fade. In other cases, the maladaptive host response, despite the fitness lost to exploiters, still has aggregate positive fitness value to the host. Although the deceived host pays a fitness price by responding to “illegitimate signalers”, a complete failure to respond may be much more costly. For instance, the Photinus males would fail to reproduce and willow tit would fail to respond to life-saving alarm signals [99]. Thus, the modulation of host responses by other entities can be evolutionarily stable even if it is associated with asymmetric fitness consequences. This view has led to the suggestion that deception by illegitimate signalers should exploit host responses that have clear adaptive value to the host under most circumstances [103]. Modulation of host autonomic balance by cancers and viruses could be viewed as example of an adaptive manipulation.

Implications

Autonomic balance, a function generally under host control, is subject to modulation by other entities. Modulation may be induced by a legitimate partner, as may be the case when male seminal catecholamines shift the autonomic and immune balance in the female reproductive tract to enhance fertility [104]. In some cases, modulation of host autonomic function through behavioral and physical stressors exerted by another individual may have negative consequences for the stress recipient by inducing sympathetic bias.

We hypothesize that cancers and viruses may remodel systemic host functions such as autonomic balance to promote their own survival. Our theory has implications for management of these conditions. For instance, while obviously multi-factorial in etiology, the side-effects of chemotherapy such as nausea, colonic pseudo-obstruction, fever, QTc prolongation, decreased HRV, and tachycardia suggest a component of autonomic overdrive related to such treatments [105–110]. Similarly, the stress of oncologic surgery could theoretically induce sympathetic bias during the post-operative period [111,112]. Such sympathetic bias may partly undermine the beneficial effects of the chemotherapy and surgical resection. Better understanding of the role of autonomic balance may enable novel approaches for treating cancer and viral diseases.

In essence, cancers and viruses may have broken human biologic codes and are distorting host systems such as autonomic balance for their own benefit. Humans, too, have broken the biologic codes of viruses and other species and are harnessing their pathways to produce agricultural, industrial, and biopharmaceutical goods that enhance their own fitness. There may be other dimensions to the fitness transfer between viruses and hosts. For instance, retroviruses can act as sources of genomic innovations for hosts such that imperfect viral clearance mechanisms, not unlike low-fidelity DNA polymerases, may actually increase host fitness. Selfish modulation of host biology by tumors can promote their survival, but the ultimate fitness benefit is less apparent since cancers, excepting those mediated by retroviruses, can not outlive the host. Although cancers may represent host maladaptations unmasked by modern lifespan expansion, can cancers be adaptive for the host in certain situations? For example, could cancers enhance inclusive fitness of the host by enabling altruistic self-termination, thereby benefiting relatives at the expense of the individual under certain conditions? Alternatively, is it possible that tumors, which eschew apoptosis and seem to acquire capabilities for perpetual youth, represent failed fledgling attempts by the host organism to endow itself with the capabilities for perpetual lifespan? Future study of cancers may yield insights that permit us to harness their biologic pathways for purposes that enhance human fitness.
Article Titles

VIII. Tumors may modulate host immunity partly through hypoxia-induced sympathetic bias.
IX. Hypertrophic osteoarthropathy may be a marker of underlying sympathetic bias.
X. Modulation of host immunity by HIV may be partly achieved through usurping host autonomic functions.

References

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