



Nervous system regulation of the cancer genome

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ABSTRACT

Genomics-based analyses have provided deep insight into the basic biology of cancer and are now clarifying the molecular pathways by which psychological and social factors can regulate tumor cell gene expression and genome evolution. This review summarizes basic and clinical research on neural and endocrine regulation of the cancer genome and its interactions with the surrounding tumor microenvironment, including the specific types of genes subject to neural and endocrine regulation, the signal transduction pathways that mediate such effects, and therapeutic approaches that might be deployed to mitigate their impact. Beta-adrenergic signaling from the sympathetic nervous system has been found to up-regulate a diverse array of genes that contribute to tumor progression and metastasis, whereas glucocorticoid-regulated genes can inhibit DNA repair and promote cancer cell survival and resistance to chemotherapy. Relationships between socio-environmental risk factors, neural and endocrine signaling to the tumor microenvironment, and transcriptional responses by cancer cells and surrounding stromal cells are providing new mechanistic insights into the social epidemiology of cancer, new therapeutic approaches for protecting the health of cancer patients, and new molecular biomarkers for assessing the impact of behavioral and pharmacologic interventions.

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1. Introduction

Cancer is fundamentally a disease of dysregulated gene function that originates from structural genomic damage such as chromosomal amplifications, deletions, mutations, and rearrangements. The biological consequences of that structural genomic damage in cancer cells interacts with dysregulated expression of physiologic genes in neighboring healthy “stromal” cells to facilitate the unchecked growth and survival of cancer cells and their metastatic dissemination to distant tissues (Hanahan and Weinberg, 2011; Kinzler and Vogelstein, 1998, 2004). The development of high-throughput molecular technologies for mapping the structure of the human genome (e.g., “next generation” DNA sequencing) and quantifying the expression of all ~21,000 human genes (e.g., RNA sequencing and gene expression microarrays) has revolutionized cancer biology. Molecular genetics now constitutes the primary paradigm through which cancer is understood as a biological phenomenon, and genomics-based analyses are playing an increasingly prominent role in clinical cancer diagnosis and treatment selection (Kim and Paik, 2010), and in mapping the molecular lesions that cause cancer (Tomlins et al., 2005). In this review, we consider

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another domain in which genomics-based approaches have begun to revolutionize our understanding of cancer – in mapping the biological pathways by which patient-level social and psychological processes can influence the development, progression, and treatment of cancer. The human genome has evolved a broad transcriptional sensitivity to hormones and neurotransmitters that convey information from the social and psychological realm into molecular biological alterations that help the body respond to both current and anticipated homeostatic challenges (Cole, 2009). As pathological derivatives of normal human cells, cancer cells are also sensitive to neural and endocrine regulation, as are the surrounding immune cells, blood vessels, and other stromal cells that interact with tumor cells within the “tumor microenvironment” (Antoni et al., 2006). Thus, the same gene regulatory programs that allow social and psychological processes to modulate healthy human genome function can also modulate the altered cancer genome, and thereby influence the development and progression of neoplastic disease.

2. Social and psychological regulation of the human genome

2.1. Gene programs

The potential for psychosocial regulation of human gene expression first emerged in the context of studies analyzing the

effect of social stress on viral genomes such as Herpes Simplex viruses (Glaser et al., 1985; Jenkins and Baum, 1995; Kupfer and Summers, 1990; Leib et al., 1991; Padgett et al., 1998; Rasmussen et al., 1957; Schuster et al., 1991), Human Immunodeficiency Virus (HIV-1) (Capitani et al., 1998; Cole et al., 1996, 1997; Sloan et al., 2007), Epstein–Barr virus (Glaser et al., 1985; Yang et al., 2010), Cytomegalovirus (Glaser et al., 1985; Prosch et al., 2000), and the Kaposi's Sarcoma-Associated Human Herpesvirus 8 (Chang et al., 2005). As obligate parasites of human host cells, viruses have evolved within a micro-environment structured by our own genome. If social factors can regulate the expression of viral genes, it stood to reason that our own complement of ~21,000 genes might also be regulated by social and psychological processes.

Over the past 5 years, a series of genome-wide transcriptional profiling studies has found that extended periods of psychological or social stress are often associated with a specific pattern of differential gene expression in human immune cells. Across several distinct types of adversity such as social isolation (Cole et al., 2007, 2011; Creswell et al., 2012), imminent bereavement (Miller et al., 2008b), low socioeconomic status (SES) (Chen et al., 2009, 2011), early life social deprivation (Miller et al., 2009b), late life social adversity (Cole et al., 2010), traumatic stress (O'Donovan et al., 2011), diagnosis with a life-threatening illness (Antoni et al., 2012; Cohen et al., 2012), and experimentally imposed social threat (Cole et al., 2010; Sloan et al., 2007, 2010), circulating leukocytes show a common pattern of transcriptional alteration involving increased expression of genes involved in inflammation (e.g., *IL1B*, *IL6*, *IL8*, *TNF*) and decreased expression of genes involved in innate antiviral responses (*IFNB*, *IFIs*, *MX*, *OAS*) and antibody production (particularly the IgG1 isotype) (Cole, 2009, 2010; Irwin and Cole, 2011; Miller et al., 2009a). Each type of adversity is also associated with other transcriptional alterations that are relatively unique to that condition. However, this core pattern of pro-inflammatory and anti-antiviral transcriptome shift emerges much more consistently across diverse types of adversity than would be expected by chance, and similar patterns also emerge in response to experimentally imposed adversity in animal models of social instability, low social rank, and social threat or defeat (Cole et al., 2010, 2012; Irwin and Cole, 2011; Tung et al., 2012). With the statistical challenges of multiple hypothesis testing across ~21,000 genes, these studies rarely find identical sets of differentially expressed genes (although all studies apply standard False Discovery Rate analyses to limit the rate of false positive findings). Consistent patterns are most apparent in subsequent bioinformatic analyses extracting common functional themes from the lists of 10s–1000s of differentially expressed genes (e.g., Gene Ontology annotations regarding shared biological functions and analyses of transcription control pathways regulating expression of multiple genes) (Cole, 2010). The recurrence of these core pro-inflammatory/anti-antiviral biological themes across both different adverse environments and different mammalian species suggests that there may exist a conserved transcriptional response to adversity (CTRA) which is triggered whenever individuals experience extended periods of stress, threat, or uncertainty (Antoni et al., 2012; Irwin and Cole, 2011). This general transcriptional program may be expressed somewhat variably at the level of individual gene transcripts depending upon specifics of individual history, genetic background, and particulars of the current environment (Cole, 2010). A key role for psychological experience in triggering the CTRA dynamic is suggested by results from several small randomized controlled experiments showing that stress-reducing interventions can reverse CTRA transcriptional dynamics in human immune cells (Antoni et al., 2012; Black et al., 2012; Creswell et al., 2012).

CTRA transcriptional dynamics appear to represent an evolutionarily adaptive “defensive program” that redeploys

transcriptional resources to counter the changing patterns of microbial exposure historically associated with changing life circumstances (e.g., increased risk of wound-related bacterial infection during periods of acute threat vs. increased risk of viral contagion during extended periods of close social contact) (Cole et al., 2011; Irwin and Cole, 2011). Because antiviral and pro-inflammatory gene modules are to some extent mutually exclusive (Amit et al., 2009), the immune system must “choose” which gene module to favor at any given time. The CTRA dynamic suggests that that choice is informed in part by the broader physiological and environmental conditions surrounding the individual (i.e., organism-level adaptive fitness) (Cole et al., 2011; Irwin and Cole, 2011). However, when the CTRA defensive program is chronically stimulated, the resulting pro-inflammatory/anti-antiviral shift in leukocyte transcriptional equilibrium may promote the complex pattern of “modern mortality” diseases involving both up-regulated immune function (e.g., inflammation-related diseases such as heart disease, neurodegenerative diseases, and some types of cancer) and down-regulated immune function (e.g., impaired response to vaccines and viral infections) (Finch, 2007). At the level of gene regulation, the CTRA profile underscores the fact that stress is not broadly immunosuppressive, but instead selectively suppresses some groups of immune response genes (e.g., Type I interferons and some immunoglobulin genes) while simultaneously activating others (e.g., pro-inflammatory cytokines) (Irwin and Cole, 2011).

Adverse social conditions can also regulate gene expression in a wide variety of other tissues besides circulating leukocytes, including the central nervous system (Karelina et al., 2009; Karszen et al., 2007; Weaver et al., 2006) and peripheral lymphoid organs such as the lymph nodes and spleen (Cole et al., 2010; Sloan et al., 2007). Given the much smaller number of social genomics analyses targeting solid tissues, and the relative difficulty in ascertaining the functional significance of specific transcriptional alterations outside the well-charted territories of immune response, it is not yet clear what specific “gene programs” are being activated in these other tissue contexts (e.g., are these tissue “defensive programs” analogous to the leukocyte CTRA, or do they represent some other type of functional adaptation specific to the organ system involved?).

2.2. Signal transduction

The widespread penetrance of social and psychological conditions into gene regulatory dynamics in diverse tissue sites implies that there must exist some specific transcription control pathways that are sensitive to socio-environmental conditions. Pharmacologic and molecular dissection of the leukocyte CTRA dynamics has provided a prototype for mapping such “social signal transduction” pathways (Irwin and Cole, 2011). Biologists have traditionally construed “signal transduction” as the set of events that translates extracellular biochemical signals, such as hormones or neurotransmitters, into changes in gene expression through the activation of protein “transcription factors” which bind to DNA and flag it for transcription into RNA (Fig. 1). “Social signal transduction” extends this analysis to include the upstream neural dynamics that translate social conditions into specific systemically distributed signaling molecules (e.g., glucocorticoids from the hypothalamus–pituitary–adrenal (HPA) axis or catecholamines from the sympathetic nervous system (SNS)), and to include the specific downstream gene modules that are activated by a given transcription factor. For example, when norepinephrine is released from the SNS during fight-or-flight stress responses, cells bearing beta-adrenergic receptors translate that signal into activation of the transcription factor CREB (cyclic 3'–5' adenosine monophosphate response element-binding protein) (Sanders and Straub, 2002).

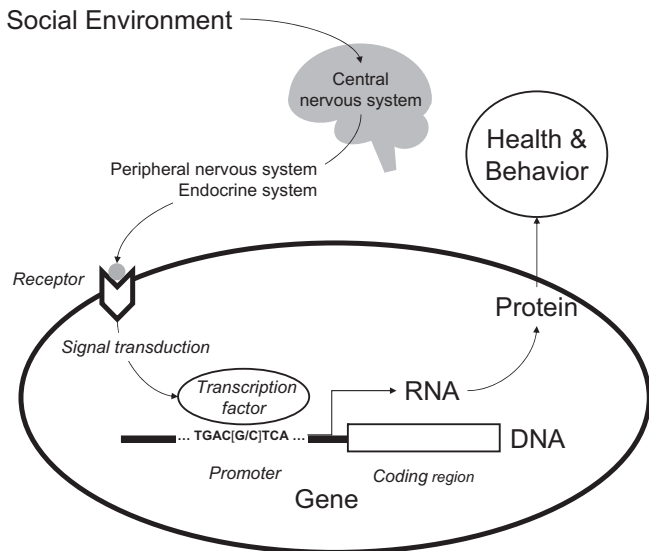


Fig. 1. Social signal transduction. Socio-environmental processes regulate human gene expression by activating central nervous system processes that subsequently influence hormone and neurotransmitter activity in the periphery of the body. Peripheral signaling molecules interact with cellular receptors to activate transcription factors, which bind to characteristic DNA motifs in gene promoters to initiate (or repress) gene expression. Only genes that are transcribed into RNA actually impact health and behavioral phenotypes. Individual differences in promoter DNA sequences (e.g., the [G/C] polymorphism shown here) can affect the binding of transcription factors, and thereby influence genomic sensitivity to socio-environmental conditions.

Activated CREB proteins can up-regulate the transcription of hundreds of cellular genes (Zhang et al., 2005). Which genes can be activated by CREB is determined by the nucleotide sequence of the gene's promoter – the stretch of DNA lying upstream of the coding region of the gene that is transcribed into RNA. For example, CREB binds to the nucleotide motif TGACGTCA, whereas the pro-inflammatory transcription factor NF- κ B targets the motif GGGACTTCC. These two transcription factors are activated by different receptor-mediated signal transduction pathways, providing distinct molecular channels through which extra-cellular signaling molecules, and by extension, their upstream environmental triggers, can regulate intracellular genomic responses. The distribution of transcription factor-binding motifs across our ~21,000 genes' promoters constitutes a “wiring diagram” that maps specific types of environmental processes (e.g., infection vs. a fight-or-flight stress response) onto a specific pattern of genome-wide transcriptional response (e.g., CREB vs. NF- κ B target genes). In that sense, each transcription factor can be said to represent some type of evolutionarily significant characteristic of the environment outside the cell (e.g., CREB = “threat or stress”, NF- κ B = “microbe or damaged cell”), and the distribution of transcription factor-binding motifs across our 21,000 genes can be understood as an evolved “wisdom of the genome” regarding which genes should be activated to optimally adapt to that environment.

Signal transduction research initially analyzed the role of physicochemical or microbial stimuli in activating transcription factors, but studies of social signal transduction have begun to highlight an additional role for subjective psychological perceptions in regulating gene expression (Cole, 2009, 2010; Irwin and Cole, 2011). Several studies suggest that activation of the leukocyte CTRA is more closely linked to subjective perceptions of social threat than to objective characteristics of the social environment (Chen et al., 2009; Cole, 2009; Cole et al., 2007, 2011; Irwin and Cole, 2011; Miller et al., 2008b), and CTRA transcriptome skewing can be

reversed by psychological interventions that reduce perceived threat (Antoni et al., 2012) or isolation (Creswell et al., 2012). These subjective psychological experiences may also be transduced into gene expression via different receptor systems than are microbial or chemical stimuli (e.g., through activation of the glucocorticoid receptor (GR) by the HPA-axis or activation of β -adrenergic receptors by the SNS). The extensive cross-talk among post-receptor signal transduction pathways within the cell may also allow stress-responsive mediators such as the SNS and HPA-axis to modulate other signaling pathways that are more classically activated by physicochemical or microbial stimuli. For example, β -adrenergic signaling can up-regulate activity of immune response transcription factors such as NF- κ B (Bierhaus et al., 2003) and GATA family factors (Cole et al., 2010), and inhibit activity of Interferon Response Factors (IRFs) (Collado-Hidalgo et al., 2006). In contrast, activation of the GR inhibits all 3 of those pathways (Irwin and Cole, 2011). The contrasting gene regulation programs of the SNS/ β -adrenergic and HPA/GR pathways suggests that different types of psychological adversity may elicit different transcriptional responses by triggering different profiles of neural or endocrine responses (Cole, 2010; Frankenhaeuser et al., 1980; Henry, 1992; Lundberg and Frankenhaeuser, 1980).

Identification of the specific transcription factors mediating social and psychological influences on gene expression has been greatly accelerated by bioinformatics analyses that make use of gene promoter sequence data to infer functional activation of transcription factors based on patterns of differential gene expression derived from genome-wide transcriptional profiles (Cole, 2010). This approach scans the promoters of activated genes for transcription factor-binding motifs that are highly over-represented relative to their prevalence across the genome as a whole, and might thus indicate which transcription factor is structuring the observed differences in gene expression (Cole et al., 2005). For example, the genes up-regulated in tissues from people experiencing extended social adversity often bear a high prevalence of CREB target sequences (Cole et al., 2007; Lutgendorf et al., 2009), which is consistent with CREB's role in mediating transcriptional effects of β -adrenergic receptor activation (Sanders and Straub, 2002). In the context of the leukocyte CTRA, promoter bioinformatics have implicated increased NF- κ B activity in the up-regulated pro-inflammatory gene component and decreased IRF activity in its anti-antiviral component (Cole, 2009, 2010; Irwin and Cole, 2011). Several studies have also linked chronic stress to reduced (not increased) expression of GR target genes despite the presence of stable or increasing levels of glucocorticoid hormones (Cole et al., 2007; Miller et al., 2008b, 2009b; O'Donovan et al., 2011). That paradoxical effect appears to stem from a stress-induced functional desensitization of the GR, which renders the leukocyte transcriptome partially deaf to glucocorticoid signaling (Cole et al., 2007; Miller et al., 2008b). A similar “glucocorticoid desensitization” dynamic has been observed in mice repeatedly exposed to social threat and appears to be mediated by increased SNS activation of β -adrenergic signaling pathways (Hanke et al., 2012).

2.3. Limitations and prospects

Although much has been learned in the past 5 years regarding how social and psychological processes can potentially regulate human gene expression programs, this literature is still nascent and much remains to be clarified regarding when and how these dynamics actually operate in the context of human health and disease. Most “social genomics” studies have focused primarily on mRNA levels and involve limited, if any, assessment of their downstream impact on protein expression, cellular function, and clinical health outcomes. Human social genomics studies of risk factors such as social isolation, bereavement, PTSD, and low SES generally

involve observational designs subject to potential confounding or reverse causation (Chen et al., 2009; Cohen et al., 2012; Cole, 2008; Lutgendorf et al., 2009; Miller et al., 2008b; O'Donovan et al., 2011; Segman et al., 2005). However, the predicted reversal of CTRA dynamics by positive psychological interventions in randomized experiments (Antoni et al., 2012; Creswell et al., 2012) and the parallel impact of experimentally imposed social adversity in animal models (Cole et al., 2010, 2012; Irwin and Cole, 2011; Tung et al., 2012) both suggest that the human observational associations could potentially reflect, at least in part, causal effects of social conditions on gene expression. The first generation of human social genomics studies also involved relatively small sample sizes (Chen et al., 2009; Cohen et al., 2012; Cole, 2008; Lutgendorf et al., 2009; Miller et al., 2008b; O'Donovan et al., 2011; Segman et al., 2005), as does the currently available stock of human experimental intervention studies (Antoni et al., 2012; Black et al., 2012; Creswell et al., 2012). It is promising, however, that some of those initial observational studies have now been replicated in more robust study samples (Chen et al., 2011; Cole et al., 2011; Miller et al., 2009b), that relatively similar patterns of results provide some measure of conceptual replication across the existing set of small human intervention studies (Antoni et al., 2012; Black et al., 2012; Creswell et al., 2012), and that similar CTRA dynamics are observed in experimental animal models (Cole et al., 2010, 2012; Irwin and Cole, 2011; Tung et al., 2012). It is also important to recognize that, although there are some core similarities in the nature of the gene programs regulated across different types of adversity (i.e., the CTRA), most social environmental risk factors are also associated with a distinctive set of transcriptional alterations not observed in other settings. Those distinctive profiles may be mediated by objective physicochemical, microbial, or behavioral exposures associated with those environments (e.g., social network influences on transmissible disease exposure (Cole et al., 2011), sleep disruption (Irwin et al., 2006), adiposity, physical activity (Zieker et al., 2005), depression/fatigue (Bower et al., 2011; Landmark-Hoyvik et al., 2009; Ohmori et al., 2005), or medication exposures (Felger et al., 2012)). In addition, little is currently known about social and psychological influences on gene expression profiles in neural, reproductive, or other tissue systems in humans or other primates. Much also remains to be learned regarding the kinetics and molecular mechanisms of CTRA dynamics. Leukocyte transcriptome shifts can emerge within the course of one week of overt social conflict (Cole et al., 2010) or a few months of general social instability (Cole et al., 2012), and human intervention studies have shown that reversal of the CTRA pattern can occur within periods as short as 8 weeks (Black et al., 2012; Creswell et al., 2012) and persist for at least a year (Antoni et al., 2012). However, finer-grained time-course studies will be required to more precisely quantify the kinetics of CTRA development, persistence, and reversal. The developmental stage of the individual may also play a major role in determining how deeply and persistently socio-environmental conditions influence gene expression (Chen et al., 2011; Cole et al., 2012; Miller et al., 2009b). Pharmacologic interventions (e.g., the β -adrenergic antagonist Propranolol) can block some pro-inflammatory responses to social adversity in mice (Hanke et al., 2012), but the transcriptome-wide impact and human applicability of these effects remains untested. Despite those limitations, the emerging multi-level analysis of the leukocyte CTRA in terms of psychological processes, neural and endocrine mediators, transcription factor activity, and specific target gene programs has provided a general biological framework for understanding how psychological and social processes might affect gene expression throughout the rest of the body's tissue systems, including potential effects on cancer cells and the tumor microenvironment.

3. Social and psychological regulation of the cancer genome

3.1. Clinical studies of human cancer

Several studies have now linked individual psychosocial conditions to altered patterns of gene expression within tumor tissues and immune cells from human cancer patients. Some of these studies have taken a purely "discovery-based" approach to describe empirically how social risk factors or a biobehavioral intervention modulate gene expression profiles at a global level. Other studies have used gene expression analyses to test specific hypotheses regarding social signal transduction pathways and the role of the immune system in modulating effects. Although the results of these studies are broadly consistent with the possibility that patient-level biobehavioral processes might influence gene expression in human cancer, no study has yet provided a clear causal demonstration of that dynamic.

In a study of 30 low-risk prostate cancer patients undergoing an intensive lifestyle modification program, Ornish and colleagues (Ornish et al., 2008) carried out genome-wide transcriptional profiling of prostate cancer needle biopsies collected at baseline prior to the intervention and again 3 months later. Results showed significant reductions in expression of several metabolic and growth-related gene modules (e.g., RAS family oncogenes and *FLT1*) as well as a reduced expression of the matrix metalloproteinase *MMP9*, which plays a role in tumor metastasis. Although no control group was available in this study, the observed gene expression changes paralleled pre-to-post intervention improvements in psychological function, body mass index, blood pressure, and lipid profiles.

Lutgendorf and colleagues (Lutgendorf et al., 2009) surveyed genome-wide transcriptional profiles in 10 primary ovarian carcinomas and found that tumors from patients with high levels of biobehavioral risk factors (high depressive symptoms and low social support) showed alterations in the expression of 266 genes relative to grade- and stage-matched tumors from low-risk patients. Promoter-based bioinformatics analyses tested the hypothesis that the observed transcriptional differences might be shaped by β -adrenergic signaling (as observed in previous cell culture models and in vivo animal models of ovarian cancer (Landen et al., 2007; Lutgendorf et al., 2003; Nilsson et al., 2007; Sood et al., 2006; Thaker et al., 2006)). Results indicated increased activity of β -adrenergic-regulated transcription factors from the CREB, NF- κ B, STAT, and Ets families. Also consistent with potential β -adrenergic regulation was the observation that high biobehavioral risk was associated with elevated intra-tumor concentrations of norepinephrine (Lutgendorf et al., 2009, 2011).

Fagundes and colleagues (Fagundes et al., 2012) carried out targeted profiling of four immune response genes (*CD25*, *CD3E*, *ICAM1*, *CD68*) in 91 basal cell carcinoma biopsies and found reduced average expression of those transcripts in patients who reported both early life emotional maltreatment and a severe life event within the year prior to biopsy. All participants in this study had a previous history of basal cell carcinoma prior to the diagnosis and biopsy of the analyzed tumor specimen, which provided an unusual opportunity to examine tumor-related immune response gene dynamics as they evolved in the aftermath of their primary antigenic challenge.

As part of a larger study on biobehavioral risk factors for disease progression in 217 patients with metastatic renal cell carcinoma, Cohen and colleagues (Cohen et al., 2012) conducted genome-wide transcriptional profiling of peripheral blood leukocytes from 31 patients to determine whether depressive symptoms were associated with increased inflammatory gene expression. Patients with high levels of depressive symptoms showed both shorter survival times

in the total-sample analysis and up-regulated expression of genes involved in inflammation (including *COX2/PTGS2*, *IL1A*, *IL1B*, *IL6*, *TNF*), oxidative stress (*SOD2*), and immunologic activation (*CD69*, *HLA-DR*, *CD83*) in the gene expression sub-study. Promoter-based bioinformatics analyses implicated increased activity of pro-inflammatory transcription factors (NF- κ B, STAT1) and transcription factors involved in myeloid cell differentiation and activation (EGR family factors, MEF2, MZF1) in structuring the gene expression alterations associated with high depressive symptoms. Histological analysis of primary tumor tissues confirmed leukocyte gene expression analyses in documenting increased density of tumor-associated macrophages and increased expression of pro-inflammatory and metastasis-related gene products. Together, these results suggest that systemic alterations in inflammatory and immune system homeostasis may mediate the relationship between biobehavioral risk factors and localized disease dynamics within the tumor microenvironment.

To determine whether a cognitive-behavioral stress management (CBSM) intervention might reverse leukocyte pro-inflammatory/CTRA dynamics in early stage breast cancer patients, Antoni and colleagues conducted genome-wide transcriptional profiling of peripheral blood mononuclear cells collected at baseline and at 6- and 12-month follow-ups from 79 stage 0-III patients randomized to a 10-week CBSM or active control condition (Antoni et al., 2012). At baseline, negative affect was associated with up-regulated expression of genes involved in inflammation (including *COX2/PTGS2*, *IL1A*, *IL1B*, *IL6*, *TNF*), oxidative stress (*SOD2*), and metastasis (*MMP9*). In analyses of pre-to-post-intervention changes in gene expression, CBSM showed significantly greater down-regulation of pro-inflammatory and metastasis-related genes and significantly greater up-regulation of type I interferon response genes compared to controls. Promoter-based bioinformatic analyses implicated decreased activity of NF- κ B and GATA family transcription factors and increased activity of IRF transcription factors and the glucocorticoid receptor as potential mediators of CBSM's effects on gene expression. This randomized intervention study provides the first demonstration that a psychologically-targeted intervention can causally influence gene expression in cancer patients. No measures of tumor tissue gene expression were available in this study, but several of the transcriptome changes observed in circulating leukocytes paralleled those observed within primary tumor tissues in experimental animal models of stress effects on breast cancer (Sloan et al., 2010).

The studies reviewed above show that patient-level psychological, neural, and endocrine processes are associated with differences in tumor-level gene expression. However, the majority of these studies reflect cross-sectional or longitudinal associations, and no experimental data have yet definitively demonstrated that psychological or neural/endocrine dynamics causally influence tumor cell gene expression. Given the potential for tumor-produced inflammatory mediators to influence CNS-related psychological and behavioral parameters (Dantzer et al., 2008), the observed associations could potentially reflect a reverse causal dynamic originating from naturally occurring variations in tumor biology. To help resolve the causal relations and more clearly define their molecular mechanisms, laboratory experimental models of human cancer have provided valuable new insights into the pathways by which biobehavioral processes can regulate gene expression in cancer.

3.2. Experimental laboratory models of human cancer

Many aspects of human cancer can be modeled in xenograft mouse systems, in which human tumor cells are introduced into immunodeficient mice, or in syngeneic tumor models in which mouse cancer cells are introduced into immunocompetent mice.

General results from this literature are reviewed elsewhere in this Special Issue (Armaiz-Pena et al., 2012), but some of these findings can be re-summarized specifically through the lens of gene expression. Many studies have shown that chronic stress can increase tumor development and/or disease progression (e.g., metastasis of solid tumors or dissemination of hematopoietic tumors). Pharmacologic and molecular dissection of these models has identified a diverse array of gene modules that appear to play a role in mediating such effects, including glucocorticoid-induced activation of the *SGK1* gene and associated inhibition of the key tumor suppressor p53 (Feng et al., 2012), and β -adrenergic induction of genes involved in macrophage recruitment and inflammation (Sloan et al., 2010), induction of pro-inflammatory cytokine genes such as *IL6* and *IL8* by tumor cells (Cole et al., 2010; Nilsson et al., 2007; Shahzad et al., 2010) and immune cells (Cole et al., 2010), VEGF-mediated increases in angiogenesis (Chakroborty et al., 2009; Thaker et al., 2006; Yang et al., 2006), matrix metalloproteinase-related increases in tissue invasion (Landen et al., 2007; Sood et al., 2006; Yang et al., 2006), tumor cell mobilization and motility (Drell et al., 2003; Lang et al., 2004; Palm et al., 2006), FAK-mediated resistance to anoikis/apoptosis (Sood et al., 2010), BAD-mediated resistance to chemotherapy-induced apoptosis (Sastry et al., 2007), and RANKL-mediated modulation of osteoclast function and bone metastasis (Campbell et al., 2012). Other studies have also shown that glucocorticoids can up-regulate a diverse array of genes involved in cell survival and resistance to chemotherapy (Kamradt et al., 2000a; Mikosz et al., 2001; Moran et al., 2000; Pang et al., 2006; Petrella et al., 2006; Wu et al., 2004, 2005), and activate oncogenic viruses such as Epstein-Barr Virus (EBV) (Cacioppo et al., 2002; Glaser et al., 1995; Yang et al., 2010) and Human Papilloma Viruses (Kamradt et al., 2000b; Mittal et al., 1993; Pater et al., 1988), and that β -adrenergic signaling can inhibit p53-mediated DNA repair (Hara et al., 2011), inhibit expression of Type I interferons (Collado-Hidalgo et al., 2006; Sloan et al., 2010) and interleukin 12 (Goldfarb et al., 2011), upregulate the *Her2* signaling pathway implicated in breast cancer (Gu et al., 2009; Shi et al., 2011), stimulate arachadonic acid signaling (Cakir et al., 2002), activate gene expression by tumor-promoting viruses such as HHV-8 (Antoni et al., 2006; Chang et al., 2005), and upregulate the *SNAI2* transcription factor regulating epithelial-mesenchymal transition (S. Cole, S. Lutgendorf, and A. Sood, personal communication). Each of the later molecular dynamics could plausibly mediate biobehavioral influences on tumor progression, but has not yet been shown to do so definitively through direct inhibition of in vivo tumor incidence or progression. However, it is clear that neural and endocrine dynamics can causally influence gene expression in cancer via both direct regulation of the cancer cell transcriptome and regulation of gene expression by other cells present in the tumor microenvironment such as macrophages, lymphocytes, and vascular cells.

Other studies have also documented stress effects on gene expression in tumor tissues without identifying specific neural or endocrine mediators. For example, stress can up-regulate the expression of pro-inflammatory chemokines and basal cell carcinoma development in the skin of UV-irradiated mice (Dhabhar et al., 2010; Parker et al., 2004; Saul et al., 2005) and modulate gene expression and tumor development in breast tissue (Hermes et al., 2009; McClintock et al., 2005; Williams et al., 2009).

Collectively, the data from experimental animal models of cancer suggest that tumor-level gene expression is shaped in significant ways by the broader physiological "macroenvironment" of the host (Antoni et al., 2006). Moreover, stress mediators such as glucocorticoids and catecholamines generally act to facilitate the progression of cancer (albeit with some exceptions (Cao et al., 2010)) because the molecular genetic "defense programs" they activate (e.g., inflammation, angiogenesis, cell survival,

proliferation, and epithelial-mesenchymal transition) are also those that are co-opted by cancer (Hanahan and Weinberg, 2011). As a result, pharmacologic antagonists of biobehavioral signaling pathways, such as the β -adrenergic receptor system, are often effective in blocking the effects of experimental stress on both tumor-level gene expression and macro-level measures of cancer incidence and progression in laboratory models of cancer (Cole and Sood, 2012).

3.3. Implications for cancer treatment

Given the generally salutary effects of non-selective β -adrenergic antagonists in laboratory experimental systems, there is growing interest in the potential translation of such approaches into human clinical oncology (Cole and Sood, 2012). A number of observational studies have found reduced disease progression rates and extended survival times in breast cancer, prostate cancer, liver cancer, and malignant melanoma patients who were incidentally receiving β -adrenergic antagonists at the time of cancer diagnosis (Barron et al., 2011; De Giorgi et al., 2011; Grytli et al., 2012; Lemeshow et al., 2011; Melhem-Bertrandt et al., 2011; Nkontchou et al., 2012; Powe et al., 2010) (though some studies fail to note such effects) (Shah et al., 2011). Epidemiologic analyses show little indication that β -antagonists can protect against the initial development of breast cancer (Bangalore et al., 2011) or most other types of cancer (Grossman et al., 2001), which is consistent with epidemiologic data suggesting that biobehavioral factors likely exert their greatest effects on the progression of incident cancer, rather than on the initial development of tumors (Antoni et al., 2006; Chida et al., 2008). Consistent with that observation, three studies have shown that psychosocial risk factors measured in patients at the time of diagnosis are associated with more adverse gene expression profiles in primary tumor tissues (Lutgendorf et al., 2009) and circulating immune cells (Antoni et al., 2012; Cohen et al., 2012), independently of established clinical pathology parameters such as tumor grade, stage, and other histological characteristics. Given these links between biobehavioral risk factors and adverse gene expression profiles, evidence of reduced disease progression in people receiving β -antagonists, and effects of CBSM in reversing adverse gene expression profiles in immune cells (Antoni et al., 2012) (as well as similar effects of behavioral interventions on leukocyte transcriptomes in non-cancer settings (Black et al., 2012; Creswell et al., 2012)), the time appears ripe for Phase II randomized controlled biomarker trials examining the effects of pharmacologic and/or CBSM interventions on gene expression profiles in tumor tissue and/or immune cells. Results of such studies would provide important proof-of-principle data to help rationalize larger Phase III trials gauging impacts on clinical outcomes (e.g., disease recurrence, survival, etc.), and help optimize interventions to achieve maximal biological impact. Further observational studies are not likely to decisively address such issues due to the confounding of biobehavioral risk factors (e.g., β -blocker indications such as cardiovascular disease, or socio-environmental risk factors such as depressive symptoms or isolation) with cancer-relevant host physiologic processes such as inflammation (Cole and Sood, 2012).

No human studies have examined associations between HPA-axis antagonists (e.g., RU-486) and clinical cancer outcomes or cancer-related gene expression, so the clinical relevance of that biobehavioral pathway remains poorly understood in humans. However, given the key role of endogenous glucocorticoids in inhibiting inflammation (an effect which should be salutary in the context of most cancers) and the key role of pharmacologic glucocorticoids in treating some types of cancer (e.g., hematological malignancies), pharmacologic antagonism of glucocorticoids would be a more challenging concept to advance. At the very least,

much more pre-clinical research will be required to understand the causal relationship between HPA-axis function, gene regulation, and tumor biology before HPA-axis-targeted interventions are contemplated in humans.

Beyond direct effects on tumor biology, biobehavioral gene regulation may also contribute to the quality-of-life decrements that constitute some of the most profound burdens of cancer and its treatment (Miller et al., 2008a). Two genome-wide transcriptional profiling studies have implicated dysregulated expression of immune response genes in the development of cancer-related fatigue (Bower et al., 2011; Landmark-Hoyvik et al., 2009), which is one of cancer's most debilitating sequelae. One study identified up-regulated expression of B lymphocyte-related transcripts (Landmark-Hoyvik et al., 2009) and a second identified increased expression of genes regulated by the pro-inflammatory transcription factor NF- κ B (Bower et al., 2011). The second study also indicated down-regulated expression of GR target genes, suggesting potential involvement of the leukocyte CTRA and its associated glucocorticoid insensitivity dynamic. Several studies have also linked cancer-related fatigue to promoter polymorphisms that up-regulate expression of the *IL1B*, *IL6*, and *TNF* genes (Saligan and Kim, 2012). In addition to shedding new light on the molecular etiology of cancer-related fatigue, these genomics-based analyses have identified specific transcription control pathways that may serve as targets for therapeutic intervention to improve quality of life in the aftermath of cancer.

3.4. Frontiers in cancer biology

In the decade that has passed since the initial sequencing of the human genome, molecular genomics analyses have vastly expanded our understanding of basic cancer biology and now provide a comprehensive mechanistic framework for mapping how psychological and social factors might influence those dynamics via neural and endocrine control of gene expression. Given recent developments in cancer genomics, we can anticipate several new areas in which our growing map of cancer's "genomic landscape" and the tumor microenvironment will intersect with our burgeoning understanding of social signal transduction in the broader "macroenvironment" of the human body (Antoni et al., 2006).

Perhaps the most significant opportunity lies in more precisely defining the specific molecular mechanisms by which social signal transduction interacts with the tumor genome. Major efforts are now underway to map the structural genomic landscape of cancer, and define the specific patterns of genomic damage (i.e., individual chromosomal deletions, amplifications, translocations, and mutations) the serve as causal drivers of tumor development and progression. As profiles of "usual suspect" genomic alterations become increasingly well-defined for specific types of cancer by The Cancer Genome Atlas and other projects (Cancer Genome Atlas Research Network, 2008; Wood et al., 2007), it will become increasingly apparent how those genomic alterations functionally affect cell growth, survival, metastasis, and other cancer-related biological dynamics. As a result of that convergence in structural and functional genomics, a broad range of new opportunities will arise to mechanistically determine when biobehavioral processes are most influential in the context of cancer (e.g., when their neural and endocrine representations physically interact with or functionally complement the genomic lesions that initiate a tumor) and when those processes may be comparatively unimportant (e.g., when a tumor has developed genomic alterations that mimic or supplant cancer-promoting effects previously supplied by the nervous or endocrine system). This potential can be understood as a Gene x Environment interaction in which social/psychological/neural/endocrine "environments" interact with genetic differences between healthy somatic cells and cancer cells in the same way

that biobehavioral signaling pathways have already been shown to differentially regulate alternative alleles of naturally occurring genes (Caspi and Moffitt, 2006; Cole et al., 2010). These developments open the possibility of extending the “personalized” diagnosis and therapy of cancer into the context of biobehavioral interactions to determine when and for which patients neural/endocrine or behavioral interventions might have the most clinical impact. Viewing biobehavioral influences on cancer genomes as a Gene x Environment interaction also raises the possibility that neural and endocrine dynamics might help shape the evolution of the tumor genome, for example, by selecting for genomic alterations that take advantage of the “ecological niche” supplied by stress biology. Combining our growing molecular portrait of biobehavioral influences and social signal transduction with the explosion of data on tumor genome sequences will revolutionize our ability to precisely specify how psychological and social dynamics influence the molecular pathogenesis of cancer.

Other areas in which genomics-based approaches will revolutionize biobehavioral cancer research include the increasing use of gene expression biomarkers to evaluate the impact of neural/endocrine or behavioral interventions on immune cells (Antoni et al., 2012; Cohen et al., 2012) and tumor tissue (Fagundes et al., 2012; Lutgendorf et al., 2009; Ornish et al., 2008), genomics-driven bioinformatics analyses to identify the basic biological “programs” that are subverted by cancer and modulated by the neural and endocrine systems (e.g., activation of the CTRE in leukocytes and the epithelial-mesenchymal transition in tumor tissues) and map the specific social signal transduction pathways mediating these effects (Cole, 2009; Irwin and Cole, 2011), as well as analysis of the gene expression dynamics in brain that mediate the conversion of socio-environmental stimuli into neural and endocrine influences on the tumor microenvironment (e.g., as in a pioneering analysis of hypothalamic *BDNF* activation dynamics in mouse models of melanoma and colon cancer) (Cao et al., 2010). Also critical will be more extensive studies of gene expression dynamics in tumor tissue itself, both in clinical human cancer samples and in experimental animal models, using in situ molecular mapping and genetics-based imaging strategies to provide both spatial/cellular resolution and longitudinal temporal resolution of the complex network of molecular transactions that develop between tumor cell populations and the cells of their surrounding microenvironments (Lamkin et al., 2012; Sloan et al., 2010). These developments will provide a much more comprehensive, integrative, and dynamic view of the interface between the biobehavioral macroenvironment of the human body and the complex molecular evolutionary dynamics of the tumor microenvironment. To the extent that these analyses can define some of the key regulatory forces that connect those two domains (e.g., particular transcription factors mediating biobehavioral influences), cancer patients may benefit from new therapeutic approaches that harness the “wisdom of the body” in the service of health.

Conflict of Interest

The authors of this manuscript have nothing to declare.

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