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INVITED REVIEW

Elevating the perspective on human stress genomics

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Summary Functional genomics strategies have been slow to penetrate research on human stress and coping, but recent conceptual advances have yielded a raft of new findings relating social and psychological conditions to broad alterations in human gene expression. This article reviews the field of human stress genomics, analyzes some of the conceptual and technical issues that initially hampered its progress, and outlines an abstractionist approach to genomic data analysis that has revealed a surprisingly consistent pattern of human transcriptional responses to diverse types of socio-environmental adversity. This field is now poised for another round of significant advances as research begins to incorporate the effects of DNA polymorphism, target a broader array of healthy and diseased tissues, and identify general teleologic and regulatory themes by pooling results over a growing body of studies analyzing the human transcriptional response to stress.

Contents

Genome-wide transcriptional profiling has revolutionized many areas of biology, but it has been slow to penetrate studies of human stress, coping, and biobehavioral health dynamics. This is ironic given that some of the earliest studies of genome-wide transcriptional regulation featured neuroendocrine response pathways such as the glucocorticoid receptor (Wang et al., 2004) and the catecholamine-linked cAMP/PKA signaling pathway (Zhang et al., 2005). The big impediments to a genomic conception of human stress response have not stemmed from the absence of a biological phenomenon, or from a lack of theory regarding the psychoneuroendocrinologic mechanisms and teleologic significance of such responses (Sapolsky, 1994; Weiner, 1992). What has slowed the field's progress has instead been conceptual

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limitations in the nature of the questions asked and the analytic infrastructure used to derive answers—issues that have also hampered functional genomic approaches to a wide variety of other fields as well. What is the human genomic response to stress, and how can we reliably detect it amidst a cacophony of ~22,000 gene transcripts that each serve multiple physiologic masters? Early interpretations stumbled on the complexity, but recent analytic advances now leave the field very much on the rebound.

1. The concept of stress genes

Initial studies of human stress genomics implicitly assumed the existence of a specific set of "stress response genes" (e.g., akin to specific "cancer genes") that were distinct from other types of genes and reliably associated with psychological states such as acute stress, PTSD, or depression (Kawai et al., 2007; Morita et al., 2005a,b; Nater et al., 2009; Rokutan et al., 2005; Segman et al., 2005). When stressed, the reasoning went, our sympathetic nervous system (SNS) or hypothalamic–pituitary–adrenal (HPA) axis should release hormones and neurotransmitters that ultimately trigger transcriptional up-regulation (or repression) of genes bearing response elements for mediator-linked transcription factors (e.g., the catecholamine-responsive CREB factor or the glucocorticoid receptor). Empirically, however, few individual genes showed consistent, reliable changes in expression in response to stress. Even repeated analyses from the same laboratory yielded inconsistent results (Kawai et al., 2007; Morita et al., 2005a,b; Ohmori et al., 2005; Rokutan et al., 2005). As we have learned more about the basic biology of functional genomics, several drivers of inconsistency have emerged.

First, measurements of individual gene transcripts are quite noisy, due to both technical variability (measurement error) and true biological variability across time and individuals. The poor signal-to-noise ratio, combined with limited replicate observations (due to the expense of microarray assays), left early analyses with extremely low statistical power to resolve differences in the expression of individual genes. Theoretical statistical analyses of representative microarray data sets suggest that an average 2/3 of true differences in gene expression are missed in typical microarray studies due to limited statistical power (Cole et al., 2003; Norris and Kahn, 2006). One implication of such poor power is that the failure of Study B to replicate differences observed in Study A may not imply that the positive results in A were false; the fault may lie in B's meager ability to detect the true result that fortuitously cleared the power threshold in A. This problem is exacerbated by the need to amortize the limited statistical power available over ~22,000 individual genes to protect against Type I error (even when utilizing comparatively powerful multiple testing strategies such as False Discovery Rate analysis) (Benjamini and Hochberg, 1995). As a result, many true results have likely either been missed or been erroneously discarded when they failed to replicate.

A second obstacle stems from the tissue-specific nature of gene expression. Unlike DNA, which is identical across tissues (barring some minor wrinkles involving germ cells, rearranged immune cells, damaged cancer cells, etc.), RNA expression varies substantially across cell types. There is no a priori reason to assume that stressful experiences, which most directly involve brain cell activity, will register similarly in the transcriptome of other more conveniently studied cell types such as circulating leukocytes. Several studies have shown that extended periods of social stress can induce broad alterations hippocampal and cortical gene expression profiles (illustrative examples include Karssen et al., 2007; Weaver et al., 2006a,b). However, no research has determined whether changes in CNS gene expression can be reliably gauged through more accessible proxy cells such as circulating leukocytes (Liew et al., 2006). It is theoretically plausible that some central-peripheral correlations might exist, because leukocytes bear receptors and signal-transduction apparatus for stress-responsive hormones regulated by the CNS (including catecholamines and glucocorticoids) (Gladkevich et al., 2004; Liew et al., 2006; Sanders et al., 2001). Immune cells "listen in" to neural and endocrine stress responses in much the same way as do other cells of the body. However, their transcriptional responses to such signals may be very different from those of other cells. The interpretive complexities arising from early studies' use of leukocyte reporter cells rendered it difficult to interpret the few gene expression dynamics that were empirically linked to stressful experience. We simply do not know whether any observed results represent general physiologic principles or leukocyte-specific dynamics.

A third problem hampering the stress genomics literature stems from the dynamic composition of the leukocyte reporter cell population. Most tissues maintain a relatively stable cellular composition over time, but the composition of the circulating leukocyte pool can change dramatically in response to stress. Rapid remodeling is driven by selective mobilization of specific leukocyte subsets such as NK cells and memory T cells via catecholamine effects on adhesion molecules and hemodynamics (Benschop et al., 1996; Richlin et al., 2004). HPA axis activation can also remodel the circulating leukocyte pool over the course of hours by altering activity of adhesion molecules and chemokines/receptors, thereby boosting neutrophil numbers and suppressing lymphocyte and monocyte representation (Cole, 2008; Cole et al., 2009; Miller et al., 1994). Redistribution of NK cells and monocytes is especially problematic because those cell types express high concentrations of mRNA and thus exert disproportionate influence on the total leukocyte RNA pool (Eady et al., 2005). Different leukocyte subsets express very different sets of genes (Eady et al., 2005; Palmer et al., 2006; Radich et al., 2004; Whitney et al., 2003), leaving it unclear whether any stress-induced changes in the population-level leukocyte transcriptome stem from alterations in the particular types of cells present in that pool or from per-cell changes in gene transcription (for a similar issue in the context of exercise, see Zieker et al., 2005). Studies have shown that the population-level transcriptome of circulating leukocytes can change significantly within 30–120 min of acute stress (Morita et al., 2005a,b; Nater et al., 2009). However, those effects are likely driven in large part by leukocyte redistribution, and the contribution of true transcriptional change remains highly uncertain. Per-cell transcriptional changes can easily be distinguished from redistribution effects through physical isolation of leukocyte subsets (e.g., capturing monocytes or NK cells by immunomagnetic isolation, as in Chen et al., 2009; Miller et al., 2008;

Richlin et al., 2004) or through analyses of covariance that assess the effects of stress after stripping away variations in gene expression that could be attributed to changing leukocyte subset composition (e.g., as measured by parallel flow cytometry or CD marker mRNA levels measured on the microarray, e.g., Cole et al., 2007a,b). Given the availability of such clarifying solutions, there is no reason to countenance further studies that fail to control for the effects of cellular redistribution on the population transcriptome of circulating leukocytes. In principle, other tissues composed of heterogeneous cell types such as CNS can also undergo compositional remodeling over time during normal development, ageing, and response to injury (e.g., epithelial–mesenchymal transition). The same analytic approaches of isolation and adjustment would clarify the mechanism of transcriptional remodeling in those contexts as well.

A fourth problem has to do with the basic concept of ''stress genes.'' Many investigations have simply presumed that stress genes are a real biological phenomenon—that some fixed set of genes embodying a generic stress response program would be activated in response to a given stressor in a relatively consistent way across individuals. This assumption is reminiscent of the ''cancer gene'' hypothesis in oncology and other essentialist conceptions in genomics, and none has fared well empirically. Cancer biologists now realize (actually rediscovered) that many different molecular damage profiles are capable of causing a single cancer phenotype (Vogelstein and Kinzler, 1998; Kinzler and Vogelstein, 2004). Psychoneuroendocrinologists are likely to discover many different transcriptional responses to stress. People exposed to the same objective conditions can develop different subjective (and by extension, physiologic) stress responses (Sapolsky, 1994; Weiner, 1992). The activated neural and endocrine mediators can also have different effects on different cell types, and can affect the same cell differently over time depending upon its current state of differentiation or health (e.g., involvement in a pathological signaling syndrome, viral infection, etc.). Most gene promoters are regulated by multiple transcription factors (Smale, 2001), allowing multiple physiologic processes to regulate a given gene's expression. Additional layers of regulatory complexity can arise from epigenetic modifications that block transcription factor access to DNA (Meaney et al., 2007) and trans-repression of one transcription factor by another (Pascual and Glass, 2006). It is unlikely that any gene is regulated solely and consistently by glucocorticoids or catecholamines, and thus constitutes a pure, reliable indicator of stress uncontaminated by other regulatory influences. Both at the cellular level, and by extension to the aggregate organismic level, there likely exists no unitary functional genomic response to stress. Which genes are stress-responsive depends on a wide variety of other considerations that are likely to vary across individuals, over time, and across cell types within an individual (Eady et al., 2005; Palmer et al., 2006; Radich et al., 2004; Whitney et al., 2003). To the extent that many different transcriptional responses can potentially be evoked by stress, the hunt for a single conserved set of stress genes in a small sample of individuals is a fool's errand at best.

As a consequence of these four issues, it remains difficult to interpret the early literature on the human functional genomic response to stress. The second and third problems suggest that some reported findings may not be true, the first implies that many true findings have may have been missed, and the fourth problem implies that there may not be any generally true findings to be found. Amidst all this trouble, however, the field of human stress genomics gained a new lease on life with the development of ''abstractionist'' approaches to data analysis.

2. Gene themes

The abstractionist approach to functional genomic data essentially concedes that individual gene-level data are intrinsically noisy, and shifts the focus of analysis instead toward higher order themes involving the biological causes and consequences of gene transcription. One type of aggregate theme involves commonalities in the functional characteristics of differentially expressed genes. Virtually all human genes are tagged with Gene Ontology (GO) functional annotations such as ''immune response,'' ''oxidative metabolism'' or ''receptor activity'' (Ashburner et al., 2000). These annotations map the names of differentially expressed genes into changes in their projected cellular function. So, a list of 1000 differentially expressed genes might translate into 10–100 functional characteristics shared in common by those genes (i.e., GO tags that are over-represented among the 1000 differentially expressed genes relative to those tags' basal prevalence over the entire genome). The GOstat bioinformatics site provides one straightforward implementation of this approach (http://gostat.wehi.edu.au) (Beissbarth and Speed, 2004). GO analyses automate the production of teleologic insight—what biological change is our genome trying to accomplish with a given transcriptional shift? Remarkably, the functional themes that emerge from GO annotation analyses show greater consistency across individuals and across different types of stressful situations than do the specific gene expression signatures themselves. For example, several recent studies of leukocytes sampled from people confronting long-term social adversities such as low socio-economic status, imminent bereavement, and subjective social isolation (loneliness) show a consistent profile of up-regulated ''immune response'' and ''inflammation''-related GO annotations (Cole et al., 2007a,b; Miller et al., 2008, 2009a,b), even though no single mRNA transcript was commonly up-regulated across all of those studies. That up-regulation appears to be specific to inflammation, as GO annotations related to ''antibody production'' and ''interferon antiviral response'' show recurrent down-regulation. These substantive findings have provided new biological insight because they can potentially explain the focal increase in prevalence of inflammation-related diseases in people confronting long-term social adversity, despite the fact that stress is often associated with increased levels of the anti-inflammatory glucocorticoid hormones. More on that regulatory paradox in a moment. The main point here is that higher order themes involving the biological consequences of transcriptional alteration can provide both deeper biological insight and a more stable profile of results than do analyses focused at the level of individual genes.

A second abstractionist approach focuses on commonalities in the regulatory pathways that cause differences in

gene expression. One approach scans the promoters of differentially expressed genes for transcription factor-binding motifs that are over-represented in those activated promoters relative to their basal prevalence across the genome as a whole (e.g., see http://www.telis.ucla.edu; (Cole et al., 2005). This analysis is based on the assumption that the activation of a given transcription factor should most strongly enhance transcription from those promoters which bear binding sites for that particular factor. As a result, the sub-population of activated promoters should show a statistical enrichment in binding sites for currently active transcription factors. Validation studies have confirmed that, for example, a pulse of glucocorticoid does indeed enhance the prevalence of promoters bearing Glucocorticoid Response Elements (GREs) among the group of genes showing empirical up-regulation (Cole et al., 2005) (for similar validations involving other transcription factors, see Cole et al., 2005, 2010a,b; Irwin et al., 2006, 2008). These promoter-based bioinformatic analyses have identified a common theme of decreased glucocorticoid receptor (GR)-mediated transcription in leukocytes from people subject to chronic social adversity (Cole et al., 2007a,b; Miller et al., 2009a,b, 2008). Decreased GR activity provides a molecular explanation for parallel indications of increased NF-κB signaling also observed in these studies, and for GO results indicating increased expression of pro-inflammatory genes. Indications of decreased GR signaling emerged in the absence of any decrement in circulating cortisol levels or GR mRNA expression that might explain them. Instead, reductions in GR-mediated transcription appear to reflect a post-translational modification of GR sensitivity to glucocorticoid ligands, which undermines the normal physiologic regulation of inflammation by the HPA axis (Cole et al., 2009; Pace et al., 2007). By identifying a change in GR transduction of glucocorticoid signals into gene expression, these abstractionist analyses provided new insights into the signaling basis for chronic stress effects on inflammation and their impact on the basal leukocyte transcriptome (i.e., these effects emerged in the absence of the artificial ex vivo TLR stimulation used in previous studies of glucocorticoid resistance). Also striking has been the consistency with which the GR desensitization/NF-κB activation dynamic has emerged across multiple studies involving distinct types of social adversity (Cole et al., 2007a,b; Miller et al., 2009a,b, 2008). As for functional "consequence themes," transcription factor "cause themes" yielded both new biological insights into the basic nature of stress genomics and a consistent pattern of effects that had not been apparent at the individual gene level of analysis.

How is it that abstractionist analyses can identify consistent biological themes when the specific gene expression changes they derive from are themselves inconsistent across studies? Part of the answer lies in the statistical advantages of mapping ∼22,000 genes onto ∼200 higher order themes involving gene function or regulation. The resulting ∼100-fold reduction in individual hypothesis tests yields a substantial increase in per-test statistical power as the study's total statistical power is dispersed over ∼100-fold fewer targets (Miller, 1986). In addition, the projection of ∼22,000 genes into ∼200 higher order constructs implies that each aggregate construct is measured by a large number of individual indicator genes. Assuming each aggregate construct is indicated by the activity of ∼100 genes (the number is likely higher because each gene can associate non-exclusively with multiple GO annotations or transcription factor motifs), this yields a ∼10-fold increase in the reliability with which aggregate constructs are measured relative to measurement reliability for individual genes (sampling variability decreases with the square root of sample size) (Cole et al., 2005; Miller, 1986). Between a 100× increment to statistical power and a 10× increment to measurement reliability, the statistical advantage of treating genes as noisy indicators of higher order functional or regulatory themes becomes quite substantial indeed. Pivoting the massively parallel measurement structure of genome-wide assay platforms such as DNA microarrays converts the statistical burden of ∼22,000 outcomes into a highly advantageous multi-indicator model involving a ∼1000-fold increment to measurement precision.

Another advantage of the abstractionist approach lies in its conceptual congruity with the structural invariants in transcriptional biology. As noted above, stress-induced activation of a single transcriptional control pathway such as the GR (Wang et al., 2004; Yamamoto, 1985) or β-adrenergic/cAMP/PKA pathway (Montminy, 1997; Zhang et al., 2005) can elicit heterogeneous transcriptional responses across individuals, cell types, and cellular conditions. Stress-evoked gene expression responses can be highly diverse even if they share a common regulatory feature (e.g., transcription factor etiology) or functional teleology (e.g., GO annotations). To the extent that aggregate regulatory or teleologic themes are more consistently evoked than are specific individual transcripts, analyses focusing on those aggregate themes will yield more consistent results. If, for example, GR signaling can evoke many different gene transcriptional responses that all share in common a general enrichment of GRE-containing promoters, that abstract regulatory characteristic may be reliably detected even when the gene expression alterations themselves are heterogeneous. Abstractionist analyses yield more consistent results in part due to their statistical advantages and in part because they simply aim at more stable biological targets.

3. Opportunities

Having learned our lesson to seek abstract themes, several major opportunities for clarifying the genomic response to stress now lie close at hand. One underexplored topic involves the functional gene modules activated in the CNS in response to stress. Studies have begun in animal models (Karssen et al., 2007; Weaver et al., 2006a,b), but we still know little about the time course of CNS transcriptional responses, their regularity vs. variation across differing types of stress and across differing CNS structures, and the teleologic basis for those dynamics. The complex cellular microstructure and potential distribution of small transcriptional responses over large arrays of cells make these inquiries particularly challenging. We also know little about the specific neural or endocrine mediators of CNS transcriptional responses, or about the relationship between CNS responses and stress-induced transcriptional remodeling in peripheral immune cells or other organ systems. Identifying the psychological experiences that trigger neural- or endocrine-mediated transcriptional responses is a

critical area of opportunity given the central role of psychological processes in triggering biological stress responses (Sapolsky, 1994). Multivariate analytic infrastructure has been developed for such analyses (Cole et al., 2007a,b), and a few studies have begun to identify psychological mediators (Chen et al., 2010, 2009; Cole et al., 2007a,b), but much more remains to be discovered in this domain. Almost nothing is known about the genomic basis for resilience to stress, although some research has begun to examine a small number of genes (Feder et al., 2009). Studies mapping the transcriptional response to psychotherapy or antidepressant pharmacotherapy could be highly illuminating. Another significant opportunity lies in the analysis of transcriptional responses to stress in diseased tissues such as tumors from cancer patients (Lutgendorf et al., 2009), atherosclerotic plaques in heart disease, or lymphoid organs in viral infections (Sloan et al., 2007).

Current abstractionist analyses assess functional or regulatory themes using a priori, theory-defined gene sets, but this approach could easily be expanded to include de facto gene sets reflecting the empirical transcriptional effects of neural, endocrine, pharmacologic, or behavioral stimuli. Gene set expression analysis utilizes an initial discovery study to define a group of genes that show empirical changes in expression in response to a given stimulus (e.g., pharmacologic glucocorticoid treatment). Subsequent empirical data sets are then scanned to assess transcriptional similarity to an array of empirical criteria. Such an approach might discover, for example, that psychologically resilient people show minimal glucocorticoid-like transcriptional response to a model stressor, whereas more vulnerable individuals show pronounced glucocorticoid-like transcriptional responses. Such analyses could be employed to gauge hormone- or neurotransmitter-like dynamics, or dynamics evoked by behavioral features such as positive affect, social support, or adaptive coping (Cole, 2009a,b; Lutgendorf et al., 2009). Gene set expression analysis has already proven helpful in interpreting transcriptional alterations in circulating leukocytes following acute stress (Nater et al., 2009). Assembly of large-scale data sets capturing stress dynamics across a diverse sample of people could potentially overcome some of the heterogeneity challenges outlined earlier, particularly if data are analyzed using cluster discovery algorithms to accommodate inter- and intra-individual variability (Segman et al., 2005).

Another growing opportunity involves the integration of results from multiple small stress genomics studies to discover new generalities regarding the signal transduction pathways that mediate transcriptional responses to stress and adversity. One example of this approach is the recent discovery that SNS activation of the GATA1 transcription factor plays a key role in conveying the effects of adverse social conditions into changes in inflammatory gene expression (Cole et al., 2010a,b). Other examples are likely to emerge as the number of social genomics studies grows large enough to drive more powerful meta-analytic approaches to theme discovery.

New opportunities are also developing to integrate the structural genomics of DNA polymorphism with the functional genomics of stress-induced RNA remodeling to map the molecular basis for Gene—Environment interactions. Computational models linking activated transcription factors to promoter DNA motifs can be superimposed on the growing census of human DNA sequence polymorphisms to predict how different individuals' genomes might respond to the same environmentally-induced transcription factor activity. One recent example involves the rs1800795 G > C transversion in the human *IL6* promoter, which has been found to block the ability of the SNS-induced GATA1 transcription factor to activate pro-inflammatory gene expression in response to adverse socio-environmental conditions (Cole et al., 2010a,b). Given $\sim 10^7$ known SNPs in the human genome, many other interactions likely await discovery as we learn more about the transcription control pathways that mediate environmental and psychological influences on gene expression. A new era of human stress genomics does lie close at hand, and we can best realize its opportunities not by searching for another needle in the genomic haystack, but by climbing atop that haystack to survey the biological countryside from on high.

4. Precis

Analyses of the human genome-wide transcriptional response to stress began as largely descriptive enumerations of genes that showed empirical changes in expression in response to adversity in easily available cells such as leukocytes. As in many other domains of functional genomic research, initial findings proved difficult to interpret due to statistical challenges, effects of cellular heterogeneity and temporal dynamics, and a fundamental mismatch between traditionally unitary conceptualizations of stress response systems and the reality of multifactorial gene regulation. The field showed a recent burst of progress as new analytic strategies began to re-express differences over 100s—1000s of individual genes in terms of a much smaller number of higher order themes involving those genes' teleologic function and regulatory influences. This abstractionist approach to gene expression analysis has yielded both stable empirical findings and new theoretical insights into the causes and consequences of the human transcriptional response to stress. Having defined some of the key signal transduction pathways mediating those effects in accessible cell types such as leukocytes, the field of human stress genomics is now poised to extend those insights into a broader array of physiologic systems and social/psychological contexts, and to map the interaction of those systems with DNA genetic polymorphism to illuminate the human genome's overarching strategy for individual adaptation to environmental challenge.

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Conflict of interest statement

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Further reading

Cole, S.W., 2009b. Social regulation of human gene expression. Curr. Dir. Psychol. Sci. 18 (3), 132—137 In addition to surveying the broad field of social genomics, this review develops some of the theoretical implications of socio-environmental gene regulation for long-term individual developmental trajectories.

Cole, S.W., Hawkley, L.C., Arevalo, J.M., Sung, C.Y., Rose, R.M., Cacioppo, J.T., 2007b. Social regulation of gene expression in human leukocytes. Genome Biol. 8 (R189), 1—13 This pivotal study provided the first indication that long-term social adversity is associated with broad transcriptional alterations in the human immune system. Several recurring biological themes initially emerged in this paper, including indications of glucocorticoid resistance, NF-κB-linked chronic inflammation, and suppression of innate antiviral responses.

Cole, S., Arevalo, J., Takahashi, R., Sloan, E.K., Lutgendorf, S., Sood, A.K., Sheridan, J.F., Seeman, T., 2010b. Computational identification of gene—social environment interaction at the human IL6 locus. Proc. Natl. Acad. Sci. U.S.A. 107, 5681—5686 Combining stress genomics with analyses of genetic polymorphism, this study presents a new computational strategy for discovering gene-environment interactions. This study also mapped a new transcription factor pathway through which stress can regulate gene expression.

Miller, G.E., Chen, E., Fok, A.K., Walker, H., Lim, A., Nicholls, E.F., Cole, S., Kobor, M.S., 2009b. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc. Natl. Acad. Sci. U.S.A. 106 (34), 14716—14721 A remarkable study showing that early life social conditions can leave an enduring imprint on human gene expression decades later in adulthood. This is one of a number of studies documenting a pro-inflammatory shift in leukocyte gene expression in response to socio-environmental adversity.

Morita, K., Saito, T., Ohta, M., Ohmori, T., Kawai, K., Teshima-Kondo, S., Rokutan, K., 2005b. Expression analysis of psychological stress-associated genes in peripheral blood leukocytes. Neurosci. Lett. 381 (1/2), 57—62 One of the first studies of the human transcriptional response to stress, this paper analyzed the effects of a truly acute stressor (Ph.D. thesis defense!) on a targeted subset of the human transcriptome.

Weaver, I.C., Meaney, M.J., Szyf, M., 2006b. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. Proc. Natl. Acad. Sci. U.S.A. 103 (9), 3480—3485 One of the few analyses focusing on the CNS transcriptome, this study shows how early life social conditions can remodel gene expression profiles in the hippocampus. This study is part of a broader line of research showing that salutary social conditions in early life can reduce "defensive programming" of the developing body and thereby optimize later neuroendocrine responses to stress.

Glossary

Acute Psychological Stress: A transient state of comparatively intense subjective stress that develops rapidly (e.g., within minutes) in response to a discrete event (e.g., a perceived threat or challenge) and resolves relatively quickly thereafter (e.g., within minutes to hours) following cessation of the triggering condition. Acute stress contrasts with the more durable, and possibly biologically different condition of chronic stress, which may last for many days or years.

cAMP/PKA pathway: Cyclic-3′,5′ Adenosine MonoPhosphate and Protein Kinase A provide a biochemical pathway by which a diverse array of cell surface receptors can activate intracellular

responses via PKA phosphorylation of cellular proteins. The cAMP/PKA pathway plays a key role in mediating the effects of catecholamines on cellular function by conveying signals from cell surface β-adrenergic receptors. One key target of the cAMP/PKA pathway is the transcription factor, CREB (cAMP Response Element Binding protein).

False Discovery Rate: A statistical parameter expressing the number of ''false positive'' results as a fraction of the total number of positive results (i.e., false positive/true positive + - false positive).

Functional Genomics: The analysis of gene expression. Structural Genomics generally refers to the DNA sequence of the genome, whereas Functional Genomics refers to the selective transcription of genes into mRNA (which can subsequently be translated into the proteins that actually mediate cellular function).

Gene Ontology/GO: A set of tags that can be attached to a specific gene to indicate its known or predicted function (e.g., cell surface receptor, immune response gene, cytokine, neuropeptide, etc.).

Genome: The total DNA sequence of an organism; often used to reference the total set of genes in a genome (e.g., ~22,000 genes in the human genome).

Glucocorticoid receptor/GR: A receptor protein that mediates the effects of glucocortioids (including cortisol) on gene expression. After interacting with glucocorticoids, the GR translocates into the nucleus of a cell to act as a transcription factor by binding onto DNA sequences known as Glucocorticoid Response Elements.

Glucocorticoid Response Element/GRE: A stereotyped sequence of DNA nucleotides to which activated GRs can bind. When present in the promoter of a gene, a GRE allows that gene to potentially be transcribed in response to GR activation by glucocorticoids. GREs may also inhibit gene transcription if they bind GRs at a site that hinders DNA access by other transcription factors essential for gene expression.

Monocyte: A subset of leukocytes that mediate innate immune responses, orchestrate many types of inflammatory response, and initiate adaptive immune responses by activating T lymphocytes.

NF-κB: A key transcription factor mediating the expression of inflammation-related genes. NF-κB activity is potently inhibited by glucocorticoids.

NK cell: Natural Killer cells are a subset of leukocytes that mediate innate immune responses and can kill foreign cells.

Promoter: A stretch of DNA that regulates the expression of a gene by serving as a target for binding by transcription factors. The ''core promoter'' generally lies adjacent to the coding region of the gene (the segment of DNA that is transcribed into mRNA), and typically provides a target for multiple transcription factors that interact cooperatively to activate gene transcription.

Single Nucleotide Polymorphism/SNP: A position in a DNA genome at which different members of the same species may bear different nucleotides. DNA polymorphism — the variation in specific DNA nucleotides at a given position across different members of the population — can affect gene expression (e.g., by influencing the binding of transcription factors) or the protein structure of a gene product (e.g., by encoding a different amino acid during translation).

Toll-Like Receptor/TLR: Toll-Like Receptors recognize conserved molecular characteristics of pathogens (e.g., bacterial components such as lipopolysacharide, viral DNA or RNA) and activate transcription factors involved in immune responses and inflammation (e.g., NF-κB).

Transcript: Expression of a DNA-encoded gene in RNA form. Generally refers to the processed messenger RNA (mRNA), which often differs from the ''primary transcript'' due to the removal of large RNA segments (introns) through RNA splicing.

Transcription factor: A protein that mediates gene transcription. Following their activation by a cellular signaling molecule (e.g., hormone or neurotransmitter), transcription factors translocate to the nucleus and bind onto specific stereotyped DNA sequences (transcription factor response elements) in the promoter of a gene. When bound to DNA, transcription factors flag a gene for transcription by generic transcription-mediating factories. Transcription factors can also inhibit gene expression by blocking access to DNA by other transcription factors that are required for gene transcription.

Transcriptome: The subset of all genes that is actively transcribed in a given cell (i.e., expressed as mRNA).