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Early adversity and the regulation of gene expression: implications for prenatal health

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Early life, including prenatal development and childhood, is a period of sensitivity, with potential for developmental programming under conditions of adversity. The intergenerational effects of early adversity have received attention, most often studied in relation to fetal development according to maternal exposures. Less often considered but critically important is the effect of early adversity on future prenatal risk (e.g. risk for preeclampsia, preterm birth), which threatens the health of mother and infant. The body's ability to turn collections of genes 'on' or 'off' across a range of tissues via receptor-driven transcription factors and epigenetic mechanisms (i.e. chemical modifications to the genome) in response to the perceived environment may help to explain such associations. This review aims to summarize discoveries surrounding the effects of early adversity on gene expression, emphasizing prenatal populations. First, we review findings from gene expression studies examining the effects of early adversity on various tissues known to contribute to prenatal health in adulthood. Next, we review several gene regulatory mechanisms thought to underlie differences in gene expression. Finally, we discuss potential implications for prenatal risk among early adversity-exposed mothers according to our current understanding of the biology that contributes to the development of prenatal syndromes.

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Introduction

Early life, including prenatal development and childhood, is a period of particular sensitivity, with the potential for developmental programming of biological systems under conditions of adversity. First studied among individuals exposed to physiologic stressors during development (e.g. gross nutrient deprivation [1–3]), it has become clear that early adversity imposed in the form of psychosocial stressors can also have lasting effects on health. This has now been shown to be true across a broad range of early adversity exposures, including abuse, neglect, and various forms of interpersonal or financial loss or instability, particularly among women [4–9]. While a dose–response effect of early adversity on health parameters appears to be at play [10,11,12•], it is noteworthy that a single instance of adversity in early life shows associations with notable differences in health into adulthood [13]. As such, it is particularly concerning that more than 10% of children experience abuse or neglect of a severity capable of substantiation by protective services and more than 50% of children report exposure to some form of early adversity [14,15].

The potential for intergenerational effects of early adversity has also received increasing attention, most often studied as it relates to the development of a fetus according to maternal exposures during pregnancy (e.g. maternal socioeconomic status [16], prenatal psychosocial stress [17,18]). Less often considered but also critically important to intergenerational health is the effect of early adversity on prenatal risk among expectant mothers who were exposed to adverse experiences during their own childhood. Indeed, though the biological pathways remain unclear, there is a growing body of literature linking early adversity to major complications of pregnancy, including preeclampsia [19••] and preterm birth [19••,20,21•]. As such, exposed women and their children face a heightened risk for perinatal, neonatal, and infant mortality and both generations of survivors bear a disproportionate burden of lifelong morbidity [22–24].

Since realizing that time-limited exposures in early life are capable of affecting adult health trajectories, the scientific community has pursued the discovery of lasting 'biological marks' or persistent physiological alterations that convey early adversity-associated disease burden, including in the context of pregnancy. Early research in this area focused largely on gross differences in neurobiology (e.g. regional volume, fiber tract integrity [25–27]), as the developing brain has long been known to display enormous plasticity. With the discovery that collections of genes can be 'turned

on' or 'turned off' via receptor-mediated alterations in transcription factor activity and via epigenetic mechanisms (i.e. chemical modifications to the genome) in response to one's perception of their environment, a literature focused on what has been coined 'social genomics' is swiftly developing and beginning to provide insight into the potential pathways by which early adversity affects disease risk across a wide range of biological systems [28,29•,30].

The purpose of the current review is to summarize recent discoveries surrounding the effects of early adversity on gene expression, with special emphasis on implications for prenatal health among early adversity-exposed expectant mothers. Indeed, pregnancy may be an ideal time to disrupt the intergenerational cycle of childhood maltreatment by targeting the molecular underpinnings of impaired prenatal health that establish the foundation for subsequent development. First, we review findings from gene expression studies examining the effects of early adversity on various tissues known to contribute to prenatal health in adulthood. Next, we review several gene regulatory mechanisms that could potentially mediate early adversity-associated differences in gene expression. Finally, we discuss potential implications for prenatal risk among early adversity-exposed mothers according to our current understanding of the biology that contributes to the development of prenatal syndromes.

Early adversity and gene expression

Gene expression is a cell-specific parameter. In fact, our ability to generate tissues with diverse functions despite an identical genetic code is reliant upon our capacity to refine which genes are readily expressed dependent upon cellular conditions. Therefore, similar to the structural neuroplasticity exhibited during critical periods of development, our cells appear to exhibit 'genomic plasticity' in the expression of genes. As the literature base grows, patterns in gene expression have emerged across cell types that lend biologic plausibility to the associations witnessed among early adversity and various health sequelae into adulthood.

Many studies have focused on neuroregulatory gene expression, with investigators often turning to animal models of early adversity (e.g. maternal separation, social isolation) delivered in the context of carefully controlled conditions. Effects of such exposures have been witnessed among model organisms (e.g. rodents, rhesus macaques) on the expression of genes related to, for example, synaptic transmission within sensory processing brain regions [31], stress resilience within the amygdala [32], stress-related neuronal dysfunction within the hippocampus [33], synaptic plasticity within the prefrontal cortex [34], and dopaminergic signaling within the nucleus accumbens [35•], with some follow-up periods extending into adulthood. Corresponding differences in behavior (e.g. sensory gating, anxiousness, reward seeking) have also been noted. Thus, social genomic mechanisms may contribute to lasting early adversity-associated differences in both neural anatomy and fundamental cell signaling pathways critical to processing sensory inputs, threats, emotions, and reward.

The effect of early adversity on gene expression within the hypothalamus, which serves as the bridge between the brain and endocrine system, has also received particular attention. Multiple studies now show that genes involved in hypothalamic-pituitary-adrenal (HPA) axis activation (e.g. *CRH* [36,37], *AVP* [36,38], *EGR1* [39•,40]) show heightened expression under static conditions as a function of adverse early life conditions. The ready expression of stress-responsive genes within the hypothalamus may contribute to the disturbances in basal levels of glucocorticoids and the blunted HPA-mediated stress response witnessed among adults with a history of maltreatment, a common finding [41–43] with recent extension to pregnant adults [12•,39•]. Morrison *et al.* for example, recently revealed associations among preadolescent chronic variable stress and the expression of 24 genes within the hypothalamic paraventricular nucleus during murine pregnancy [39•]. This group went on to show that the expected rise in glucocorticoid levels during maternal-offspring separation was blunted among postpartum adolescently stressed mice and adverse childhood experience-exposed women [39•].

Inflammatory parameters also appear to be particularly susceptible to regulation via social genomic mechanisms. For example, Zajdel *et al.* report that maternally separated, bacterially challenged C57Bl/6 mice show augmented expression of interleukin(IL)-6, IL-1β, and tumor necrosis factor(TNF)-α within the hypothalamus [44]. Similar findings have been reported in examining the brains of maternally separated rodents under basal and acute stress conditions (hypothalamus [45], hippocampus [46]), with neuroinflammation thought to contribute to differences in social behavior [47]. In relation to psychosocial stress, immune cells themselves also show gene expression patterns consistent with enhanced proinflammatory and dampened anti-inflammatory activity (e.g. [48••,49,50–52]). In fact, the prevalence of this pattern has led to its coining as the 'conserved transcriptional response to adversity' (CTRA) [28]. While the CTRA-related literature has focused primarily on the effects of chronic psychosocial stress conditions in adulthood, several animal and human studies have now linked early adversity with similar patterns of differential gene expression that appear to persist into adulthood [41,53••,54]. Such studies are sorely lacking among pregnant populations, though there is evidence to suggest that early adversity is associated with peripheral inflammation [55,56•] and up regulation of pro-inflammatory genes [57] during pregnancy. Studies of placental tissue also suggest that psychosocial conditions during pregnancy can affect fetal tissue development [58,59].

Potential biological mechanisms

As discussed, despite a stable genetic code, cells display a remarkable ability to turn genes 'on' or 'off' dependent upon their physiologic needs. This feat is accomplished through a combination of gene regulatory processes that include receptor-mediated activation of transcription factors that stimulate transcription of specific genes as well as epigenetic mechanisms that gate the access of transcription factors to the DNA genome. These processes work in concert to establish and transmit patterns of gene expression by dynamically regulating transcription of our DNA-encoded genes into messenger RNAs that subsequently guide the production of proteins that give rise to cellular structure and function [60–62]. Gene regulation by transcription factors represents the primary biological pathway through which extracellular processes induce acute effects on gene expression profiles. By contrast, epigenetic mechanisms are more often endogenously regulated as part of basic cellular development and differentiation programs, and as such their effects tend to be more durable over time. Non-Mendelian inheritance and environmental exposures shape the epigenome and some epigenetic marks are capable of perpetuation across cycles of cell replication and even during meiosis, providing a foundation for highly persistent effects on gene expression within an individual and across generations [63,64]. The joint effects of acutely responsive transcription factor activation (and feedback circuits that can propagate such effects over development) and more protracted epigenetic modifications allow social conditions early in life to affect the physiological underpinnings of disease process that manifest clinically much later in life.

DNA methylation, described as the classic epigenetic mark, involves the addition or removal of methyl groups to phosphate-linked cytosine-guanine (CpG) dinucleotides, which tend to be concentrated in promotor regions of genes [65]. Typically, loss of CpG methylation promotes gene expression by allowing transcription factors to access DNA. Gain of CpG methylation promotes gene silencing by hindering the binding ability of transcription factors. However, DNA methylation across varying genomic regions can also have transcriptional implications via alternative mechanisms [60,66]. DNA methylation has been increasingly examined as a function of early adversity, with differential methylation of DNA now witnessed in a number of epigenomic regions approximating with genes critical to navigating the social world (e.g. *CRFR2* [corticotropin-releasing factor 2] [67], *NR3C1* [glucocorticoid receptor] [68–70], *FKBP5* [affects glucocorticoid receptor sensitivity] [71], *BDNF* [nerve growth factor] [72]). Moreover, DNA methylation measured in peripheral tissues (e.g. leukocytes) has been linked to, for example, a blunted HPA response following challenge [68], suggesting that, at least under some circumstances, peripheral epigenomes may provide a glimpse into the epigenetic regulation of central neuroendocrine processes. DNA methylation has received attention for its potential role in conveying risk to the developing fetus via prenatal exposures to their mother (e.g. by examining cord blood [73,74]), though the effects of early adversity on future gene expression among gravid adults via the methylome remains to be determined.

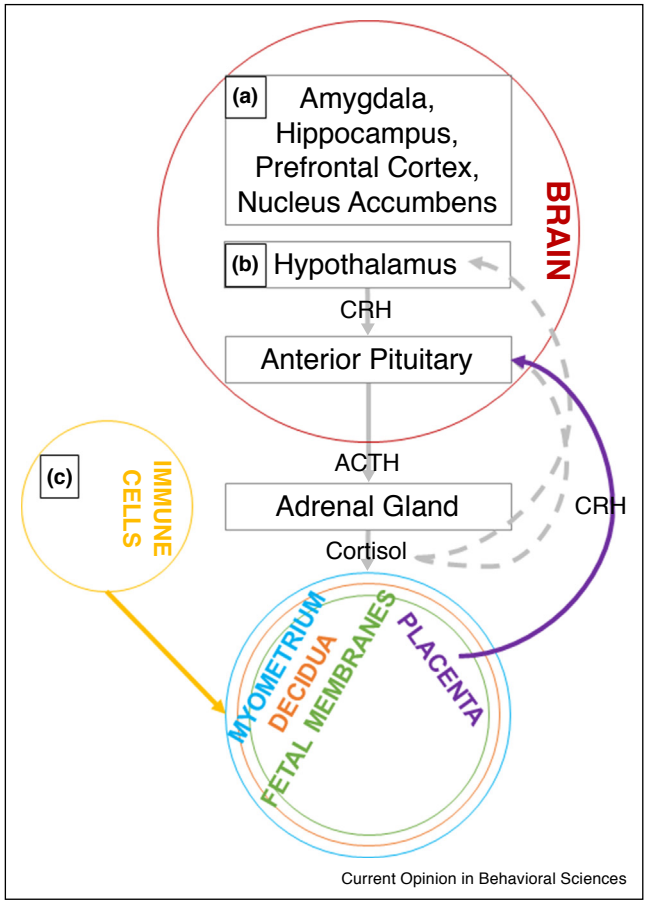
Noncoding RNAs (e.g. microRNA [miRNA]) are transcribed, untranslated RNA molecules with the ability to affect gene expression through pre-transcriptional and post-transcriptional mechanisms [60,75]. Several studies now link adverse early life experiences to differences in miRNA expression and/or activity [76,77]. miRNA expression has also been shown to target genes active in brain regions critical to threat perception, emotional processing, reward circuitry, and stress responsiveness (e.g. amygdala, hippocampus, prefrontal cortex, nucleus accumbens, hypothalamus) [78]. The regulatory role of miRNAs in immune adaptation is relatively well established, with the deleterious effects of aberrations in miRNA expression more recently realized (e.g. potentiated pro-inflammatory nuclear factor κ B signaling) [79]. During murine pregnancy, gene expression appears to be susceptible to psychosocial stress paradigms via miRNA-based mechanisms [80•]; though, human studies are lacking.

Implications for prenatal health

The aforementioned biological effects of early adversity have potential implications for prenatal health in adulthood among exposed mothers, with hypothesized pathways depicted in Figure 1. First, a robust literature links early adversity to numerous behavioral and psychiatric sequelae during non-pregnant and pregnant adulthood, including smoking, alcohol use, drug use, depression, and anxiety [81,82]. For example, compared to their counterparts, pregnant women with a history of childhood physical abuse are approximately 1.4 times more likely to smoke during pregnancy and at 2.8 times the odds of experiencing persistent, significant perinatal depressive symptoms [83,84]. Maternal tobacco use and prenatal depression, in turn, increase the odds of preterm birth by roughly 3.9-fold and 1.6-fold, respectively [85,86]. Prenatal depression also increases the odds of preeclampsia by 1.5-fold [87]. Such findings suggest that early adversity is associated with future prenatal complications, at least in part, through its effects on behavior and mental health during pregnancy. However, associations among early adversity and prenatal complications persist despite exertion of statistical control over such covariates, suggesting the potential for direct effects.

In this regard, neuroendocrine perturbations have received particular attention for their potential etiologic contributions to complications of pregnancy. Specifically, the theory of the accelerated 'placental clock' has been

Figure 1



Proposed pathways linking early adversity to prenatal health. Adversity during prenatal development and childhood is hypothesized to affect gene expression among the future expectant mother within: **(a)** regions of the brain critical to processing sensory inputs, threats, emotions, and reward, increasing risk for behaviors and perturbations in mental health linked to risk for complications of pregnancy; **(b)** the hypothalamus, ultimately dysregulating cortisol and placental CRH production, posited to contribute to preeclampsia and preterm birth; **(c)** immune cells, enhancing pro-inflammatory and dampening anti-inflammatory activity, which is thought to contribute to preeclampsia and preterm birth. CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropin-releasing hormone; solid lines = positive feedback; dashed lines = negative feedback.

put forward to explain the heightened risk for preterm birth witnessed in the context of psychosocial stress, as over activity of the HPA axis is thought to accelerate the rise in circulating glucocorticoid levels expected and well described during pregnancy [88]. In response, the placenta (i.e. the organ responsible for fetal oxygenation and nutrient exchange) produces increasing amounts of corticotropin-releasing hormone, which promotes early labor by, for example, disrupting the integrity of the baby's bag of water and exciting the mother's uterine smooth muscle to encourage contractions [89,90]. Heightened expression of corticotropin-releasing hormone has also been witnessed in the blood and placental extracts of preeclamptic versus normotensive women [91,92], which may be related to the effects of corticotropin-releasing hormone on, for example, placental apoptosis (e.g. by activating Fas ligand-positive macrophages [93]) or function (e.g. by promoting greater umbilical artery resistance [94]). While studies of the mediational role of neuroendocrine disruption in early adversity-associated complications of pregnancy are rare, some data suggest lasting effects of the exposure on prenatal neuroendocrine biology [95], including when psychosocial stress in adulthood is held constant [12•].

Decades of research also support that inflammation (of sterile or infectious origin; at the systemic or local level) promotes several processes involved in the premature initiation of labor (i.e. dilation of the uterine cervix, contraction of the uterine smooth muscle, rupture of the baby's bag of water) [96]. Here, activated leukocytes infiltrate maternal and fetal tissues and produce large amounts of pro-inflammatory cytokines, driving labor through a unique feed-forward cascade [97–99]. However, factors promoting or deterring initiation of this cascade remain elusive and interventions such as antibiotics fail to prevent preterm birth [100,101], positioning the inflammatory origins of preterm birth as a continued topic of inquiry. Similarly, preeclampsia is marked by maternal inflammation both in examining placental tissues and in interrogating the maternal circulation [102,103]. Though, it remains unclear whether aberrations associated with preeclampsia such as placental ischemia drive processes known to promote inflammation (e.g. reduced T regulatory and enhanced CD8(+) T cell composition [104], upregulation of leukocyte nuclear factor κ B signaling [105]) or inflammatory processes play an etiologic role in the onset of the syndrome. As above, formal tests of mediation are sorely lacking. Though, associations among childhood maltreatment, peripheral inflammation, and preterm birth have been witnessed [56•] and Miller *et al.* [19••] recently reported that, among 744 U.S. women, economic hardship during childhood was associated with greater risk for preterm birth, with both elevated plasma interleukin-6 and heightened risk for preeclampsia identified as significant mediators in the association.

Conclusions

We have reviewed data suggesting that early adversity exerts lasting effects on the neural regulation of behavior and emotion, the neuroendocrine response to psychosocial stress, and inflammatory signaling across cells and tissues. While the structural neuroplasticity of fetal development and childhood has long been a topic of interest, the scientific community has only begun to appreciate the potential for 'genomic plasticity' during critical periods of development and the implications of such plasticity across a broad range of disease processes in adulthood.

Pregnancy may represent a time of particular vulnerability to early adversity-associated differences in gene expression, as prenatal health is clearly susceptible to the indirect effects of behavioral and mental health sequelae of early adversity and potentially susceptible to the direct effects of early adversity via neuroendocrine and immune pathways. Prenatal syndromes such as preeclampsia and preterm birth, in turn, threaten the health of mother and baby, perpetuating early adversity-associated risk across generations. Though considerable work remains in the elucidation of mechanistic pathways linking early adversity to poor prenatal health, recognition of the potential for 'social genomic' underpinnings represents a significant advancement in the field.

Conflict of interest statement

Nothing declared.

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