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Research Article

Maternal Diet During Pregnancy and COVID-19 Susceptibility of Offspring: The "Thrifty Phenotype Hypothesis" Connection

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ABSTRACT

There is accumulating evidence suggesting that ACE2, the host cell receptor for the spike (S) protein of the SARS-CoV-2, mediates viral entry and infection, is under epigenetic control. Here, we discuss studies suggesting a nutritional strategy for down-regulating ACE2 expression in tissues of offspring through the phenomenon of maternal epigenomic reprogramming mediated by maternal diet. The "thrifty hypothesis" was first proposed by Hales and Barker, which posits that specific genes are programmed based on early-life experience to promote efficient fat deposition and storage in adulthood. Our analysis of the proposed mechanism for "early life programming" in this paper *via* nutritional modulation of histone acetylation and DNA methylation goes beyond the physiological consequence of boosting the innate cellular resistance to a viral transmission. During the pandemic, where there is still no specific antiviral drug or a widely disseminated vaccine for COVID-19, we hypothesize that an epigenomic nutrition approach may be a practical approach to help mitigate viral transmission offspring.

Keywords: SARS-Cov-2, COVID-19, ACE2, Maternal reprogramming, nutrition epigenomics, perinatal, plant-based diet, high-fat diet effects, thrifty phenotype hypothesis

Introduction

Although there is still no evidence of vertical transmission of SARS-CoV-2 in fetuses of women with COVID-19 in late pregnancy, there have been increasing cases for secondary transmission to infants after delivery, as was reported in Italy, China, and Vietnam [1-3]. While children seem to show milder disease than adults [4], the most recent and most extensive pediatric population-based study with 2,143 cases reveals that 10.6% of the population with severe symptoms are less than one year age. The current statistics strongly suggest that infants may be at higher risk of death due to COVID-19, as was initially thought [5]. Hence, special attention is needed to develop interventions and improve the prevention of COVID-19 infection in this vulnerable pediatric population. As infants have weak immune systems and are unable to wear protective masks, it is pivotal to find strategies that can prevent viral infection and mitigate the severity and fatality associated with it.

Recent studies have found that angiotensin-converting enzyme 2 (ACE2) is the primary receptor targeted by spike (S) protein of SARS-CoV-2, permitting viral entry into the host mucosa and causing an active infection. ACE-2 is a type I transmembrane metallocarboxypeptidase that is part of the renin-angiotensin system (RAS) and serves as a critical regulator of systemic blood pressure by breaking down angiotensin II to its metabolites, including angiotensin-(1–9) and angiotensin-(1–7) [6]. ACE2 is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels. Its widespread distribution accounts for the myriad of clinical manifestations that have

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been reported so far, including acute respiratory syndrome, renal failure, intestinal perforation, and disseminated vascular thrombosis [7]. Compared with SARS-CoV-1, SARS-CoV-2 is more pathogenic and infective at least, in part, because of its 10- to 20-fold increased binding affinity to ACE2 [8]. It was found that ACE2 expression in the lung increases with age, correlating with higher disease severity observed in older patients with COVID-19 [9]. Accumulating data also indicate a gender-associated predisposition to COVID-19, with men being more prone to develop severe symptoms than women. These observations are consistent with results from the single-cell transcriptomics study by Zhao et al., demonstrating that ACE2 expression was higher among Asian men than their women counterparts [10]. The bioinformatics analysis by Heialy *et al.* likewise hinted that obese individuals might be more susceptible to COVID-19 due to the up-regulation ACE2 in the lung mediated by SREBPs, a class of transcription factors involved in lipid synthesis [11].

With the appreciation that a dysregulated expression of ACE2 is a critical factor in the susceptibility to and symptoms of COVID-19, in this review, we explore maternal diet as a potential "early life programming" intervention in the context of improving resilience against COVID-19 among infants. As the binding of SARS-CoV-2 to ACE2 is primed by protease cleavage of spike proteins. It is catalyzed by the type II transmembrane serine protease (TMPRSS2) together with the action by a vast number of other proteases, e.g., furin protease TMPRSS, cathepsin L and human airway trypsin-like protease [12]. The scope of this paper will be limited to the the nutri-epigenetic link of ACE2 regulation.

Nutri-Epigenetics and "Thrifty Phenotypes"

Epigenetic processes are believed to play a role in fetal development and are likely candidates for developmental programming that pregnant mothers can exploit during the COVID-19 pandemic. Perinatal programming was first observed by David Barker and colleagues when they discerned, as a result of maternal experiences during the Dutch Famine, the striking correlation between low birth weight and the risk for obesity/overweight among babies in later life. In their "thrifty phenotype hypothesis," they posited that with the absence of sufficient calories in the fetal environment, neonatal metabolism primes or "programs" individuals to conserve calories, even in adulthood [13]. More recent data from the Dutch Famine birth cohort reveals that prenatal famine exposure during early gestation is associated with altered DNA methylation within the INSR and CPT1A loci, genes involved in prenatal growth and fatty acid oxidation, respectively [14]. Conversely, perinatal overnutrition leads to similar metabolic programming and disease risk. For example, exposure in utero to a maternal high-fat diet leads to increased body size at birth and insulin resistance throughout life in several animal studies [15]. These are examples consistent with the "thrifty phenotype hypothesis" that highlight possible lifelong metabolic imprinting of pre-term infants.

Epigenetic mechanisms could mediate the modulation of offspring phenotype in response to the maternal environment. Epigenetic modifications include DNA methylation, histone methylation and acetylation, ubiquitination, and action by noncoding RNAs. Among these numerous pathways, DNA methylation is perhaps one of the best understood. However, it does not act alone because it also recruits histone deacetylases' concerted enzymatic activity (HDACs) to repress gene transcription [16]. It has been argued that DNA methylation may be a risky approach for fetal programming because the yields stable epigenetic modifications. That modification is a result of the direct DNA demethylating enzyme absence [17]. In contrast, histone acetylation may be more suited given its reversibility because of the multiply coordinated action of histone acetyltransferases (HATs) and HDACs.

Panchenko *et al.* reported that one-third (18/60) of the epigenetic machinery genes screened were differentially expressed in mice who given a control diet versus a high-fat diet for four months during the pre-conceptional period. Interestingly, out of the 18 genes, thirteen genes are involved in the histone acetylation pathway (Hdac6, Hdac2, Hdac3, Hdac10, Sirt4, Kat13d, Kat2a, Kat6b, Kat3a, Kat1, Kat13b, Kat3b, Brd2). A high-fat diet up-regulated lysine acetyltransferases and bromodomain-containing protein 2 while downregulated HDACs in fetal tissues [18]. These findings corroborate with a more recent genome-wide mapping study of histone modifications in rat cardiac tissue. In the study, a maternal high-fat diet was demonstrated to cause metabolic programming characterized by site-specific acetylated and methylated chromatin regions. Fifty-four

% of the annotated genes in rat offspring exposed to maternal high-fat diet have the signature gene-activating histone H3 lysine four trimethylation marks. Most of the acetylated promoter regions are from genes associated with the metabolic process, particularly as positive regulators of cholesterol biosynthesis [19]. Given the genetic imprinting potential of maternal diet, the question then arises – can a low-fat diet be a possible intervention for epigenetic reprogramming of tissue-specific ACE2 expression among infants and children?

Maternal Epigenetic Programming for COVD-19 Resistance: The Hypothesis

A growing body of literature demonstrates that ACE2 gene expression is under epigenetic control [20-21] (Figure 1). Fan et al. reported aberrant methylation in the ACE2 promoter in patients with essential hypertension; however, they were unable to show causal disease association due to the limited patient size [22]. As opposed to the results in lung epithelial cells by Corley and Ndhlovu, a higher degree of hypomethylation in the promoter region of ACE2 was noted in male compared to female subjects, as well as in older compared to younger cohorts. This trend conforms with the known age and gender-related potential risk factors for COVID-19. There also appears to be almost no expression of ACE2 protein in neurons and leukocytes due perhaps to the hypermethylation status of the promoter region in these tissues [23]. Pinto *et al*.'s recent systems biology analysis point to the potential epigenetic regulation of ACE2 via histone modifications through HAT1, HDAC2, KDM5B, among others.

Interestingly, SIRT1 was also up-regulated in the lungs of patients with severe COVID-19 comorbidities [24]. SIRT1 can epigenetically regulate ACE2 under conditions of cell energy stress [25]. Atorvastatin, a synthetic HMG-CoA reductase inhibitor that lowers plasma cholesterol levels, was found to induce histone H3 acetylation on rabbit hearts' ACE2 promoter region. This response indicates direct or indirect epigenetic up-regulation of ACE2 [26]. Although there appear to be different effects on ACE2 expression by these epigenetic changes, it should be noted that such responses are often tissue-specific. What matters more in the context of COVID-19 transmission is the level of ACE2 in tissues that mediated contact to aerosols, such as the nasal and bronchial epithelial cells, that allow viral infection.

Conclusion

By far, there is evidence for epigenetic regulation of ACE2 and for maternal diet-induced regulation of histone acetylation suggesting a potential role for maternal dietary programming in increasing resistance against COVID-10 among infants

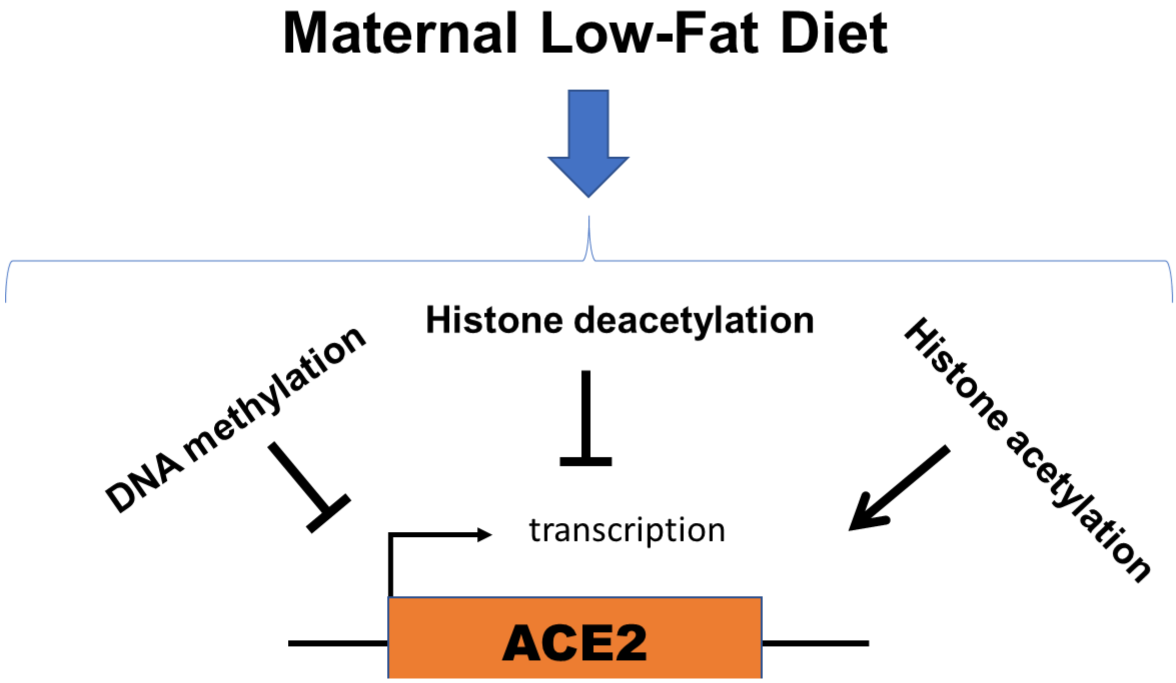

Figure 1. Tissue-specific expression of ACE2 gene in an infant can epigenetically modulated via maternal nutrition

and children. As one may hypothesize that since SARS-CoV-2 infects cells by exploiting cellular factors promoting viral attachment and entry, it is likely that mucosal epithelial cells with lower levels of ACE2 would provide more protection for the infant from COVID-19 than those expressing higher amounts of the protein. Any downregulation in ACE2 may have an additive, if not synergistic, protective effect since it has been recently hinted that the maturity and function (e.g., binding ability) of ACE2 in children may also be lower than that in adults [27].

Since it has been found that ACE2 is highly expressed in the maternal-fetal interface cells [28], it is speculated that there is a sound theoretical basis to consider a low-fat diet as a practical intervention for pregnant mothers by induction of histone deacetylation at the promoters of ACE2. While the ‘thrifty phenotype hypothesis’ has continued to receive strong support based on more detailed and recent molecular analysis, there is yet no direct evidence that a low-fat diet, which is composed mainly of a plant-based diet, can lead to epigenetically mediated down-regulation of ACE2. The proportion of dietary fat in the low-fat diets may be consistent with the latest American Dietary Guidelines recommendation on fat intake (<30 % of total energy consumption) [29]. Suppose anything, there is concern about mothers and babies being harmed with such an intervention. In that case, the available evidence shows that well-planned vegetarian and vegan diets are considered safe during pregnancy and lactation. However, it still requires a keen awareness for a balanced intake of key nutrients given the risk of nutritional deficiencies associated with vegan or vegetarian diets, such as proteins, iron, vitamin D, calcium, iodine, omega-3, and vitamin B12 [30].

As with the hypothesis of "thrifty phenotypes" where dietary factors and lifestyle during pregnancy is posited to determine the risk of developing chronic diseases later in life, perinatal nutritional interventions may offer a critical window of opportunity for infants to acquire not just COVID-19 resistance, but also empower mothers to activate epigenetic priming mechanisms to extend the biological effects over multiple generations [31].

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