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REVIEWS: CURRENT TOPICS

Pathophysiological basis for compromised health beyond generations: role of maternal high-fat diet and low-grade chronic inflammation

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Abstract

Early exposure to a fat-enriched diet programs the developmental profile and thus is associated with disease susceptibility in subsequent generations. Chronic low-grade inflammation, resulting from maternal high-fat diet, is activated in the fetal environment and in many organs of offspring, including placenta, adipose, liver, vascular system and brain. The prevalence of an inflammatory response is highly associated with obesity incidence, cardiovascular diseases, nonalcoholic fatty liver disease and brain damage. Substantial studies using high-fat model have consistently demonstrated the incidence of such inflammatory reactions; however, the potential contribution of active inflammation toward the physiological outcomes and developmental diseases is neither discussed in depth nor systemically integrated. Therefore, we aim to summarize the current findings in regards to how a maternal high-fat diet influences the inflammatory status, and probable pathogenic effects on the offspring. More importantly, since limited research has been conducted to reveal the epigenetic regulation of these inflammatory markers by maternal high-fat diet, we sincerely hope that our review will not only outline the pathophysiological relevance of inflammation but also identify a future direction for mechanistic investigation and clinical application.

Keywords: Maternal high fat (MHF); Inflammation; Cytokines; Epigenetics; Programming

1. Introduction

Compromised nutritional environment during early development targets both immediate health problems in newborns and continuing consequences in adulthood. Significant outcomes were revealed in earlier studies that focused on undernourished pregnancies [1–3]. These changes initially occurred in tissue structure, further leading to impaired organ functions and biological systems [4]. Recently, a dietary intake greatly shifted towards the consumption of increasingly accessible fat-enriched food combined with poor eating habits has contributed to the increased prevalence of chronic diseases. Many studies have reported higher incidences of obesity, hyperglycemia and systemic insulin resistance as well as other disturbances in metabolic functions as a result of prolonged high-fat consumption [5–7]. More importantly, such phenomenon not only affects these fat-consuming individuals but also predisposes subsequent generations to similar health concerns. Mounting evidence supported by a substantial amount of animal studies has demonstrated that perinatal exposure to high-fat diet profoundly alters the intrauterine environment and leads to permanent phenotypic alterations with adverse outcomes that persist through the adulthood of the progeny. These outcomes manifest at certain physiological levels including growth, learning ability and susceptibility to chronic diseases [8–10]. Postnatal high-fat/carbohydrate challenge [11–13] or of drug treatment [14] will even aggravate these symptoms.

Our review mainly focuses on maternal high-fat diet (MHF)-induced low-grade chronic inflammatory response and its associated pathophysiological consequences. Inflammatory cytokines can be expressed in multiple cell types, including monocytes, macrophages, fibroblasts, epithelial cells, endothelial cells and T cells [15,16]. Tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-10 and IL-12 [17,18] are mediators of natural immunity; they are expressed during postnatal inflammatory activation. IL-2, IL-4, IL-5 and IL-10 [19,20] are mediators of adaptive immunity; they partake in the growth and development of T cells and B cells. We recognize that some of these inflammatory cytokines, such as IL-6, TNF and hepatocyte growth factor/scatter factor (HGF/SF), play essential functions in tissue development at certain life stage [21–23]; therefore, in this review, we address only the scenario in which these cytokines are abnormally produced compared to their own control and raise pathophysiological consequences. Inflammation is a part of the natural defense system that the body has against injury and disease. As a response to environmental factors/stimuli, inflammation instantly triggers a series of physiological reactions and nonspecific immune responses, such as increased blood flow and cellular metabolism, vasodilatation and fluid influx [24]. Conversely, chronic

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Table
The effects of cytokines in different organs and their physiological consequences

	Organ/system	Regulated inflammatory markers	Inflammatory-relevant physiological consequence	Ref. for physiological impact
Maternal	Circulation	TNF-α, IL-1β [42]		
	Placenta	IL-1β, MCP-1, TLR4 [44]	Decreased blood flow on the fetal side	[44]
Progeny	Adipose		Increased adiposity capacity	[76,77]
		TNF-α [78]	Insulin resistance	[74]
			Increased body weight gain	[9,82,159]
			Increased fat percentage of whole body composition	[40,79]
	Cardiovascular	IL-1β, TNF-α [42]	Hypertension	[98]
	Liver	IL-6, TNF-α [100,128]	Worsened the insulin signaling	[100,104]
		CRP, Mmd2, TNFsf1, IL-12b [83]	Stimulated gluconeogenesis	[39,81,104]
			Lipid synthesis	[104]
		Interleukin-10 and Arginase-1 [35]	Increased liver weight and glycogen content	[79]
	Brain	IL-6[80]	Brain injury	[115]
		IL-1β [41]	Impairs spatial learning, Increases hypothalamic–pituitary activity and reduces neurogenesis in the hippocampus	[116–118]
			Learning difficulties	[80]
			Susceptible to dysregulated brain chemicals, including serotonergic system	[119,120]

low-grade inflammation is often linked to disease and long-term adverse consequences; it is inevitably associated with the pathogenesis of nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) [25], cardiovascular diseases [26], renal failure [27], nervous system disorders [28], aging [29], diabetes [30] and several types of cancer [31]. This type of inflammatory response is commonly observed in obese individuals and sustained-high-fat-eating populations. More importantly, nowadays, we know that overconsumption of high-fat food prior to or during pregnancy also spreads the inflammatory response to the next generation, with specific organ distribution and in a life-stage-dependent manner.

Overall, MHF regulates a broad range of genes in the progeny, including the activation of proinflammatory genes that further initiate a series of undesirable and pathogenic physiological imbalance, leading to the early onset of metabolic disorders and chronic diseases. In this review, we aim to present the current findings of activated inflammatory genes with a tissue-specific focus in a maternal high-fat model, as well as a potential interaction between the activated inflammatory responses and the subsequent metabolic and systemic disorders (Table). Meanwhile, we will consider what is known of epigenetic modulation as a causative mechanism for regulating inflammatory gene expression in this particular model in an attempt to provide a novel insight for therapeutic strategies. It is worth mentioning that this review will mainly focus on maternal high-fat model, in which high-fat diet was usually given to the pregnant animals only during gestation and lactation. Although the lactation period faces usual metabolic challenges and is sensitive to dietary contents [32,33], high-fat feeding to mothers during lactation alone has not been proven to trigger inflammation in the offspring in any studies. The offspring in most of our cited papers were not exposed to high-fat diet after weaning. High-fat consumption during maternal period does not necessarily increase either dams' or offspring's body weight gain [34–36]. Therefore, increased adiposity and inflammatory response in the offspring are mostly attributable to the maternal high-fat exposure. Although we provided evidences that induced cytokines are contributing factors to adiposity, we also acknowledged that obese individuals do produce more cytokines. Hence, it is difficult to draw conclusions regarding which one is the main driver: diet or adiposity. As we know, pregnant women are an extremely susceptible population given their higher nutritional demands in terms of not only the quantity but also the quality. Inappropriate nutrient supply during this critical period of time inevitably results in an early onset of chronic diseases in the subsequent generations. Therefore, a better understanding of the physiological origin of inflammation will not only benefit the success of conception but also protect the progeny against the unfavorable environmental challenges.

2. Inflammatory state during pregnancy

Fat overconsumption prior to or during pregnancy results in an unfriendly intrauterine environment, on which the concentrations of energy, hormones and blood supply are less optimized, and not surprisingly leads to abnormal fetal development and growth [37–41]. Excessive circulating levels of the proinflammatory cytokines TNF-α and IL-1β were detected in high-fat-fed pregnant mouse [42]. High-fat consumption prior to mating can result in the induced IL-6 and TNF-α in lactating mammary gland and consequentially impede milk synthesis and secretion [43]. Although the researchers did not observe a similar effect in another nonhuman primate study, it is noteworthy the naturally existed biological differences between these two animal models, and the four years of high-fat exposure prior to pregnancy which may alter the subjects' susceptibility than those from other maternal high-fat models [44]. Besides, gut microbiome content was known to affect the early development of immune system [45]. In a parental high-fat model, fatty acid exposure causes changes in the microbiotic composition; these alterations can be inherited by offspring and result in hyperinflammatory colonic responses [46].

Placenta, the primary organ that forms the maternal–fetal interface and transports nutrients from the mother to the fetus, has received much attention during fetal development. Rodents have long been used to study inflammatory scenario in both regular and pregnant models. There have not been any data available to draw conclusions regarding the poor/good of using rodents as model to study human inflammation in pregnancy and development. Early studies suggested that although primate and rodent differ in many aspects, their placental structures highly resemble each other [47]; these similarities make the rat an appropriate model for studying human placental function [48] and uterine immune response to the implanting placenta.

Impaired functionality of the placenta is one of the major causes of fetal disease. Keeping up the normal function of placenta during fetal growth excludes the predisposition to preeclampsia [49], preterm labor [50] and stillbirth [51]. Hypoxia results from insufficient oxygen delivery; it elicits inflammation under the circumstance of the rapid expansion of adipose tissue in obese individuals [52]. Although chronic hypoxia stress and excessive inflammatory response were both observed in the placenta of high-fat-fed dams [53,54], there have not been other maternal high-fat studies providing further evidences for the causal relationship between placental hypoxia and inflammation activation in the offspring. Moreover, perinatal high-fat intake impairs/affects the fetal environment by triggering not only the placental inflammation but also its associated complications [55].