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Review Series

An understanding of the events that initiate metabolic inflammation (metainflammation) can support the identification of targets for preventing metabolic disease and its negative effects on health. There is ample evidence demonstrating that the initiating events in obesity-induced inflammation start early in childhood. This has significant implications on our understanding of how early life events in childhood influence adult disease. In this Review we frame the initiating events of metainflammation in the context of child development and discuss what this reveals about the mechanisms by which this unique form of chronic inflammation is initiated and sustained into adulthood.

The initiation of metabolic inflammation in childhood obesity

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An understanding of the events that initiate metabolic inflammation (metainflammation) can support the identification of targets for preventing metabolic disease and its negative effects on health. There is ample evidence demonstrating that the initiating events in obesity-induced inflammation start early in childhood. This has significant implications on our understanding of how early life events in childhood influence adult disease. In this Review we frame the initiating events of metainflammation in the context of child development and discuss what this reveals about the mechanisms by which this unique form of chronic inflammation is initiated and sustained into adulthood.

Introduction

The prevalence of obesity and metabolic disease continues to increase from year to year in the US adult population (1) and generates an immense burden on quality of life and healthcare expenditures (2). More ominously, the rate of childhood obesity has increased in parallel with adult obesity, resulting in pediatric patients presenting with diseases traditionally associated with adulthood such as dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes. Despite some reports to the contrary, the latest data show that the prevalence of childhood obesity between 1999 to 2014 has not declined and continues to increase in all age groups (17.4% of children have a BMI greater than the 95th percentile for their age and sex) (3). More alarmingly, 10.5% of adolescents meet the pediatric modified criteria for metabolic syndrome (4), a prevalence that exceeds that of diseases such as asthma and food allergies in children.

The insidious effects of metabolic disease and the limited treatments to prevent the long-term morbidities of metabolic syndrome on cardiovascular disease (CVD) make obesity a threat to both child and adult health. Longitudinal studies demonstrate that the early onset of dyslipidemia and high blood pressure in children is associated with premature atherosclerosis in adults (5). Therefore, an understanding of the initiating events that occur in children that contribute to insulin resistance and CVD has the potential to positively influence how we treat and prevent metabolic disease and its morbidities in all ages. These problems are compounded by the fact that most pediatric caregivers are restricted in their abilities to manage metabolic disease and obesity due to limited resources for nutrition and exercise counseling, the need for multidisciplinary teams for intensive obesity treatment, and the lack of medical treatments available for pediatric obesity.

The evidence above suggests that obesity-associated metabolic dysfunction can be framed as a disease of childhood in which growth, development, the environment, and genetic predisposition are intertwined. Such a framework provides a novel perspective on the potential mechanisms by which inflammation and metabolism interact over the lifespan and may change the face of metabolic disease treatment and prevention for decades to come. Many of the developmental windows that are sensitive to the patterning of metabolic physiology are also crucial in the patterning of the immune system and its responses. As such, in the setting of obesity, codependent interactions between metabolism and inflammation have been observed in the prenatal environment, infancy, early childhood, and adolescence. In this Review we highlight the evidence that metabolic inflammation (hereafter referred to as metainflammation) is initiated in childhood and discuss the mechanisms by which this is triggered in the context of child development.

What is the nature of the inflammatory response to obesity?

Inflammation is the coordinated biologic response to the disruption of normal cellular or systemic physiology. Disruptors can be external pathogens such as bacteria, intrinsic disturbances such as cell death or an oncologic process, or physiologic alterations in response to environmental signals such as fasting or overfeeding. Host inflammatory responses can be acute with the goal of eliminating the effects of a negative stimulus and restoring the system back to its state prior to the disruption (e.g., rapid control of local infection). Chronic inflammation can be seen in circumstances in which rapid clearance mechanisms fail or are incomplete or are generated by gradual or repeated alterations in normal physiology, such as obesity. The protective goal of restoration of homeostasis is retained with chronic inflammation and therefore involves many of the same patterned responses utilized in acute inflammatory settings, such as the production of chemokines, leukocyte activation, activation of innate pattern recognition receptors, and activation of adaptive immunity.

In chronic metabolic disease, inflammatory mediators are both dominant and antagonistic to the homeostatic system of controllers and sensors that regulate physiologic variables such as blood glucose (6, 7). Metabolic disease–associated inflamma-

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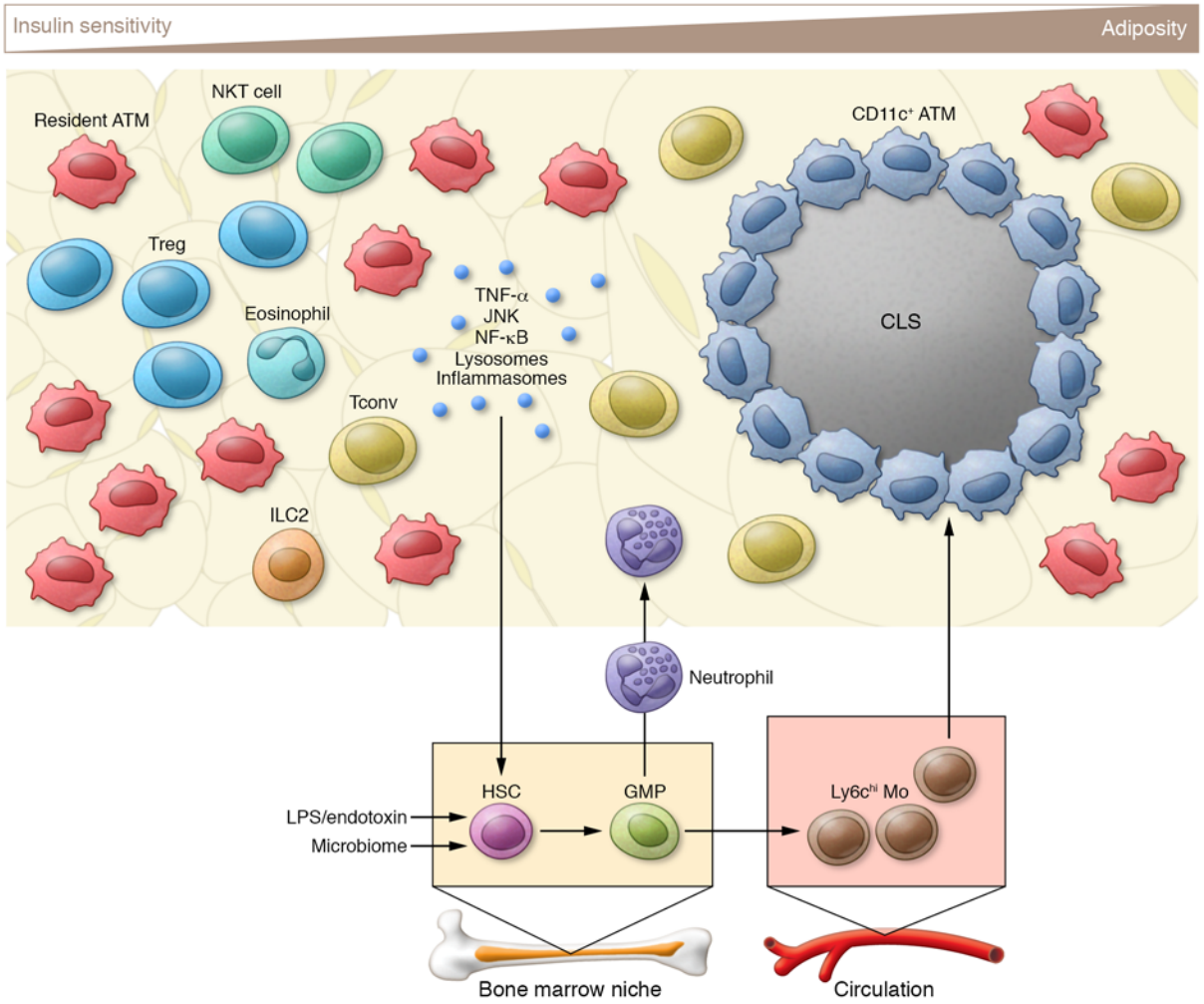

Figure 1. The changing inflammatory environment in adipose tissue with obesity. The progression from a lean to obese state leads to adipocyte expansion. The lean environment contains numerous leukocytes that play regulatory roles in maintaining low inflammatory tone in adipose tissue. These serve to buffer acute metabolic changes in adipose tissue nutrient storage and return the system to baseline. Chronic obesity leads to early events such as conventional T cell (Tconv) activation and neutrophil accumulation that enhance adipocyte damage and CLS formation. A high proinflammatory tone is triggered and maintained by signals from adipose tissue and the environment that drive HSC expansion and production of monocytes (Mo) and neutrophils from granulocyte/macrophage progenitors (GMPs). The net result is the sustained accumulation and activation of ATMs that potentiate continued adipose tissue dysfunction.

tion, or metainflammation, can be detected in numerous tissues involved in nutrient regulation. Since the early 1970s, adipose tissue has been recognized as a nexus between inflammation and metabolism with the demonstration that endotoxin amplifies the release of free fatty acids from visceral adipose tissue (VAT) (8). The identification of the chronic release of cytokines such as TNF-α from obese adipose tissue initiated a wave of studies that have unveiled a complex and integrated adipose tissue immune system that includes both innate and adaptive components (refs. 9, 10, and Figure 1). Within this network, numerous innate inflammatory signaling pathways such as the inflammasome, lysosomes, NF-κB, and JNK are activated in adipose tissue and contribute to metabolic disruption (11–14). These acute inflammatory signals may not always antagonize metabolic adaptation to over-nutrition and in fact may be required for the appropriate response in adipose tissue. Proinflammatory cascades within adipocytes are required for adipogenesis and adipocyte hypertrophy with high-fat diet (HFD) challenge (15). During a short-term HFD challenge in mice, insulin resistance develops independent of inflammation and is characterized by NKT cell–mediated promotion of alternative activation of resident adipose tissue macrophages (ATMs) (16, 17). Thus, inflammatory responses in this context likely represent an adaptive response that permits healthy adipose tissue expansion and efficient lipid storage. The nature of the inflammatory response in short-term HFD exposure may be tissue specific, as reactive gliosis and neuronal damage are observed in the hypothalamus in conjunction with proinflammatory signals (18).

With chronic obesity, leukocytes within adipose tissue generate a sustained proinflammatory tone that has negative effects on adipocyte insulin sensitivity and contributes to systemic insulin resistance (17). Adipose tissue leukocytes such as eosinophils and innate lymphoid cells interact with ATMs in the lean state to maintain homeostasis and counteract the proinflammatory signals (19).

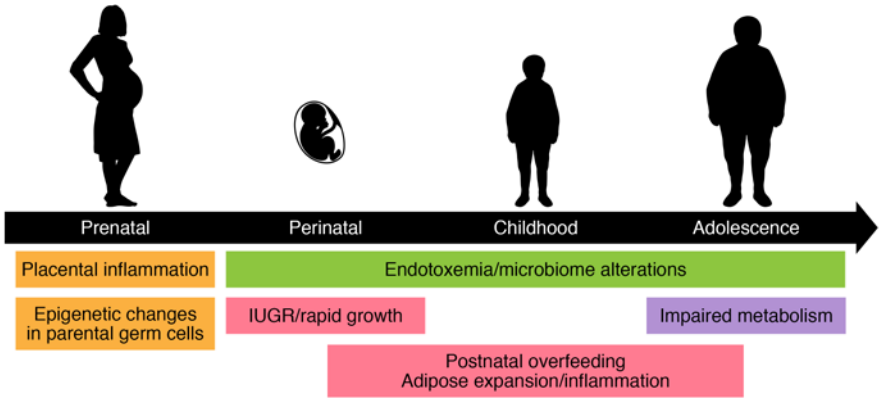

Figure 2. A developmental framework for the initiation of metainflammation. Throughout the life-course there are multiple initiating events that can lead to the expansion of adipose tissue and systemic chronic inflammation. These include programmed inheritance (orange), environmental factors (green), intrinsic growth rates of the child (red), and adipose tissue metabolic impairments (purple).

In mice and humans, qualitative and quantitative changes in ATMs occur in obesity that are mediated by proliferation and leukocyte trafficking from the circulation (20, 21). Events that precede and may amplify ATM recruitment include the activation of conventional $CD4^+$ T cells and the accumulation of adipose tissue neutrophils (22–24). Recruited ATMs prominently express the marker CD11c in mice and home to crown-like structures (CLSs), which form around dead or dying adipocytes and are a recognized sign of adipose tissue dysfunction in many contexts (25, 26). ATMs assume phenotypic changes characterized by lysosomal activation and the formation of a metabolically activated phenotype distinct from classical (M1) or alternative (M2) activation (13, 27). Adaptive immunity is also triggered by chronic inflammation via the function of ATMs and adipose tissue dendritic cells as antigen-presenting cells (28, 29). This promotes Th1 immunity in adipose tissue by stimulating conventional T cell activation at the expense of Tregs (24, 30).

When does metainflammation begin?

The increase in obesity prevalence at all ages suggests that the initiating events for metainflammation may occur in the earliest developmental stages. This concept is emphasized in the developmental origins of health and disease paradigm, which postulates that prenatal and perinatal factors influence adult diseases such as diabetes and obesity via epigenetic and physiologic programming (31). There is evidence to support the induction of metainflammation in all developmental stages, with the potential for life-long consequences on metabolic regulation as well as immune responses to non-metabolic stimuli (Figure 2). These include factors both intrinsic and extrinsic to the developing child that influence metabolic and inflammatory responses.

Prenatal period. The prenatal period can be influenced by multiple factors from both the maternal and paternal environment. Rodent studies suggest that maternal obesity enhances adipose tissue inflammation in the offspring independent of offspring adiposity (32–34). Paternal obesity leads to epigenetic alterations in the sperm in rodents and can potentiate hypothalamic inflammation in offspring (35). Similar epigenetic mechanisms have been observed in a multigenerational HFD feeding model in mice that lead to an increase in ATM infiltration and amplification of immune responses associated with hypomethylation in innate pattern recognition genes such as *Tlr1* and *Tlr2* (36).

The clinical evidence that obesity during pregnancy can lead to proinflammatory activation in the fetus is somewhat sparse (37). In obese mothers, placental inflammatory macrophages are increased and produce proinflammatory cytokines, although fetal blood leukocytes do not appear to be altered (38, 39). Maternal obesity and overweight status are also risk factors for increased serum inflammatory markers in preterm infants, but not in term newborns (40). After adjusting for childhood BMI, C-reactive protein (CRP) levels were increased in 12-year-old children born to mothers with higher pre-pregnancy BMIs, suggesting that maternal obesity may alter the immune system in the long term (41).

In terms of inflammation and disease risk, low birth weight (LBW) is a well-documented and strong risk factor for metabolic disease — a concept encompassed in the Barker hypothesis linking poor in utero growth to CVD and diabetes (42–44). In rodents, intrauterine growth restriction (IUGR) is associated with increased inflammatory markers in the circulation of the offspring (45–47). Proposed mechanisms for this effect include alterations in the circadian clock and downregulation of *Pparg* and *Ppara* with IUGR (48). Longitudinal studies such as the Bogalusa Heart Study also show that LBW induces chronic elevations in wbc counts and inflammatory biomarkers such as CRP in childhood (49, 50). Similar to LBW, high birth weight is associated with increased adult visceral adiposity and insulin resistance; however, the evidence that this occurs in association with elevated levels of inflammatory biomarkers such as CRP is not strongly supported (51, 52). These findings suggest that for some children the initiating events of metainflammation may occur in the postnatal setting and less so in the prenatal environment.

Perinatal/infancy period. The transition from the intrauterine to the extrauterine environment during the perinatal period is characterized by intense remodeling of both metabolic physiology and the immune system. These two processes intersect in places like the gut where the establishment of the intestinal microbiome after birth is coupled to the development of the immune system that is permissive towards colonization in early life (53). The immune system in infants is immature and over time transitions from one dependent primarily on innate immunity for host defense to one that is able to mount adaptive responses to pathogens over the first years of life (54). This early post-natal stages are also a critical window where tissue resident leukocytes such as Tregs take residence in adipose tissue (55). Events that disrupt or modify the developing immune system in this critical window may have long-term consequences for health and disease.

Preclinical studies using HFD to model perinatal nutrient excess demonstrate activation of JNK and IκB kinase subunit β (IKKβ) pathways in the liver and hypothalamus in association with insulin

resistance and fatty liver in the offspring (56, 57). Rodent models of postnatal overnutrition and accelerated growth by manipulation of litter size show that a HFD may not be required to trigger inflammation and generate lifelong effects on metabolic dysfunction (58–60). Postnatal overfeeding (PNOF) in rats is sufficient to induce hypothalamic inflammation and gliosis as early as postnatal day 14 and leads to a persistent increase in hypothalamic NF-κB activity in adulthood (61, 62). PNOF can enhance microglial activation in response to HFD in adults, which suggests that the inflammatory set point in the brain is permanently modified with accelerated early life growth (63, 64). The mechanism of the persistent alterations in hypothalamic inflammation with PNOF may be different than HFD-induced hypothalamic inflammation in adult mice, which is reversible (18, 65). PNOF can also amplify adipose tissue inflammation in response to a HFD in adulthood and can also increase ATM infiltration and CLS formation (66, 67). Reprogramming of inflammatory responses by perinatal overnutrition does not seem to be limited to metainflammation, as PNOF can alter global responses to pathogen-associated molecular pattern molecules such as LPS and modulate pulmonary inflammation (68, 69).

While there are few clinical studies focused on the inflammatory effects of rapid infant growth, they demonstrate a consistent finding that rapid postnatal growth in the first 6 to 12 months of life is a strong risk factor for metabolic disease independent of birth weight (70–73). In fact, the loci that contribute genetic susceptibility to obesity play a dominant role in regulating weight and fat mass in the first three years of life but do not appear to affect birth weight (74). Weight gain in infancy is a risk factor for elevated CRP and great carotid intima-media thickness in non-diabetic children (75). Large cohort studies have identified surprising links between infant growth and inflammatory diseases such as type 1 diabetes (76) and asthma (77), suggesting that early rapid growth rates may have broad effects on inflammatory responses to environmental stimuli during childhood. Overall, the immediate postnatal period is clearly a sensitive window for the patterning of nutritional and inflammatory responses that is understudied in the context of metainflammation. Future work is needed in this area, as this time period may be amenable to interventions in the primary care setting, in which growth rates are closely monitored but few guidelines are set regarding how to manage infants with rapid growth.

Childhood/adolescence. While many preclinical studies have examined the effects of obesity on inflammation in prenatal and early postnatal periods, there are limited basic studies assessing the effects of childhood and adolescent obesity on life-long disease risk. Clinically, obese children are more likely to become obese adults (78), and excess BMI and high BMI trajectories in adolescents are associated with a future risk of adult diabetes (79). The observation that normal-weight adults who were obese only as children retain a four-fold increased risk for type 2 diabetes further suggests that the effects of childhood obesity can be long lasting, even if BMI is normalized by adulthood (80).

Evidence is strong that metainflammation is triggered by childhood obesity. Overweight and obese children as young as 3 years of age demonstrate elevations in CRP and absolute neutrophil counts (81, 82). Several studies have shown that elevated wbc counts in obese children track into adulthood and correlate with the number of metabolic syndrome components (83). Rapid weight gain during childhood predicts both future weight gain (84) and CRP levels (85). In children, these inflammatory biomarkers are strongly associated with adiposity (86), and in severely obese adolescents the risk of elevated CRP, impaired fasting glucose, and hypertension increase in concert with increased BMI (87, 88). Protective factors such as adiponectin have been shown to have a similar decrease with increasing BMI and increased CRP (88).

Beyond these changes in circulating biomarkers, tissue-specific inflammation in obese children parallels what is seen in obese adults. NAFLD is present in 59% of adolescents referred for bariatric surgery, with 10% of these showing evidence of non-alcoholic steatohepatitis (NASH) (89). Severity of NAFLD in this cohort correlated with wbc count, and liver samples from adolescents with NASH had increased expression of genes involved in macrophage chemotaxis. Obese adolescents with NAFLD have increased CLSs in their subcutaneous adipose tissue that correlates with liver fibrosis independent of BMI (90). Adipose tissue in obese adolescents, similar to adults, has ATM infiltration and evidence of inflammasome activation that correlates with decreased insulin sensitivity (91). Adipose tissue CLSs have been identified in children as young as six years old in association with elevated CRP (92). Overall, these findings demonstrate that adipose tissue metabolic stress and inflammation are common in obese children and adolescents and may set the stage for decades of dysfunctional adipose tissue.

What are the initiators of metainflammation?

Characterizing the events that initiate metainflammation in children may be key to identifying prevention strategies throughout the lifespan and identifying those individuals most at risk for metabolic disease morbidities. Inflammation is observed in a range of tissues involved in nutrient control. For example, proinflammatory macrophage signatures are observed in sites that include adipose tissue, gut (93), liver (94), pancreas (95), muscle (96), and CNS (18, 97). Animal models suggest that short-term HFD feeding leads to acute proinflammatory signals in the hypothalamus without significant leukocyte activation in other tissues that may be largely reversible (65). In the setting of chronic obesity, while multiple tissue-specific triggers may be activated, there is evidence to suggest that circulating inflammatory mediators are induced by obesity and generate broad effects on tissue inflammation.

The important role of innate immune responses to bacterial products such as endotoxins and LPS has advanced the hypothesis of metabolic endotoxemia as both acute and chronic stimuli for metabolic tissues (93, 98). This concept is supported by the observations that circulating endotoxin levels are higher in diabetic adults compared with non-diabetic adults (99). Obese mothers have two-fold higher endotoxin levels associated with elevated ATMs and inflammatory cytokine secretion from adipose tissue (100). In obese children, inflammatory biomarkers associated with cardiovascular risk, such as plasminogen activator inhibitor 1 and TNF-α, correlate with serum endotoxin levels (101). Animal models suggest that HFD feeding compromises gut barrier function that contributes directly to endotoxemia and that gut-delivered antiinflammatory agents may limit systemic LPS (93). Innate pattern recognition receptors such as toll-like receptors are present on multiple metabolic cells, and LPS has been shown to

negatively influence substrate metabolism, storage, and absorption in these tissues (93, 102–104). In adipose tissue, experimental endotoxin infusion in humans rapidly induces chemokine and T cell activation genes and therefore may potentiate leukocyte crosstalk and amplify initial inflammatory responses (105). This concept still remains somewhat controversial, as limitations in endotoxin measurement methods prevent the wide use of endotoxin as a true biomarker for metainflammation (106). However, the observation that treatment of obese adolescents leads to both improvements in insulin resistance and decreased endotoxin levels suggests that early interventions may limit metabolic endotoxemia (107).

Another initiating event in metainflammation is the direct influence of the obesogenic environment on the generation of leukocytes and the potentiation of their responses to tissue stress and damage (108). The observation of increased circulating neutrophils and monocytes in obese children suggests that obesity fundamentally alters leukocyte production and/or turnover, and this has been supported in preclinical studies. Bone marrow–derived hematopoietic stem cells (HSCs) are the primary source of mature leukocytes (109) and have the capacity to alter their cellular output in response to environmental cues (110). For example, in sepsis, endotoxin can "push" HSCs to increase myeloid cell production and potentiate innate immune responses (111).

A similar stimulation and expansion of HSCs in obesity may be a mechanism by which activated myeloid responses can be propagated to different metabolic tissues (112, 113). Nutrients can directly stimulate myelopoiesis from HSCs. For example, hyperglycemia can induce the calcium-binding proteins S100A8 and S100A9 and stimulate monocyte production from myeloid progenitor cells in models of type 1 diabetes (114). Fish oil–rich diets promote hematopoiesis through the activation of MMP12 in the bone marrow (115). TLR4 activation induces HSC expansion and myelopoiesis and may be another mechanism by which metabolic endotoxemia imparts its effects on metainflammation (116–118). ATMs can generate inflammasome-dependent signals that activate bone marrow granulocyte and macrophage progenitors via IL-1β (119). In addition, obesity may also influence HSC function indirectly by modifying the bone marrow niche populated with specialized adipocytes (120). The obese gut microbiome has been implicated in stimulating myelopoiesis via modification of the bone marrow niche (121).

As in metabolic tissues, epigenetic regulation of the immune system plays crucial roles in leukocyte production and in altered immune responses after severe illness such as sepsis (122). Such epigenetic programming in leukocytes by obesity may explain why the risk for diabetes is sustained in formerly obese adults and why persistent adipose tissue inflammation is seen after weight loss (123, 124). HSCs from obese mice have the enhanced capacity to generate proinflammatory $CD11c^+$ ATMs compared with lean HSCs, even after serial bone marrow transplantation (112), suggesting that HSC-autonomous mechanisms contribute to metainflammation. Obesity can alter methylation patterns in circulating lymphocytes (125) and modify histone methylation of genes regulating macrophage production in the bone marrow such as *IL12* (126). Differential DNA methylation is seen in adipose tissue from individuals with type 2 diabetes, and target genes include those involved in inflammation and carbohydrate and lipid metabolism (127). Similar mechanisms may contribute to the impaired fetal hematopoiesis that is observed with maternal obesity (128). There is a paucity of information about the point at which epigenetic alterations may occur in obese children; however, it is reasonable to postulate that early nutritional stress associated with rapid weight gain may trigger long-term alterations in immune function.

The quantitative and qualitative alterations in HSCs and leukocytes are potential priming events that shift a healthy adaptive inflammatory response to one that is deleterious to homeostasis. This may occur either by increasing the amplitude or the duration of the inflammatory response to adipocyte stress and death. VAT is a site where these competing forces are held in a delicate balance to maintain the robust ability to store and release nutrients on demand. Under the stress of excess nutrient availability, hypertrophic adipocytes are subjected to stress, leading to cellular degeneration that activates the inflammasome and initiates proinflammatory programmed cell death (pyroptosis) (129). Hallmarks of adipose tissue that has lost this flexibility include fibrosis and inflammatory clusters of leukocytes in CLSs (130, 131), both of which have been observed in obese children and adults. Subsequent production of chemoattractants such as CCL2 and lipolytic signals triggers the recruitment of monocytes from the circulation to form the CLS that engulfs the dying adipocytes and potentiates new adipocyte formation (132, 133). Mouse models in which macrophage recruitment or activation are attenuated show a phenotype of permissive adipocyte hypertrophy, reduced adipocyte death, and preservation of metabolic health, suggesting that macrophages may accelerate adipocyte death and not merely passively respond to it (21). VAT CLS formation is seen in obese children, suggesting that these events are initiated in early life and not only in obese adults (134, 135). $CD206^+$ ATMs are prominent in adipose tissue from children and are positively associated with adipocyte size (136). However, the existing VAT gene expression profiling data from obese and non-obese children demonstrates a relative paucity of differentially expressed inflammatory genes (137). This contrasts with what is seen in obese adult VAT, which is enriched for inflammatory gene pathways (138, 139). These findings suggest that the nature of the metainflammatory response in adipose tissue may be fundamentally different in children despite the similar formation of CLSs. It may be that the duration of obesity influences the magnitude of the inflammatory response or that children retain more of the homeostatic pathways meant to dampen inflammation despite the same stimulus of adipocyte stress.

Conclusion

Obesity has lifelong effects on metabolism and immune system activation that may have multiple starting points from the prenatal period through adolescence. The existing data suggest that whenever it is initiated in children, many features of metainflammation persist through adulthood. Weight reduction in children can normalize inflammatory markers, which gives us hope that metainflammation can be modified after it has begun (140). However, there remain many gaps in our understanding of how early life events (e.g., rapid post-natal growth) affect lifelong risk for metabolic disease and what interventions may be tenable in this

window of development. Advancing this line of inquiry will require efforts such as the NIH Environmental influences on Child Health Outcomes (ECHO) Program (141), which has replaced the National Children's Study and will leverage extant cohorts to understand how environmental exposures influence pediatric outcomes such as obesity. Environmental exposure is broadly defined to encompass the biological, chemical, behavioral, social, physical, and built environments that have undergone major changes in the past several decades in concert with the increase in obesity. This program provides an opportunity for scientists and physicians to engage with a broader research community to solve this wide-ranging problem.

Reframing metainflammation and metabolic disease as a pediatric morbidity also provides opportunities for discovery in basic science by framing inflammation in a developmental context. All pediatric chronic diseases require a developmental biology framework to deliver optimal care and to understand their pathogenesis. It is clear that a similar framework is required to understand how metainflammation begins (Figure 1). Investigations focused on these early inciting events have the potential to identify preventative therapeutics for metainflammation that are currently lacking. A careful intersection between basic and clinical research is needed to fully identify the mechanisms involved in the initiation of metainflammation during childhood. This is particularly important given the known limitations of mice for the study of immunology, as current husbandry practices generate mice with persistent immature immune systems with features that more closely match newborn humans than adult humans (142). This developmental perspective is not unique to children and is also required to evaluate adult metabolic disease, given the diversity of settings in which metabolic health is compromised throughout an individual's lifespan.

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