NUTRITIONAL DETERMINANTS IN THE DEVELOPMENTAL PROGRAMMING OF AUTOIMMUNE DISEASES – FACTS AND HYPOTHESES

A Narrative Literature Review

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Abstract

Autoimmune disorders (AID) are a group of debilitating non-communicable chronic diseases (NCDs) affecting the immune system's capacity to differentiate between foreign and autoantigens. This set of pathologies has experienced a fast-tracked increase in incidence over the last decades. Other types of NCDs, especially the metabolic syndrome, cardiovascular diseases and diabetes have been shown to have their origins in early life, early life nutrition being a key predictor of their occurrence. This observation has opened an entirely new field of research which, today, is known as Developmental Origins of Health and Disease (DOHaD). Literature on AID in adulthood is abundant, however, aside from type 1 diabetes (T1D), research on AID in the context of DOHaD remains relatively scarce. Due to the prevalence of AID in modern society and the public health challenge it represents in numerous countries, this review will 1) present the state of the literature to explore mechanisms that link perinatal nutrition to the development of autoimmunity in later life, and 2) build hypotheses for the purpose of future research in the domain of nutritional programming of AID. Its purpose is to provide an oversight primarily for an audience of early-career researchers and practitioners who have an interest in the subject and who might find it useful to develop and test hypotheses of their own. It should also be clarified that this review does not test the cited hypotheses. Rather, the purpose of this review is to attempt to answer the following question: Given the state of the literature on the development of the immune system, as well as on pre-and post-natal nutrition, what can be said to be the nutritional determinants in the developmental programming of autoimmune disorders (AID)?

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I. Introduction

This literature review pertains to a field of medical research known as Developmental Origins of Health and Disease (DOHaD). DOHaD is dedicated to elucidating the role of early life environmental factors on later life health outcomes. It relies heavily on the work of D.P.J. Barker and his research colleagues, which established a causal link between *in utero* undernutrition and subsequent higher risk of cardiovascular disease, obesity and diabetes in adulthood when compared to individuals normally fed in early life[46]. Subsequent research on this subject has since allowed us to conclude that various other non-communicable diseases (NCDs) are equally programmed in early life[45]. Interestingly, some authors have even suggest that NCDs have common developmental origins, giving reason to believe that they are more intertwined and connected than originally presumed[45]. The same authors have also proposed chronic inflammation as a common causal mechanism, as this is a phenomenon observed in a great number of NCDs[45]. Recent evidence suggests a pathophysiological relevance of the immune system in the development of these diseases, and in particular, what this review will denominate as *programming of autoimmunity* – the developmental programming of autoimmune disorders (AID).

The main question guiding this review is the following: given the state of the literature on the development of the immune system, as well as on pre-and post-natal nutrition, what can be said to be the nutritional determinants in the developmental programming of autoimmune disorders (AID)? Having surveyed the literature for these determinants, this review will hypothesize that there are three key intermediaries linking nutrition and developmental programming of AID: early malnutrition (IUGR, obesity), the gut microbiota and gut permeability. All appear to contribute to an inbalanced immune homeostasis, more specifically to a low-grade inflammatory state, and may be associated with a higher susceptibility to developing autoimmune disorders in later life.

The rationale behind compiling this review is that in the past decades, AID have experienced a continuous and fast-paced increase – a development which has been observed to be strongly correlated with the westernization of numerous countries, including a higher prevalence of westernized diets in developing countries[4][73]. Yet despite the ever-increasing burden that NCDs represent for public health, literature describing the developmental origins of autoimmunity is scarce, and thus, calls for more attention.

Definitions

First, let us proceed to define the most relevant concepts that will be cited in this review. Developmental programming is the physiological process that links the variations in critical gene expression in a developing organism, resulting from usual environmental stimuli in early life. The Developmental Origins of Heath and Disaeses (DOHaD) is a concept that describes the putably causal association between early life stimuli (e.g. malnutrition), also called 'first hit' and the revelation of non communicable diseases in later life, after exposition to a second environmental hit. These two hits are spaced with a clinically silent period. The mechanistic processes underpinning these associations are mainly epigenetic modifications of specific promoters of developmental genes. Epigenetics is the process of altering gene expression through various DNA-marking processes that are related to environmental inputs, *without* changing the DNA sequence. This translates early life environmental insults (environmental stimuli negatively affecting the organism) to altered body function and, eventually, later life disease[33]. The relevance of epigenetics in early life comes from the fact that pre-natal life is marked by the critical phase of tissue formation and organogenesis, and the post-natal period is characterised by the maturation of organ systems, making these phases particularly "plastic" and susceptible to environmental changes[13]. As the literature shows, a great proportion of these epigenetic changes are determined by what we eat. In fact, a specific term has been developed around this concept. "Nutriepigenomics" describes the epigenetic changes induced by dietary factors[17]. This

is of great relevance to the field of DOHaD, as nutrition has been acknowledged to be a major determinant in future health of offspring[33], especially in regard to the developing immune system[17]. The paradoxical effect observed after exposition to a putative reversing agent (i.e. hypercaloric diet in an infant exposed to IUGR) is called the 'thrifty phenotype'[117]. Namely, this latter observation indicates that epigenetic mechanisms may be reversible, or at least explain some phenotypical variations during an individual's lifespan. Furthermore, the early misprogramming of an organ or function probably conditions the potential of reversibility of this phenomenon. As it will be argued in this review on the basis of current literature, epigenetic mechanisms also play a significant role in the programming of thymic central tolerance and susceptibility to autoimmune disorders.

Bearing this in mind, this review will adhere to the following structure: It will first unpack the development of the immune system in greater detail, before exploring the nutritional determinants and related epigenetic mechanisms in the developing immune system. It will then trace several contributing factors, which – according to the current state of knowledge – are likely to contribute to the development of AID. As outlined above, early life malnutrition will be presented as a key programming factor in the developing immune system; further, obesity may represent an underreported associated factor. It is conventionally described as a BMI > 30 kg/m^2[16]. To be precise, this review will discuss both maternal and early life obesity in offspring. Maternal obesity is of the utmost importance when it comes to developmental programming of health[15] [74] [75]. In westernized countries, around 20% of pregnant women are obese[15]. This condition has been shown to lead to high birth weight, low birth weight and a pro-inflammatory fetal environment. This being said, early life obesity in infants is an equally problematic circumstance in terms of future health. The outbreak of childhood obesity has been described as an epidemic and one of the most pressing public health challenges of the 21st century on a global level, as it leads to increased early manifestations of chronic diseases[44][76]. With respect to AID, a causative role of obesity in the development of autoimmunity has been strongly suggested. Hence, it seems pertinent to advocate maternal and early life obesity as corresponding risk factors.

The second contributor to the development of AID that will be discussed is the role of gut microbiota. The microbiome is both strongly influenced by nutrition as well as obesity. It is a highly sophisticated amalgamation of a select population of microorganisms that occupy the inner linings of the gastrointestinal tract[47]. It has been shown to play a major role in the developing immune system and is highly malleable depending on nutritional input. This review will therefore elaborate on the microbiome's role in the education of the infant's immune system and its causal role in the development of AID.

A final major mechanism this review will present as a possible contributor to the programming of autoimmune disorders is gut-permeability. Among other factors, gut permeability has been described to be determined by nutrition, obesity and the microbiome. While describing the mechanisms that promote autoimmunity through gut permeability in early life, this review hypothesizes that processed foods, including its additives, have a non-negligible influence on the risk of developing AID in later life. After briefly outlining the methodology behind this review, it will then transition to the phenomena of vulnerable phases during immune development and to the concepts of autoimmunity and epigenetics, in order to provide the necessary basic concepts for this review.

Methodology

The work reported here is a narrative review of the current published literature on the outlined topic. As such, it will not bring original findings or focus on a particular experiment. Rather, it will sum up the state of the available literature on what can be said to be the nutritional determinants in the developmental programming of autoimmune disorders (AID). In order to determine the state of the

current literature on the topic under discussion, original articles and reviews were selected from the following publications and reviewed for content and method, most of them having been published in the period from 2000 to 2018. Key words forming the literature search from amongst these journals include nutrition, developmental programming, immune system, autoimmune disease, early life, obesity, microbiome, gut permeability, processed foods, formula feeding and additives.

After a broad and extensive search of the existing literature, the publications finally cited in this review were specifically selected to raise questions regarding a potential relationship between specific nutritional insults and abberant immune development, more specifically, autoimmunity. Journal titles examined include:

Journal of Abdormal Child Psychology, Food and Chemical Toxicology, Autoimmunity Reviews, Current Allergy and Asthma Reports, Revista Paulista de Pediatria, Jornal de Pediatria, Best Practice & Research Clinical Endocrinology & Metabolism, Revista chilena de pediatría, New England Journal of Medicine, European Journal of Nutrition, Acta Diabetologica, British Medical Journal, American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Current Nutrition Reports, Nutrition Reviews, Autoimmunity Reviews, Nutrients, International Journal for Vitamin and Nutrition Research, International Journal of Environmental Research and Public Health, Proceedings of the Nutrition Society, Journal of Obstetrics and Gynaecology Research, Journal of Molecular Neuroscience, Journal of Immunology Research, Archives of Endocrinology and Metabolism, Clinical Rheumatology, Advances in Nutrition, The American Journal of Clinical Nutrition, Autoimmune Diseases, Advances in Gerontology, Journal of Experimental Biology, Pharmacological Reviews, Molecular and Cellular Biology, The Journal of Immunology, Nutrition Research and Reviews, Journal of Internal Medicine, Scientific Reports, Breastfeeding Medicine, The Journal of Nutrition , Nutrition Research, Reproductive Toxicology, Endocrinology, Biochemical Journal, Clinical Immunology, Journal of Developmental Origins of Health and Disease, Annual Review of Public Health, Psychosomatic Medicine, Journal of Pregnancy, Journal in Research of Medical Science, BMC Public Health, Reviews in Clinical Medicine, Acta Naturae, Trends in Endocrinology & Metabolism, Nature Reviews Immunology, EMBO Molecular Medicine, Annals of the Rheumatic Diseases, Clinical & Experimental Immunology, Frontiers in Cellular and Infection Microbiology, Frontiers in Immunology , International Dietary Journal, Annals of Medicine, The Lancet Diabetes and Endocrinology, European Journal of Epidemiology, British Journal of Nutrition, BMC Neurology, Wiener Medizinische Wochenschrift, Mediators of Inflammation, Clinical and Vaccine Immunology, Early Human Development, Metabolism, Clinical Science, Annals of the New York Academy of Sciences, Silence, Pediatric Clinics of North America, Expert Review of Clinical Immunology, Pediatrics, Nature, Placenta, Journal of Leukocyte Biology, Biological Sciences, International Journal of Epidemiology, Current Opinion in Immunology, Annals of Nutrition and Metabolism, Nature Medicine, International Journal of Obesity, Gut, Livestock Science, and *Reproductive Biology*.

II. Development of the Immune System

As they form an important component of the DOHaD literature, the following sections of this review will detail the functions, the vulnerabilities and the early development of the immune system. The idea behind going into detail on this aspect of the literature is to build up the conceptual background that will permit a better understanding of the nutritional determinants in the developmental programming of AID.

The Normal Development of the Thymus and Specific Function(s)

The thymus is a central component of the immune system with a major role in the education of the future adaptive immune system. It is the so-called "primary" lymphoid organ, representing a place of maturation, differentiation and selection of T cell precursors that stream from the bone marrow into the thymus[103]. These cells, once matured, leave the thymus to enter the blood stream and/or find their way to secondary lymphoid organs, such as the lymph nodes, gut or spleen[103], to participate in the recognition and elimination of foreign antigens or tumors. But the principal role of thymus, often underrated, is to prevent autoimmunity by educating thymocytes to tolerate virtually all auto-antigens of an individual's's organism[116].

A mature thymus can be separated into a cortical and a medullary compartment[104]. The cortex is responsible for the early stages of T cell development and selection, whereas the medullary compartment greatly contributes to the establishment of tolerance by means of further selection and T_{Reg} development[105]. The epithelial component of the thymus takes its origins in the endodermal layer of the anterior foregut[104]. Its development starts early during fetal life, undergoing a critical phase from week seven to fourteen of gestation[104]. The differentiation of the cortical and medullary epithelium takes place before lymphocytes invade the thymus[104].

At birth, the thymus is at its peak in terms of size[102] and experiences drastic growth during the first six post-natal months[103]. This is followed by a deceleration until late childhood and involution starting in adolescence[103]. The thymus is the one and only organ that will overtake its adult size during late childhood, as it will start to involuate from adolescence to maturity. Early life thymic development is known for its tolerogenic nature, largely due to a perinatal Th2 predominance[102]. Responses to foreign antigens at this stage are still weak and will gain in strength and specificity with the dramatic increase in foreign antigen exposure after birth[102]. It has been established that the microenvironment shaped during early thymic development plays a key role in determining the future function of peripheral T cell responses[103].

Developmental Vulnerability of the Immune System

Bearing this in mind, there exists a consensus in the literature that the immune system is particularly vulnerable to environmental insults, including nutritional insults, during its pre- and post-natal developmental stages[29]. The thymus plays an important part in this process. Approximately halfway through pregnancy, the thymus (which is an important centre of immune function establishment[19]), begins the education process of $CD4^+CD8^+$ lymphocytes, known as "positive and negative selection"[29]. This phase is considered particularly vulnerable[29]. As the T cells formed during fetal development only "know" foreign antigens through exposure to the maternal environment, fetal T cell function differs greatly from adult T cells[102]. Broadly speaking, innate immunity, Th1 responses as well as antibody function are all significantly weaker in foetuses and neonates than in older individuals[102]. The immune system, which is comprised of primary and secondary lymphoid organs, is subject to phases of accelerated growth and maturation during late gestation and early post-natal life, like all other organs[29]. This renders them more vulnerable to environmental influences [29], especially nutrition. Mis-programming during these phases of susceptibility can lead to aberrant immune responses, promoting immune-mediated diseases[45].

Birth, in turn, represents a major event in the maturation of the immune system. Starting in the birth canal, the new-born will experience a burst of microbial exposure, which will remain incessant for the rest of its life[102]. Through the ingestion of food and, simply, the environmental exposure, the gastro-intestinal tract will experience a dramatic colonization by bacteria and, therefore, require a large number of immune cells – approximately 20% of total lymphocytes – to provide adequate

protection[102]. Thus, it appears logical that the gut should play a significant role in the education and maturation of the adaptive immune system, namely the memory T and B cells [102]. B cells, in particular, undergo a complex process known as "somatic hypermutation", allowing them to cultivate the most efficiently binding antibodies for a given antigen[102]. The accumulation of immune experiences through infections and other antigenic exposures will create an adaptive immune memory as the individual ages[102].

However, the adaptive immune system is strongly affected by various environmental influences, which will be described later in this review. Abnormal development of the adaptive immune system can result in autoimmunity, of which autoreactive CD4+ T cells are a hallmark[113]. They are characterised by the initiation of an immune reaction when presented with a self-antigen. Yet, how do these autoreactive cells emerge? Previously, it was believed that the only cause of autoreactive cells was an inefficient selection process in the thymus. This no longer holds true, as researchers have found that only a select number of autoreactive lymphocytes are eliminated through this process[113]. Despite the escape of these cells into the peripheral blood stream, there are several peripheral counter-mechanisms, such as clonal anergy (the lack of lymphocyte response in presence of an antigen), immunological ignorance (inefficient antigen presentation) as well as $T_{Regs,}$ which counteract these autoimmune tendencies. Autoimmunity can, therefore, evolve via two pathways: 1) through the persistence of autoreactive T and B lymphocytes, and 2) through a loss of regulatory immune cells, such as T_{Regs} to contain the former. As we will see throughout this review, T_{Regs} in particular have been observed to be susceptible to nutritional insults.

Immunogenic Developmental Determinants Associated with Autoimmunity

There are three major cell types – some of them briefly mentioned above – that are commonly associated with autoimmunity and are likely to play a role in the developmental programming of AID (please see *Table 1* below).

Table 1: Cell Types Associated with Autoimmunity

Cell Type	Function
Th1	Th1 cells are a specific type of T helper cell that produce IL-2, TNF- α and IFN- γ [10]. They are frequently associated with autoimmune disorders such as Crohn's disease and MS [10].
T_{Regs}	T_{Regs} are known for their immune-regulatory function and their role in AID (FoxP3+ T cells) [25]. They express various anti-inflammatory cytokines, such as IL-10 and TGF-β, which are known to suppress Th1 and Th17 activity[25]. They are the sole producers of IL-35, which has been shown to inhibit the secretion of IL-17[25]. Contrarily, in presence of IL-6, TGF-β produced by T_{Regs} induces the production of IL-17[27]. Elevated levels of T_{Regs}, although of diminished regulatory function, have been observed in systemic lupus erythematosus (SLE), and are assumed represent an attempt to counteract the elevated levels of pro-inflammatory cytokines[28]. In multiple sclerosis (MS), T_{Reg} levels are lower and their function is impaired[25]. The importance of T_{Regs} in the developmental context is their central role in tolerance-building and the presumed peak of their production during the fetal phase[29].
Th17	Th17 are a subtype of CD4 T cells that differ from the classical Th1 and Th2 cells[26], and via their production of Th17[25], are acknowledged to play a central role in the development and maintenance of AID[16]. It has been observed that Th17 cells have the capacity to differentiate into Th17-derived Th1 cells[26], which are said to have even stronger pathogenic properties than Th17 cells[26]. Th17 levels are increased in MS and several other autoimmune disorders[25].

These cell types will be repeatedly referred to throughout this review, as they appear to be of great relevance to the programming process of autoimmunity.

III. Overview of Epigenetic Mechanisms

Having outlined the most relevant aspects of the immune system with regards to autoimmunity, we can now have a closer look at the functioning of epigenetics. A basic comprehension of epigenetic mechanisms is necessary when discussing developmental programming, as epigenetics is the main mechanism through which environmental stimuli, such as nutrition, lead to modified gene expression. Most research done in the field of DOHaD is explicit on the importance of this mechanism. Especially early life presents an unstable period during which environmental perturbations can have an important impact on the epigenome[14]. It is through this mechanism that the fetus, new-born and infant can be predisposed to an altered lecture of the genome which can be the origins of NCDs that appear in later life[7]. To unpack and explain this process in greater depth, three main known mechanisms in epigenetics will be introduced here: DNA methylation, post-translational histone modification and miRNAs.

DNA methylation is the addition of methyl groups to the 5' end of the cytosine ring of CpG dinucleotides. Hypermethylation of gene promoters leads to transcriptional silence, whereas hypomethylation leads to an increased expression of genes[48]. Methylation patterns vary greatly throughout fetal development. After complete demethylation of the genome during gametogenesis, it is remethylated shortly before fertilization[14]. There is a second wave of demethylation observed in the early embryonic phase, with methylation patterns being re-established after implantation in the uterus[14]. This demonstrates how epigenomic instability during early human development can be vulnerable to changes in the surroundings. The one-carbon metabolism fuelled by dietary nutrients such as folate, vitamins B_6 and B_{12}, as well as riboflavin, choline and betaine, provides the necessary methyl groups for methylation[39]. It is for this reason that the process of methylation can be greatly affected by dietary deficits or excesses of these nutrients[18]. The methylation reaction, in turn, is catalysed by the DNA-methyltransferases 3A and 3B (Dnmt3A and Dnmt3B, respectively)[18]. These enzymes are responsible for creating novel methylation patterns, as opposed to Dnmt1, which maintains the established configurations[48]. Interestingly, Dnmt3A and Dnmt3B are particularly active during the differentiation of embryonic stem cells, but low in adulthood[18]. This might, at least in part, explain why epigenetic modifications occurring *in utero* and early life can have such a long-lasting impact on biological processes. DNA methylation is a relatively permanent epigenetic mark[7], and once fixed, with the exception of a slow hypomethylation believed to be age-related, it remains relatively stable over the life course of an individual[7]. At this stage, it is important to note that recent literature shows that abnormal methylation patterns have a significant impact on the development of AID[48]. For example, hypomethylation of T cells seems to strongly promote the development of autoimmunity[48].

Post-translational histone modifications can vary in nature and regulate the readability of DNA by modifying the structure of chromatin. Methylation, acetylation, phosphorylation, ubiquitination and ADP-ribosylation are the principal mechanisms observed to date[15]. Whereas heterochromatin is associated with hypoacetylation and methylation of histones silencing genes, euchromatin is associated with acetylation of specific positions, and consequently, DNA expression[15]. Similar to DNA methylation, histone modifications are susceptible to nutritional influences. For example, substances such as vitamin E metabolites, lipoic acid, biotin and garlic organosulfur compounds present a biological activity very similar to that of histone deacetylase (HDAC) inhibitors[38]. Dietary composites are now being considered for therapeutic use in certain pathologies, highlighting the direct implication of histone modifications in health outcomes[38]. In addition to this dietary protein restriction, garlic, and retinoic acid are also suspected to induce histone modifications[17].

miRNAs are noncoding RNA strands of small size (20-25 nucleotides in length)[15]. They are able to interrupt the process of mRNA translation and, therefore, regulate gene expression[38][15]. miRNA can also affect DNA methylation and histone modifications[38]. Vice versa, DNA methylation and histone acetylation may alter miRNA expression, closing a very sophisticated feedback circle[38]. The regulation of miRNA is also responsive to dietary components: curcumin, genistein and retinoic acid have shown to down-regulate miRNA expression associated with carcinogenesis[17]. miRNAs are therefore, too, observed to play a role in certain diseases[38]. Finally, it is important to note that these epigenetic marks are heritable and can, therefore, be of transgenerational importance[45].

These are the main epigenetic mechanisms that will be continuously referred to as we explore how nutrition, particularly in early life, can lead to altered immune function and subsequent autoimmunity.

IV. Current Knowledge on Pre- and Post-Natal Nutritional Effects on the Developing Immune System

Having discussed the theoretical bases of the developmental immune system and epigenetics, this review will now proceed to discuss the putative links between the perinatal nutrition and the development of AID. This section is intended to bridge the gap between the development of the immune system, the nutritional determinants in the developmental programming of this system and the occurrence of AID, by emphasizing the potential epigenetic mechanisms linking these topics. In other words, the consequences of the concepts introduced in this section will be further unpacked later on to explore the epigenetic effects of selected nutrients on the developmental programming of AID. First, the quantitative nutritional insults, including pre-natal under- and overnutrition will be considered. Second, the qualitative aspects of nutritional programming, such as micronutrient deficiencies, breastfeeding (BF) vs. formula-feeding (FF), as well as the Western diet (WD) will be described. Some of these features are prominent in the current published literature, whereas others, such as the WD, are not. Beginning with the more extensively researched subjects will allow us to better understand the role of the WD, which is why the latter will be explored further in the end of this section.

Programming Effects of Maternal Malnutrition on the Developing Immune System in Offspring

Undernutrition with subsequent low birth weight (LBW) is the most extensively studied nutritional insult in the DOHaD literature. LBW is defined as a weight of <2500g at birth[49]. More accurately, a body weight under the 3rd percentile for the standardized weight related to gestational age defines the intrauterine growth retardation (IUGR). Children affected by the Dutch famine (1944-1945[50]), for instance, developed various types of chronic diseases and it has been observed that, depending on whether nutritional restriction happened in early, intermediate or late pregnancy, health outcomes varied[15]. Maternal calorie restriction during pregnancy has been widely studied thereafter and showed to result in cardiovascular disease, metabolic syndrome, hypertension, diabetes and obesity[18][77][78][79].

According to the published literature, early undernutrition also impacts the developing immune system. The thymus seems to be a major target of protein-energy variations, as well as micronutrient deficiencies during gestation[29][80]. Maternal malnutrition during pregnancy reduces thymic size and function in animal models and in humans[29]. When looking at specific immune functions, protein restriction during pregnancy strongly impairs adaptive immunity, not to mention complement function, IgA secretion and cytokine levels[30].
Epigenetic changes have been observed with only mild fluctuations in macronutrient intake during pregnancy, including demethylation of the genes PPAR-α and GR, with subsequent increased expression in the offspring's hepatocytes[33]. This displays the impact even slight nutritional changes

can have on the developing epigenetic landscape of crucial developmental genes. CD8+ cell levels have also been observed in protein-restriction models[30]. Noteworthily, a lack of CD8+ lymphocytes is a characteristic trait in the profile of individuals affected by AID[31][82][83][84]. Protein restriction also increased pro-inflammatory cytokine concentrations in vivo, possibly setting the stage for aberrant immune responses that may contribute to autoimmunity in a later stage of life[19][85][86].

The hypothalamic-pituitary-adrenal (HPA) axis is also affected by undernutrition during pregnancy. Malnutrition is a threat to the human organism and is, therefore, translated into a stress-like response in the body, leading to an elevation of glucocorticoid (GC) levels[29][87][88]. This has also been observed in states of zinc deficiency[29]. In normal circumstances, the placenta shields the fetus from elevated levels of GC via activity of the placental 11-β-hydroxysteroid dehydrogenase[29]. However, when malnourished, this enzyme decreases in activity, leaving the fetus more exposed to maternal GC[29][89]. This has a significant impact on the developing fetal immune system[29], namely, reduced thymic weight, changes in thymus structure and a reduction of cortical lymphocytes[29]. Studies have established a link between early life stress and subsequent AID in adulthood[51][90]. Similarly, despite the precise mechanisms being unclear, it can be hypothesized that an elevation of GC due to nutritional stress is likely to have the same consequence.

Another possible mechanism by which undernutrition and IUGR might condition the risk of AID in later life is early life catch-up growth. Children of low birth weight tend to compensate their growth deficit, usually within the first two years of life[52]. It can even lead to overcompensation of weight[52]. This phenomenon is known to be a main mechanism leading to later life disease in LBW children[15]. This is the so-called "thrifty phenotype"[117]. This accelerated growth leads to endoplasmatic reticulum (ER) stress, causing errors in protein folding and their abnormal accumulation[15]. Barrera et al. showed that ER stress is associated with inflammation and AID[53], the excessive accumulation of misfolded proteins causing increased intracellular stress and loss of tolerance[61]. ER stress has been observed in the very early stages of autoimmune development[61]. Thus, acknowledging the epigenetic vulnerability of early life development, its presence in infants undergoing catch-up growth permits us to hypothesize that ER stress might prompt early developmental immune disorders, including autoimmune disorders as the consequence of impairment of basic developmental immune function. In addition, the expression of miRNA-29a, which is upregulated the context of ER stress, decreases the expression of Igf-1 and pAkt-1[15]. As we will see later in this review, Igf-1 also seems to play a role in autoimmunity.

Considering the relationship between IUGR and its epigenetic implications, we may discuss two facts. First on methylation, second on the epigenetic consequences of modified levels of GC. Early life undernutrition has been linked to a decreased activity of Dnmt1[33], which is responsible for maintaining methylation patterns in the long-term. Insufficient supply of glycine has also been described to alter methylation patterns[33]. In a similar context, elevated GC levels due to undernutrition reduce folic acid availability[33][81], likewise altering methylation. Histones are also affected by greater levels of GC, the decreased binding capacity of the deacetylase-histone methyltransferase complex leading to decreased gene expression[15][33]. Knowledge on specific epigenetic modifications directly impacting immune function and tolerance is limited.

A further aspect of nutritional immune programming is pre-natal overnutrition and subsequent macrosomia at birth and obesity in childhood. Despite most studies being done on the effect of undernutrition and IUGR[18], overnutrition has also been shown to lead to increased risk of developing chronic diseases in later life[7]. This is of great importance, as overnutrition is highly prevalent globally. Being overweight is one of the most pressing public health challenges in many countries today. A link that has been established is that of macrosomia and adult-onset rheumatoid arthritis (RA)[63][64][65]. In a prospective study lead in a large cohort, a two-fold risk of RA in later life has been reported in children born with a weight above 4.54 kg at birth[63].

Overweight individuals have significantly lower Igf-1, IGFBP-3 and IGF-1/IGFBP-3 ratios as adults than normal birth weight individuals[33]. Interestingly, both undernutrition-induced catch-up growth and overnutrition lead to decreased expression of Igf-1. Igf-1 levels influence lymphocyte activity and other immune cells by binding its receptor Igf-1R[35], and T lymphocyte activation positively correlates with activity of the Igf-1 pathway[35]. The specific subtype of T is, however, not specified in the cited publication. It has been suggested that involvement of Igf-1 might "explain several aspects of human autoimmunity"[35]. More specifically, the Igf-1/Igf-1R ratio also seems to play a role in the development of autoimmune responses[35][62]. Igf-1 has been described as a potent orchestrator of T_{Reg} activity and proliferation and Igf-1 administration has been proposed as treatment of active AID to re-establish immune tolerance[62]. This raises the following question: could low serum levels of Igf-1 in early life, therefore, weaken tolerance-building?

On a different note, recent studies have found a possible transgenerational mechanism of epigenetic patterns secondary to IUGR[17], adding a level of complexity to decipher the developmental programming mechanisms in the immune system. In their experimentation, Hoffman D et al. provoked elevated DNA methylation in the hepatic Igf-1 promoter by uterine ligation. These alterations were found to persist into the next generation, despite the offspring not having undergone any nutritional insults[17]. This suggests the transmitability of acquired DNA methylation patterns, persisting for generations[33]. Assuming that it also describes epigenetic modifications predisposing to AID, nutritional insults should not only be looked for in the pregnant mother and her offspring, but also in the parents previous to conception. It seems reasonable to assume that a mother's nutritional status before conception can play a role in the health of her child. What seems harder to grasp is that there seems to be direct paternal involvement in the health outcome of the next generation. Experiments with mice have shown that paternal nutritional behaviour can influence the epigenetic alterations the offspring's genome will end up experiencing[22]. Even though there is no direct link established between paternal nutrition and AID in offspring, this shines a new light on nutritional programming and shows that the mother is not exclusively responsible for the health of the offspring. Pre-conceptional determination of obesity is one suggested way in which paternal nutritional status can contribute to the next generation's health outcomes[7] and, according to Taylor-Baer et al., "paternal effects is area of research that merits much more attention"[40].

Programming Effect of Postnatal and Early Life Nutrition on the Individual Developing Immune System

Post-natal nutrition can be defined in the following modalities, even combined: breast-feeding (BF), formula-feeding (FF) and processed foods (PF) commonly found in the Western diet (WD). The same chronology will be used to explore the effects of BF, FF and the WD on the gut microbiota later in this review. According to Cavalcante Caetano et al., the ideal infant feeding contains an "adequate amount of macro and micronutrients (with special attention to iron, zinc, calcium, vitamin A, vitamin C and folic acid), contamination-free (biologic, chemical or physical) food"[8].

Breast-feeding (BF)

Historically, breast-feeding remains the most adequate form of infant nutrition[14]. According to the World Health Organization (WHO), BF is recommended to be the sole dietary input during the first six months of life, followed by a gradual reduction until the age of two[114]. Aside from the maternal antibodies provided to infants and helpful to an initially immature immune system, breastmilk also provides vitamins and essential nutrients and metabolites, such as amino- and fatty acids[14][114]. Interestingly, the composition of breast milk changes according to the developmental stages of the infant and is highly dependent on maternal health and dietary habits[114]. The first stage of breast milk, also known as the colostrum, has been found to have a function that is predominantly immunologic, more than nutritional[114].

Breast milk also contains miRNAs and methyl donors, which are very relevant to the formation of an adequate epigenetic landscape. The miRNAs found in breast milk have been found to have an important function in controlling the expression of key regulatory genes involved in metabolic and immune function[14][91]. The content of these miRNA in breast milk vary depending on maternal nutrition and has been observed to decrease with high-fat diets[14]. Post-natal maternal dietary behaviour is, therefore, in direct link with the epigenetic maturation of the infant[14].

Further, BF plays an important role in the formation of a adequate gut microbiome, potentially favouring the process of immune tolerance[114]. It has repeatedly been shown to prevent the occurrence of several NCDs in later life, as opposed to formula feeding (FF)[14]. BF children generally have a larger thymus than those who are FF [114] and children have been shown to suffer less frequently from infectious diseases as well as AID such as celiac disease and MS[10]. AID such as idiopathic juvenile arthritis, rheumatoid arthritis and inflammatory bowel disease have also been suggested to be less frequent in BF infants, but more substantial evidence is needed[114]. As Borba et al. put it: "Breast milk is not only a completely adapted nutrition source but also a personalized medicine for the infants, programming to some degree their future health"[114].

Formula-feeding

Infant formula feeding is the other widespread option for many mothers. However, despite its benefits, a substantial body of evidence describes diverse negative impacts of FF on infants and has been suggested to promote autoinflammatory or autoimmune disorders, including inflammatory bowel diseqses (IBD), type-1 diabetes (T1D) and celiac disease (CD)[14][92]. Three major considerations of FF in the context of autoimmune developments will be discussed here.

First, 45% of FF infants present iron deficiency, and 75% present low levels of zinc[8]. A common type of infant formula is made on the basis of cow's milk, which is then further processed and adapted to infants' particular needs[118]. A partial explanation for this phenomenon is that a diet containing cow's milk has been shown to lead to anaemia secondary to a low iron status, leading to a reduction of 0.2 g/dL of haemoglobin per month of exposure[8]. As mentioned, the relationship between these nutrients and autoimmunity remains relatively unclear.

Second, components of cow's milk inhibit the immune system's tolerance-induction process[23]. This may lead to both allergic and autoimmune disease, a higher incidence of Th1/Th17 AID having been observed in FF individuals[10][12][23]. Very generally, an increase in AID mediated by Th1 immunity has been observed[10]. Hydrolysed-formulae have been evaluated and are equally likely to lead to immune-mediated diseases[12]. Winkler et al. have detected a Th1 cytokine shift in FF infants[10], which is an immune-disposition regularly contributing to autoimmunity. This cytokine shift has been attributed to excessive cow milk antigen exposure[10]. This was the first study showing T lymphocyte differentiation and cytokines to be significantly and positively impacted by BF[10]. It must be noted, however, that the participants of this study were not continually followed over a longer period of time[10]. Another proposed mechanism implicates the higher infection rates among FF children, implying that repeated infections promote a shift towards Th1 responses[10]. However, infants fed with formula within the first three months of life were not at a higher risk of T1D compared to solely BF infants[11], indicating that there must be particular windows of vulnerability during which FF has the potential to induce the changes leading to AID.

Third, an additional adverse effect of FF is its influence on infant body composition. FF children tend to present higher adiposity[93][94] and lose their "baby fat" less efficiently than BF children[13][94]. In this regard, there seems to be a relationship between the dose and magnitude of the effect[14]. In a study evaluating the impact of FF on weight excess, infants breastfed for more than 26 weeks had more than 50% less risk of developing obesity[14]. Higher levels of amino acids, in particular branched-chained amino acids (BCAAs) are

found in 6-month-old infants compared to their BF controls[14]. This may, at least in part, be responsible for the observed overweight in FF infants, as high levels of BCAAs are associated with obesity and predict the risk of subsequent insulin resistance[14]. Aside from the established mechanisms via which FF impacts infant health, Cavalcante Caetano et al. reported a high rate of incorrect dilution in the preparation of FF, which is likely to magnify the above-mentioned undesired effects[8]. As will be discussed shortly, obesity is a highly relevant component in the progression of the immune system towards autoimmunity. In this context, the global trend of growing obesity among FF infants is alarming.

Western Diet (WD)

A major nutritional culprit responsible for qualitative malnutrition and the global epidemics of obesity is the so-called "Western Diet" (WD). WD is known to be "too much, too fatty and too salty"[4], and not to mention, too sugary[68]. As the dissemination of this form of nutrition has evolved over a relatively short time span, the human body has had very little time to adapt to the drastic nutrient-related changes induced by this diet[44].

Villamil et al. state that a great number of NCDs and phenotypic features thereof such as "obesity, diabetes, atherosclerosis, essential hypertension and different types of cancer" are, to a greater extent, a consequence of Western dietary habits[44]. The increased prevalence of AID has likewise been attributed to WD[4][95]. Besides being to fatty (mainly containing saturated and trans-fatty acids), too salty and too sugary, this diet greatly contributes to the imbalance between omega-3 and omega-6 intake[44], promoting inflammation. Aberrant T lymphocyte function has been held responsible for the connection between the Western-style diet and AID[4]. The risk of developing MS has been linked to an excessive amount of animal fat consumption (e.g. milk and meat) and an overall increased calorie intake, causing obesity[4]. According to several systematic reviews, supplementing omega-3 polyunsaturated acids reduces the risk of developing ulcerative colitis, Crohn's disease and MS[4].

As mentioned, the numerous processed foods (also known as "fast foods") making up the WD contain massive amounts of salt, accounting for 75% of a person's total salt intake. Total levels of salt in processed foods can contain up to one hundred times more salt than a home-made meal[4]. This has been shown to play a significant part in the recent increase in AID[3]. Excessive consumption of salt leads to impaired function of the innate immune system, including macrophage function, but also promotes the differentiation of CD4+ T cells into Th17 cells, increasing their number and promoting a pro-inflammatory environment[3][4]. As Manzel et al. state, this underlines the fact that "single nutritional components have the capability to potently modulate autoimmune responses and inflammation"[4]. Other mechanisms in which salt promotes autoimmunity will be described when discussing gut-permeability.

Health outcomes of offspring can be affected by exposure to WD during two particularly vulnerable phases: pregnancy and early post-natal life. During these critical phases, the child is exposed to the maternal bionetwork, via placental transfer of substances and breast milk during lactation[33]. This is why Zabuga et al. propose a revision of the typical proverb "You are what you eat" to "You are what your mother ate when she bore and nursed you"[33].

Maternal WD

Maternal consumption of high fat diets has been shown to trigger infant overweight and metabolic syndrome in adulthood[38][98]. High-fat intake during pregnancy and lactation has shown to modify the level of expression of miRNA-23[17], which is also found to be altered in RA, SLE and MS[58]. In animals, diets high in fat and carbohydrates reduce the variation in gut microbiota[44], the consequences of which will be discussed in a later chapter of this review.

Early post-natal WD

Interestingly, even in very early life, Western-style diet exposition seems an equally pressing issue. A Brazilian study has found that consumption of unhealthy and ultra-processed foods is very frequent in infants less than one year of age, an observation made in all social backgrounds[6]. These foods are deemed unsuitable during early stages of life[5] due to their high contents in fat, protein and salt, not to mention an excessive amount of calories[5]. Some types of processed foods often consumed by Brazilian infants have been shown to contain more than 400% the amount of protein found in breast milk, and the authors associated this finding with a high incidence of obesity in these children[5]. In the same study, sodium and carbohydrate intake during the first year of life were more than double the appropriate intake for salt and double that of carbohydrates[3]. Studies show that this problem is not limited to Brazil's population[5][96][97].

The core of the problem does not only lie with the parents making these dietary choices for their children. Young infants and children are often directly targeted by advertisements that promote such foods[5]. These advertisements are often misleading, leading to a misinformed public and as a consequence, poor dietary decisions negatively affecting infants in a very vulnerable phase of life [5].

Hence, having explored the different nutritional factors impacting the programming of autoimmune disorders during pregnancy and early post-natal life, it is interesting to pursue the subject of qualitative malnutrition and to explore in more detail how micronutrients and vitamins, and a lack thereof, can influence the maturing immune system.

Micronutrients and Vitamins

According to currently published literature, the qualitative aspects of nutritional programming seem to be equally important as quantitative deviations. Imbalanced nutrition, as is being promoted by society's current dietary behaviour, has been described as a high-priority and pressing issue in health care[33]. Especially among children below 10 years, micronutrient deficiencies are frequent and often left untreated[19]. Especially children born to overweight and obese mothers suffer from low levels of certain micronutrients, this being a problem in many countries, independently of socioeconomic development[40].

Many micronutrients have an impact on the development of the immune system, including folic acid, zinc, selenium, iron, copper, as well as vitamins A, B6, C and E[30], among others. Even when the deficiency is mild, insufficient levels of these nutrients can result in distorted immune function[30]. When the fetus develops in its mother's womb, it is highly dependent on maternal micronutrient supply in order to accumulate its own reserves for the first half year after birth[20]. It can be said, therefore, that if this is not given due to maternal malnutrition, the infant begins life with a nutritional handicap. Also, during lactation, maternal malnutrition with low intake of micronutrients decreases the amounts delivered to the infant[20]. As the literature on the individual micronutrients is vast, this review will focus on some key micronutrients that are of interest in when considering autoimmunity.

Folate

Folate is one of the most studied micronutrients[17]. DNA methylation is dependent on the folate cycle because it delivers the methyl-THF groups necessary to convert homocysteine back into methionine[18]. This is why decreased availability of folate in early life changes methylation patterns and even predisposes the infant to further dietary insults[17] in a process closely resembling that of a "first hit", a concept commonly referred to in the pathogenesis of NCDs. In animal models, vitamin B_{12}, folate and methionine restriction around conception led to diet induced obesity and changes in immune function in adult life[38]. Definite mechanisms of whether and how folate influences the programming of autoimmunity remain undescribed in literature and represent potential fields of further investigation.

Zinc

Zinc deficiency during pregnancy is a global concern. It results from both insufficient intake and increased needs during pregnancy[19]. As previously mentioned, low levels of zinc contribute to elevated levels of GC and induce changes in immune programming[19]. It also reduces thymic size, decreases lymphocyte counts and impairs cell- and humoral immunity[19]. Supplementation has been shown to improve both immunity and neurobehavioral capacities in the offspring[19]. Despite the scientific consensus that zinc plays a major role in early life immune development, the role of altered zinc serum levels in the genesis of autoimmune disease has not been defined and, thus, holds further potential for research.

Iron

Iron has many roles in the human body homeostasis, including haemoglobin and DNA synthesis[54]. Iron deficiency leads to anaemia, which, in children, tends to weaken immune responses due to loss of phagocytic function and lower immunoglobulin production levels[19]. This may lead to an increased incidence of infections among such deficient children. Cunningham-Rundles et al. reported that iron deficiency, combined with acute infection in children leads to increased secretion of IL-6 and IL-8, creating a proinflammatory milieu[19]. These have repeatedly been observed in elevated concentrations in autoimmune conditions – especially in relation with promoting Th17 proliferation[27]. However, several authors have described a more promising association between iron overload and autoimmunity[67]. The possible mechanisms are the modification of autoantigens leading to inappropriate immune responses as well as pro-inflammatory macrophage activity[66][67]. Given that iron deficiency seems to be a highly prevalent issue in early life worldwide, the association between early life iron deficit and later life AID seems unlikely.

Polyunsaturated Fatty Acids (PUFAs)

Omega-3 is a polyunsaturated fatty acid (PUFA). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be derived from fish[21] and are potent anti-inflammatory substances[21]. Due to these properties they have been suggested as treatment of AID and other inflammatory conditions[21]. Modern nutritional habits have greatly contributed to an unbalanced relationship between omega-6 and omega-3 fatty acids[44], which have gone from a ratio of 1-2 : 1 in our early ancestors to a ratio of 20-30 : 1[44]. This results in a clearly pro-inflammatory dominance, possibly increasing the likelihood of abberant immune response development. Given the frequency and likelihood of this massive omega-3 deficiency in today's general population, it is likely that a non-supplemented pregnancy may increase the offspring's chances of developing abberant immune responses later in life, including AID.

Flavonoids

Flavonoids, are products of plant metabolism. Various foods such as grains, sees, certain beverages and nuts do contain high levels of flavonoids[26]. They are renowned for their inflammation-attenuating and antioxidant properties and recognised for their beneficial effects in occuring AID[26]. The following pathway has been suggested to be involved: PI3K/Akt inhibition → IKK/MAPK inhibition → mTORC1 inhibition → NFκB and JAK/STAT inhibition. These are all targets of flavonoid action and subdue inflammation[26]. Oroxylin A lowers concentrations of IL-1 β and IL-6, two cytokines that, when combined, induce Th17 differentiation[26]. T_{Regs} count and function increase along with oroxylin A consumption[26]. The same effects are attributed to Baicalin and Icariin[26].However, Icariin suppresses Th1 differentiation[26]. These observations were also reported in active autoimmune disorders and there are many other flavonoids exerting similar effects[26]. There is no precise estimate of flavonoids intake in infants and children. However, given its great dependence on dietary supply and the average individual dietary habits, deficient intake seems possible and potentially highly prevalent, but its association with occurrence of AID remains unclear.

Vitamin A

Retinoic acid (vitamin A) is a liposoluble micronutrient. It is necessary for many physiological processes such as vision and growth, as well as cutaneous and mucosal condition[25]. It also plays a critical role in the development of adaptive immunity and, importantly, immune tolerance[19][25]. Especially the gastrointestinal tract-associated lymphoid tissue (GALT) relies on an adequate supply of vitamin A for the development of its lymphoid cells in early stages of development[19]. Gut-permeability, as well as mucosal immunity in new-borns are fostered by vitamin A and D[19]. Retinoic acid is a metabolite of vitamin A and promotes gut-homing of T and B lymphocytes[19][21], modulates the Th1-Th2 balance[21], and inhibits the secretion of IL-6 and IL-23[25]. It also plays a central role in determining T_{Reg} and Th17 numbers[21][25]. It increases the number of T_{Regs} by up-regulating FoxP3 via the retinoic acid-related orphan receptor γt (RORγt)[25] and inhibits differentiation of Th17 cells[25]. The capacity of TGF-β1 to stimulate the differentiation of FoxP3+ T_{Regs} is strongly weakened in absence of retinoic acid[25]. Additionally, retinoic acid increases IL-10 expression, which is known for its immune-regulating activity and important for correct T_{Reg} function[25]. Thus, it is not surprising that vitamin A levels are lower in SLE patients than in healthy individuals[28]. Furthermore, conditions characterised by chronic inflammation in animals promote vitamin A deficiency by down-regulating the activity of an enzyme necessary for vitamin A storage in the liver, the lecithin retinol acyltransferase (LRAT)[28]. Could the low chronic inflammation induced by all of the factors mentioned so far in this review lead to increased methylation of LRAT, and by doing so inhibit vitamin A storage and promote autoimmunity through increased Th17 and low numbers of T_{Regs}? All-trans retinoic acid (ATRA) is already acknowledged to be a therapeutic and preventive option for fighting AID[27]. It seems probable that early life vitamin A deficiency leads to the similar modifications as during adulthood, and this in a vulnerable phase that is even more susceptible to epigenetic modifications than during adulthood. Not to mention, obesity and NCDs such as type 2 diabetes have been associated with a modified expression of genes at least partially regulated by retinoic acid[119]. Due to its widespread epigenetic regulatory activity across a large variety of genes[119], a potential therapeutic role of retinoic acid in the treatment of NCDs like type 2 diabetes might be of interest for future research.

Vitamin B

Vitamin B denotes a group of hydrosoluble vitamins implicated in several metabolic processes such as DNA synthesis and methylation processes. There is relatively little literature linking members of the vitamin B family to autoimmunity, however, it is interesting to note that pregnant women in high-income countries often suffer from insufficient blood levels of vitamins B_6 and B_{12}[20]. In addition, offspring from women with low vitamin B_{12} levels tend to be overweight or obese, and more frequently display insulin resistance than unaffected subjects[15]. This is interesting, seeing as childhood overweight appears likely to promote autoimmune responses via mechanisms that will be described subsequently in this review.

Vitamin C

Vitamin C (L-ascorbic acid) is a hydrosoluble vitamin known for its abundance in citrus fruit and some vegetables[112]. A recent study explored the role of vitamin C in the development of T_{Regs}, more specifically, the role of demethylation of a particular region in the FOXP3 gene, namely, CNS2. FOXP3, as previously mentioned, regulates the T_{Reg} immune response, which renders a stable expression of this gene indispensable for an efficient immune suppressive function[111]. The authors of this study, Sasidharan Nair et al., found that the stable expression of FOXP3 of T_{Regs} requires the demethylation of CpG groups that make up the so-called “conserved noncoding sequence 2 (CNS2)” region of FOXP3[111]. This allows the necessary transcription factors to bind to this region and maintain a stable transcription of the gene[111]. It has been observed previously that T_{Regs} with a stable expression of FOXP3 have a demethylated CNS2 region, whereas a methylated CNS2 is associated with transient expression[111]. Interestingly, the process of CNS2 demethylation occurs during thymic development via DNA

oxidation[111]. This DNA oxidation is aided by an enzyme called Tet2, which is activated by vitamin C[111], an interaction which seems to play a key role in the demethylation of CNS2, rendering the process significantly more rapid and efficient, and thus, promoting T_{Reg} function[111]. Despite these findings, the exact epigenetic mechanisms remain unknown[111].

Vitamin D

Vitamin D, like vitamin A, is a liposoluble vitamin. It is produced in the skin upon exposure to UV radiation contained in sunlight[55]. Vitamin D deficiency is often seen in AID, such as MS, SLE, psoriasis and inflammatory bowel disease (IBD)[19][21]. Moreover, obese individuals are more likely to suffer from vitamin D deficiency[16] and its metabolites are often found to be diminished in obese adults and children[18]. This group of people have been found to have a higher risk of developing MS[16]. In developmental terms, obese mothers are also more likely to be deficient in vitamin D, exposing the fetus to levels too low for adequate immune development[18]. One mechanism providing at least a partial explanation for this is the rather discriminatory suppressive function that vitamin D exerts on Th1 lymphocytes (not modifying Th2 and CD8+ cellular function)[21]. $1,25(OH)_2D3$ also seems to promote IL-10 secretion, as supplementation in IL-10 mice has shown to inhibit inflammation[19]. In developmental terms, vitamin D plays a vital role in tolerance-induction by means of pushing CD4+ differentiation towards T_{Reg} and Th2 lineages, preventing the development of autoimmunity[20]. Thus, vitamin D deficiency in early life, especially in overweight and obese infants and children, represents a very significant risk factor for the evolvement of AID in later life[20].

Vitamin E

Vitamin E is another liposoluble vitamin that has very strong anti-inflammatory and anti-oxidant properties[19]. Literature on involvement of this micronutrient in autoimmune processes is limited compared to other vitamins. However, a recent review describes the potent therapeutic and preventive effect of vitamin E supplementation on AID, such as rheumatoid arthritis (RA), SLE and scleroderma[56]. A proposed mechanism linking vitamin E deficiency to autoimmune tendencies are lysosomal membrane defects[56]. Despite the existing studies evaluating the relationship between vitamin E and AID, the causal relationship remains undefined, as a vitamin E deficiency could equally likely be a consequence of autoimmune manifestations. Symptomatic vitamin E deficiency is relatively rare in industrialized countries, nonetheless, LBW has been suggested to be a risk factor[57]. It is possible that the frequency of subclinical vitamin E deficiency is underestimated, as the average American citizen has been shown to consume less than the recommended daily amount due to inadequate nutrition[57].

Thus, in conclusion, these findings demonstrate that micronutrients and vitamins are essential contributors to a healthy immune function, especially during the critical windows of its developmental stages. As Sasidharan Nair et al. wrote: “Environmental factors, such as nutrients, […] bring about changes in immune homeostasis through epigenetic mechanisms”[111]. Literature shows that not only quantitative nutritional insults leading to high or low birthweight, but also qualitative nutritional aspects enter into the equation of immune programming. Most research in this field has been done on the former. This review calls for a more profound exploration of the developmental origins of autoimmune disease via qualitative nutritional insults. As clinical manifestations of nutrient deficiencies are relatively rare in westernized countries, a particular focus should be laid on asymptomatic micronutrient and vitamin deficiencies, which can go undetected for years and, through chronicity, may have an underestimated effect on the developing immune system.

V. Early malnutrition: A Possible Role of Obesity in the Programming of Autoimmune Disease?

As described above, formula-feeding and the early introduction of a Western-style diet are both associated with subsequent obesity (BMI > 30 kg/m^2). Due to the intricate relationship between high adiposity and autoimmunity, this review dedicates an independent section to the subject of obesity. Early life undernutrition has been the focus of research done in the field of nutritional programming and has led to the more recent suspicion that it may be implicated in the pathogenesis of AID. It is interesting, therefore, to explore the possibility of the other face of the coin – overnutrition – in the context of programming of autoimmunity. This section will describe the mechanisms leading from obesity to autoimmunity, as well as the implications of maternal obesity and early life child obesity on the development of AID in later life, according to the current state of the literature.

Obesity in the 21st Century

Whereas as undernutrition is very prevalent in non-industrialized countries, western and westernized countries are facing a different problem: obesity[33]. The prevalence of obesity has almost tripled since 1975 and, in 2016, the WHO reported 41 million children less than five years old to be either overweight or obese[59]. Despite these facts, most studies in DOHaD explore the effects of undernutrition, and only a small quantity consider overnutrition and the effect of obesity on developmental programming[34] – not to mention the programming of autoimmunity.

There is substantial data suggesting that obesity plays a central role in the development of AID[16]. The exponential rise of obesity over the last three decades strongly correlated with a similarly drastic increase in AID[16]. Obesity has been shown to significantly increase the risk of suffering from RA, MS, SLE, psoriasis and psoriatic arthritis (PsA), and very probably IBD, T1D and thyroid autoimmunity[16]. Several aspects of immune function have been found to be modified in obese subjects.

Effects of Obesity on the Immune System

Obesity decreases T_{Reg} and B_{Reg} cell counts, increases Th17 numbers and promotes the formation of autoantibodies[16]. Corresponding circulating IL-17 and IL-6 levels are significantly increased[27]. IL-6 concentrations have been shown to correlate with fat mass[27]. B_{Regs} are present in adipose tissue and counteract pro-inflammatory signals by secreting IL-10 and TGF-β. In obese subjects, their number is decreased in fat tissue, decreasing anti-inflammatory activity and promoting inflammation. This may lead to failure of self-tolerance mechanisms and, therefore, AID[16].

In this context, *how* does obesity lead to altered immune responses? Recent research has identified adipokine metabolism as a presumed pathway. Fat tissue was long assumed to be an inactive fat storage, but researchers recently discovered that it secretes a subgroup of cytokines, called adipokines, and has since been acknowledged to be an "essential endocrine organ"[16]. Leptin, adiponectin, resistin and visfatin are such adipokines[16]. All showed to be increased in obese individuals[16]. Briefly, here are a few mechanisms by which adipokines promote autoimmunity:

Leptin levels increase with calorie intake, and in animal models, high leptin levels are associated with autoimmune disorders[4]. It is a hormone that is known for its pro-inflammatory properties, stimulating the differentiation of pro-inflammatory Th1 cells and suppressing that of IL-10 and IL-4 secreting Th2 cells[16]. T_{Regs} count lowers with high leptin levels[16]. Low levels of leptin in early post-natal life promotes obesity and metabolic disorders[14]. Tying into the subject of FF and early life obesity, leptin levels showed to be

increased in both situations[14]. This raises the question whether, indirectly, such increased leptin levels in early life might promote abberant immune responses.

Adiponectin is mostly known for its anti-inflammatory action, however, as it can take many forms that differ in biological activity, it has also been observed to promote a pro-inflammatory environment[16]. It is curious that adiponectin levels are increased in obese individuals, since it increases T_{Reg} counts and should, therefore, counteract autoimmunity. However, as mentioned in the context of SLE and other AID, T_{Regs} tend to be increased even in autoimmune conditions, but with impaired regulatory ability, indicating an inefficient attempt of counteracting the heightened inflammation[16]. A final adipokine that will be mentioned here is **visfatin**. It is a very powerful at promoting an inflammatory milieu by secreting IL-6, TNF-α and IL-1β, disrupting both T and B cell balance[16].

Maternal Obesity

Bearing this in mind, literature is only beginning to describe the effects of maternal obesity on the developing fetus[34]. However, several findings can be hypothesized to contribute to the evolution of the fetal immune system toward autoimmunity.

First, maternal obesity has ambivalent effects on infant birth weight. The cause is a modified passage of nutritional components across the placenta, or more broadly, a diminished efficiency of the placenta[34][100]. Maternal obesity has shown to promote both IUGR and macrosomia, predisposing the offspring to several NCDs in both cases. As discussed earlier in this review, the contribution of these extreme phenotypes to the occurrence of later autoimmunity remains hypothetical[34][22]. A direct effect of maternal obesity on the developing immune system in the offspring is a systemic inflammation through IL-6 and TNF-α secretion[34], leading to elevated free fatty acids and cholesterol in experimental nutrition-induced obesity in sheep[22]. Remembering that high circulating levels of selected amino acids (BCAAs) are associated with obesity[14], it can be speculated that maternal gestational systemic inflammation is a contributor to child obesity, which in turn is likely to cause systemic inflammation. Additionally, pregnancies in obese mothers present lower levels of blood cortisol due to a less active HPA axis[15]. Lower activity of the HPA axis with lower cortisol levels have been suggested to be accompanied by a shift towards Th1 immunity and a tendency to develop TH1-mediated AID such as RA, MS and autoimmune thyroid disease[60]. This proposes an alternative mechanism by which maternal obesity may program autoimmune disorders in the fetus' later life.

Second, maternal obesity is associated with micronutrient deficiencies[40]. Despite their excessive calorie intake, obese individuals are more likely to lack the necessary micronutrients for proper immune function[40]. Vitamin D levels in children born to obese mothers were shown to have significantly lower concentrations of vitamin D than children born to non-obese mothers[40]. Less vitamin D passes from mother to fetus *in utero* even if maternal vitamin D is within the norm[40]. A low omega-3/omega-6 ratio in obese pregnant mothers, probably diet-induced, is often observed and likely to contribute to systemic inflammation[22].

Early life Obesity

This review argues that the elucidated pathophysiological mechanisms leading from obesity to AID in adults can be assumed to be equally applicable to obesity in early life. Villamil et al. described early life obesity as an "epidemic and a major global public health challenge of the 21st century"[44], a justified statement, given that childhood obesity predisposes the affected individuals to a wide array of debilitating, if not lethal, NCDs[5]. Not only adult obesity is associated with the rise in AID: early life obesity has experienced a similar upward swing in the predisposition of immune-related NCDs, as MS[16]. One study reported that rapid weight gain also doubles an infant's risk of developing T1D[16], the authors of these results noting, however, that it is likely that not all confounding factors were accounted for.

Versini et al. raise the question whether "birthweight and childhood obesity are acting as real risk factor or simply as accelerators"[16]. Whether as a direct risk factor or accelerator, it seems clear that obesity is a contributor to autoimmunity.

A major concern is that, with a global upward trend in the intake of processed foods many infants are being confronted with processed foods very early on in life – even only a few months after birth[5]. An appropriate early life diet is the premise of later life health. Thus, this recent development is rather distressing and calls for more research in this field, as well as public information. Chavette-Palmer et al. propose that even pre-conceptional correction of harmful nutritional habits and existing deficiencies may represent a window of opportunity in the prevention of childhood obesity[22], highlighting the necessity of intervening at very early stages of fetal development. It is therefore safe to say that increased adiposity is not a mere morphological state. It greatly contributes to the chronic inflammatory state in the body that appears to set the stage for potential subsequent autoimmunity.

VI. Microbiota: A Determinant or Biomarker in Immune Homeostasis and Autoimmune Disease ?

In addition to obesity, the second determinant in the developmental programming of AID presented in this review is the human gut microbiome. Although the human body has many different microbiomes (respiratory, cutaneous, intestinal etc), this review will specifically focus on the microbiome of the gut. This is because it has been shown to be strongly influenced by nutrition and obesity, also playing an important part in the development of autoimmunity. Early life is of great importance in the colonization of the gut, a process having been described to be susceptible to birth weight, early life nutrition, and even the parental microbiome. In turn, it tightly interacts with the developing immune system.

Importance of the Microbiota

The intestine harbours a central part of the immune system[23] and the human microbiota. Firmicutes bacteria, such as Lactobacillus and Actinobacteria (e.g. Bifidobacterium), are the two most abundant groups of bacteria in the healthy human gut[2]. They are both Gram-positive, whereas Bacteroidetes (e.g. Bacteroides and Escherichia) are Gram-negative and less abundant[2]. These Gram-negative bacteria have pro-inflammatory properties[2]. The gut microbiota has various functions, such as supporting digestion and producing short-chain fatty acids (SCFA) and certain vitamins[2]. Insults to this highly intricate system, either through modification of the microbiota composition, or through damaging the gut barrier function, are associated with the development of NCDs[2]. The microbiota is tightly linked to the immune system and determines cytokine expression and T cell differentiation[23]. The T_{reg}/Th17, as well as the Th1/TH2 equilibrium are affected by the microbiota[4][23]. Th17 lymphcytes in particular reside in the gut in large quantities and are influenced by mechanisms specific to the gut[120]. Th17 numbers are drastically reduced in mice that are either antibiotically treated or germ-free[120]. Contrarily, their numbers are increased in the presence of segmented filamentous bacteria (SFB), bacteria related to the Clostridia bacteria[120]. These SFB, via their promotion of Th17 proliferation, can even directly contribute to the development of experimental autoimmune encephalomyelitis as well as rheumatoid arthritis in mice[121], whereas B. fragilis inhibits exacerbation of EAE via its promotion of FOXP3+ T_{Regs}[121]. IL-10 producing T_{Regs} are particularly promoted by a bacteria called B. fragilis[121]. The latter are decreased in number in germ-free mice, and increased when the same mice are colonized by Clostridium bacteria[120]. Despite the precise mechanisms of these phenomena remaining obscure, the interplay between the gut microbiota and the development of the immune system is apparent. For example, a diet rich in saturated milk fats and low in polyunsaturated oil fats leads to the proliferation of Bilophila wadsworthia, which in turn, promotes the reinforcement of Th1 immunity and exacerbates gut inflammation[121]. Therefore, even slight nutritional changes have a direct impact on the gut microbiota and provokes a corresponding reaction from the immune system. Intriguingly, offences

against the gut flora not only affect organs in proximity to the intestine, but even distant physiological processes[4][99].

The gut microbiota can directly influence the epigenetic landscape, including that of genes implicated in immune function, by means of its metabolites[45]. Butyrate, a SCFA[17], is a very versatile microbial metabolite known for its inflammation-inhibiting activity, which it exerts through histone deacetylase (HDAC) inhibition, suppression of Th1 differentiation, IFN-γ and IL-12 production, and finally, increasing IL-10 concentrations[17]. A wide range of different SCFAs produced by the commensal bacteria exert similar anti-inflammatory effects on the inner linings of the gut[121].

The Developing Microbiota

A new-born is dependent on the microbiota for adequate immune programming[44][45]. An unfavourable neonatal microbiome can predispose the infant to several immune-mediated diseases, such as allergies, AID and other inflammatory conditions in later life[45][69]. For example, young individuals suffering from celiac disease present more abundant Gram-negative populations than controls[2]. Even the obesity epidemic has been attributed to an imbalanced gut microbiota[44]. As in many other contexts, nutrition is a major determinant in microbiota composition in early life[13], the first year of life being a phase of momentous changes[11]. This microbiota is considered to remain relatively stable as of two years of age, making the first two years of life, also known as the first 1000 days of life (from conception to age 2), a crucial period in establishing an optimal health-promoting gut flora[13].

Factors Influencing Gut Microbiota

IUGR Leads to Variations in the Microbiota

Even birth weight has been described to have an impact on the diversity of the gut microbiome. Children exposed to undernutrition have been reported to present a less diverse microbiota[15]. When transplanted with that of a child with a compromised gut flora, mice with an originally healthy microbiota started presenting abnormal growth[15]. Transplantation of a healthy microbiome ameliorated health status[15]. Maternal stress, which can also be undernutrition-induced, also has the capability of modifying gut colonization[45]. These changes can remain stable until later life, along with modification of the HPA axis activity and an impact on immune development[45].

C-section vs. Vaginal Delivery

The making-up of the microbial environment, including the gut microbiota, is largely determined by the mode of delivery: vaginal or cesarean section[105][106]. The so-called “C-section” has become increasingly popular worldwide and is often the preferred mode of delivery for pregnant women[106], even in absence of a clear medical indication[106]. It has been shown that while the fetus passes through the maternal birth canal, it is colonized by the vaginal flora that resides there[105]. During C-section, however, this transmission of vaginal flora onto the fetus is omitted and the colonizing microbiota will differ accordingly[107], being similar to the microbiota generally found on the skin[106]. Furthermore, the surgical procedure employed during C-section, specifically the surgical instruments used have a significant effect on microbial colonization of the newborn, even increasing the risk of colonization by Clostridium perfringens[105]. This alternate microbial colonization has been shown to have an effect on the newborn and is involved in immune and metabolic development and programming[106]. Despite the long-term effects of an aberrant colonization still remaining unelucidated, an association with later life obesity, asthmatic tendencies and deficient immunity have been suggested[106][107]. However, the causality of these correlations has not been established[106]. A study conducted by Dominguez-Bello, Maria G et al. Showed that an infant delivered by C-section can undergo a partial recolonization with the maternal vaginal flora[106]. The long-term results remain unclear[106].

Antibiotics During Pregnancy

As observed with the cesarean section, gestational use of antibiotics has also been shown to impede normal colonization of the infant gut[107]. It has been suggested by Mueller, N T et al. that maternal ingestion of antibiotics during middle and late pregnancy not only modifies the maternal microbial environment, but to a certain extent traverses the placenta to "disrupt the seeding of the offspring's intestinal microbiome"[107]. At birth and during the post-natal phase, antibiotics can affect the infant's microbiota by modifying the maternal vaginal flora and breast-milk[107]. As with infants delivered by C-section, there is also a positive correlation between later life obesity of the offspring and maternal antibiotic exposure during the last two trimesters of pregnancy[107]. Again, a causal relationship has yet to be established, ideally by means of a follow-up of individuals born to mothers who were exposed to antibiotics in middle and late pregnancy[107].

Infant Feeding

In addition to quantitative nutritional aspects such as IUGR, the microbiota is equally influenced by the qualitative characteristics of the ingested food. The concepts of BF, FF and WD, which have been previously regarded in the general context of nutrition, will now be newly explored, but in a context of microbial change. This is of interest, because it shows that the nutritional input not only leads to modified birth weight and potential nutritional deficiencies, but even effects the microbial balance within the infant gut. This next section will follow the same structure that was followed in the section on "Nutrition", with the purpose of maintaining a logical progression of the theme.

Breast-feeding

Breast milk contains bacterial metabolites tightly interacting with the immune system, one of them being butyrate[17]. BF has also been observed to encourage Bifidobacterium proliferation, which increases folate levels, and thereby, intensifies DNA methylation[13].

Formula-feeding

FF also affects the gut microbiota, promoting Firmicutes bacteria expansion and an increase in butyrate, which through histone acetylation promotes gene transcription[13]. The exact mechanism by which this affects the immune system remain unelucidated. What is known, however, is that FF leads to a gut microbiota composition that influences Th1 and Th2 activity[10]. Additionally, through an increased protein abundance in the colon induced by the high protein contents of FF, bacteria capable of breaking down these structures profit and proliferate, whereas bacteria specialized in the breakdown and fermentation of carbohydrates decrease in number[13].

Higher levels of butyrate are associated with increased adiposity in children nine to eighteen months of age, leading us to believe that an unbalanced gut microbiota not only directly affects the immune system, but is also capable of conditioning obesity in young individuals. This exposes them to the chronic low inflammatory state associated with this condition and, therey, appears to predispose them to immune-mediated diseases[14].

Processed foods (PF)

Processed foods that are prominent in the WD lead to gut microbiota modifications. Children and adults consuming these foods experience a reduction in microbiome diversity[2]. This was also the case in mice fed a WD, where increased levels of Firmicutes were detected[44]. Contrarily, Villamil et al. did not find a reduction in microbiota diversity, but rather that the WD "(1) promoted bacteria negatively associated with health (i.e., obesity, inflammation and functional bowel disorders, e.g., Dorea) and (2) inhibited bacteria positively associated with health (i.e., Akkermansia and Bifidobacterium)"[44]. A limitation of the above-named study is, however, that the mice were studied at a developmental stage that corresponds to human adolescence[44], as opposed to the early post-natal phase. A decrease in bacterial variety known to protect the gut barrier was found[44]. A very specific bacterium called Dorea spp grows

with intake of Western-style diet[44] and is not usually found in healthy subjects[44]. It is known to have deleterious effects on health and is increased in individuals suffering from IBD[44]. Surprisingly, even non-obese subjects who frequently consume a high-fat diet experience such changes in their gut colonization[44]. Interestingly, omega-3 supplementation is capable of restoring levels of Bifidobacterium and Lactobacillus[44].

Transgenerational microbiota

Intriguingly, the maternal microbiome has even been shown to impact that of the next generation. Even before birth, maternal microbial products pass over to the fetus, impacting its epigenetic architecture[17]. The inheritance of an unbalanced microbiota from the mother, either through chronic maternal health conditions, Caesarean section or administration of antibiotics, has been suggested to be a "microbially-based birth effect", conditioning the offspring's future health. Dysbiosis can, therefore, be passed from one generation to the next, for example, in the case of maternal obesity[45].

In a context of AID prevention, research elucidating the precise epigenetic mechanisms by which FF enhances autoimmune responses would be of interest. Also, studies evaluating the potential promotion of later life disease by early Western-style diets would be of high importance given global current dietary trends. Furthermore, the added transgenerational dimension increases the complexity to the concept of developmental programming. Therefore, research focusing on possible transgenerational influences on adult-onset AID would be of great interest to better estimate the efficacy of future preventive approaches.

It seems that the intestinal microbiota is a consequence of nutrition, strongly associated with obesity and an active participant in the formation of the immune system. These manifold interactions appear, although parallel to other processes, to contribute to the progression of the spiral towards autoimmunity.

VII. Gut Permeability

The third factor in this progression is gut barrier permeability. It seems to play a central role in the manifestation of AID and is strongly affected by nutrition, obesity, or microbiome. After briefly discussing the developmental aspects, this section will unpack the role of processed foods in gut permeability and, as this review hypothesizes, in AID. Nontheless, it remains relatively unclear whether an increased gut permeability is a cause, consequence or merely an associated phenomenon in autoimmune manifestations.

Gut Permeability and AID

Gut permeability matters in the context of AID, because current evidence established a link between these two phenomena. "Junctional complexes" such as tight junctions (TJ), gap junctions, adherens junctions and desmosomes create a very selective intestinal epithelial barrier by firmly bracing together the epithelial cells of the intestine[43]. The selection mechanism of this barrier is controlled by M-cells, which are responsible for "testing" luminal antigens and restricting their passage through the epithelium[2]. This is essential for adequate immune differentiation and upholding tolerance mechanisms in the long term[2]. A heightened gut permeability is often due to damage to the TJs. This allows molecules, which would normally be too big to pass, to infiltrate the barrier[2] and leads to an exaggerated communication between the gut-associated lymphoid tissue (GALT) and luminal antigens, stimulating inflammation[2]. The inflammatory substances created in this process accentuate gut permeability[2]. This is the case even for minor inflammatory states, eventually leading to gut-mediated generalized immune dysfunction[2]. Impaired gut barrier function is found in "ulcerative colitis, Crohn's disease, celiac disease, inflammatory joint disease, ankylosing spondylitis, juvenile onset arthritis,

psoriatic arthritis, T1D and primary biliary cirrhosis"[3] – all of which are autoimmune disorders. Not surprisingly, it is also a typical characteristic of the gut in obese subjects[2]. Nutrition, obesity and gut permeability are, therefore, all tightly interrelated and implicated in the pathogenesis of AID. Increased permeability of the intestinal epithelium is often observed before the onset of autoimmune diseases and, therefore, seems to play a causative role in their pathogenesis[108].

Gut Permeability During Early Life

There are two age groups who, physiologically, have higher gut permeability: infants and the elderly[2]. Whereas the physiological state of increased porousness in the infant gut tends to mature and decrease with age[42], factors like early life microbiota composition, maternal obesity and increased sensitivity for GCs have been shown to sustainably modify intestinal permeability via developmental programming[45]. Children subject to intra-uterine growth restriction (IUGR) have also been suggested to present a decreased gut barrier function with subsequent impairment of their immune development[109]. Interestingly, IUGR children present lower levels of glucagon-like peptide 2 (GLP 2), which is a hormone known to promote the development of the intestinal tract and its barrier function[110]. Even non-IUGR infants, due to their decreased intestinal integrity and highly vulnerable developmental stage are, therefore, excessively exposed to substances of higher MW (≥ 1000 Da) and their associated risks[2]. A question arising from these observations is: Does permeability-enhancing early life nutrition prevent the gut from undergoing its natural maturation process and cause a long-term decrease of gut integrity? If so, given the established association between AID and increased gut permeability, could this be a contributing factor in autoimmune development in affected children? The answer to such questions remain obscure, but this review will attempt to raise some hypotheses.

Interactions with the Microbiota

The gut microbiota is able to alter the gut barrier function by modulating mucus secretion and TJ condition[2]. The microbial product butyrate promotes grouping of TJs, and by doing so, decreases permeability[43]. Although a lot of substances ingested through every day nutrition have long been assumed to be inert in the human body, it seems that even at low concentrations, nutritional and environmental chemicals modify the gut microbiota[2]. Food contaminants and additives, a subject that will be discussed shortly, induce an increase in intestinal permeability, in part, by disrupting the gut flora[2]. Through this mechanism, these materials cause a low inflammatory state of the gut[2]. Thus, the question is raised whether this low inflammatory state also increases gut permeability, and whether this could contribute to autoimmune manifestations.

VIII. A Closer Look: Processed Foods and Intestinal Permeability

Industrially processed food consumption and AID both have significantly increased in a still ongoing upward trend[3]. This trend was trailed by a similar ascending incidence of intestinal diseases[2]. Aside from the well-known fat, salt, and calorie excess, processed foods are a substantial source of food contact materials (FCMs) and additives are highly abundant industrial foods[2]. Given that very early life consumption of highly processed foods is on the rise[6] and remembering that the developing infant gut is highly permeable, processed foods may be of high relevance in the developmental context.

Food Contact Materials (FCMs)

Food contact materials (FCMs) are environmental chemicals that come into contact with food while it is being processed and transfer so-called "food contact chemicals (FCCs)" onto the food. The same happens during production, transport, storage, packaging and every additional step until the food is ready for consumption[2]. Food contamination with these materials has been estimated to be 100x bigger in magnitude than that of pesticides[2]. What the general population is often oblivious to is that these materials increase their risk of developing chronic diseases[2]. Dietert (2017) goes so far as to say

that these materials are likely to "have potentially affected multiple generations of humans well into the future"[45]. The widespread and high exposure to such substances, even in low quantities, is considered to be a major problem[45]. These materials are usually < 600 Da in size and their lipophilic nature allows them to easily traverse the gut barrier through facilitated or passive diffusion[2]. Despite a lack of literature on this subject, this review would like to raise the following question: is it possible that the increased uptake of these materials promotes inflammatory responses in the intestinal epithelium, potentially increasing barrier permeability? Could the increased early life exposure to these substances be contributing to the rising incidence of AID?

Additives

A countless number of substances are added to the foods we end up eating. The food industry widely uses additives like salt, surfactants, nanoparticles and numerous other substances[3] for preservation and optimization of taste. Many of these substances have for a long time been assumed to be safe[45]. Recent publications state that food additives have greatly contributed to the recent rise of AID[3], due to their tendency to weaken TJs and create additive-induced neoantigens via modification of self-antigens (hapten hypothesis)[3]. Shockingly, many of these substances have been developed by the pharmaceutical industry with the purpose of increasing intestinal absorption of medical drugs – several of these substances are also approved food additives[2][3]. Regrettably, long-term studies on the effect of additives are lacking[2]. To gain a better understanding of how they may influence the developing gut, this review will briefly describe surfactants, chitosan, nanoparticles and salt.

Surfactants are amphiphile molecules widely allowed for usage as direct food additives[2]. They are most often used as emulsifiers[2] and increase paracellular pathway permeability[2] by breaking down TJs[3]. This is an effect observed at the relatively "low" concentrations of surfactant in processed foods[3]. Monoglycerides and diglycerides, polyglycerol esters and sucrose esters derived from fatty acids are examples of typical surfactants used in the food industry[3]. Polysorbate 80, a "non-ionic" surfactant, has a pro-inflammatory effect on the gut mucosa and leads to changes in the microbiota[2]. Infant formulae have been shown to contain the same surfactants used as permeability enhancers in the pharmaceutical industry, where concentrations of 50mg/L have been shown to significantly damage the integrity of the intestinal barrier[3]. Astonishingly, concentrations of 120 mg/L have been detected in infant formulae[3]. Lerner et al. strongly suggest that this is bound to have an effect on the programming of AID in early life[3]. Indirect additives are also present in processed foods via contact with FCMs[2] but, due to lack of sufficient literature with regards to autoimmunity, this will not be discussed further here.

Salt is mainly known for its effect on blood pressure. It is found in extreme quantities in processed foods, by far exceeding the recommendations for appropriate salt intake. It has been suggested that this great increase in salt consumption may have contributed to the recent rise in AID[3]. Salt, like the above-mentioned additives, is a potent permeability-enhancer in the intestine. It compromises TJ function by activating sodium-glucose co-transporter pathways, which results in myosin light chain phosphorylation and contraction of actomyosin, causing TJs to increase their permeability[3]. In a mouse model, salt has been shown to single-handedly induce inflammation of the colonic mucosa and led to an increase in gut permeability[70]. Salt has also been shown to promote the differentiation of naïve CD4+ T cells into pathogenic Th17 cells[3]. This may be worrying when considering that infants are increasingly consuming excessive quantities of salt via processed foods at an early age[5].

Sugar is a major additive widely and excessively used by the food industry[3]. Excessive ingestion of glucose leads to high luminal concentrations and increases intestinal permeability[3]. It does so by forcing the TJs to loosen (glucose absorption is to a great extent TJ-dependent) and increasing Caco-2 cell permeability[3] (Caco-2 cells are human colon adenocarcinoma cells used to experimentally evaluate intestinal permeability[71]). In Crohn's patients, a disease characterised by significantly increased

intestinal permeability, an increased consumption of sugars has been discovered[3]. Glucose has also shown to increase absorption of small molecules[3]. Given the enormous abundance of sugar in processed foods and the growing consumption of these foods by infants and children today, the elucidation of sugar's role in the pathogenesis of AID should be a priority.

Formula-Feeding Revisited

Formula feeding may be considered a processed food[72] and, not surprisingly, has been associated with a 2.8-fold higher gut permeability in infants who were exposed to it[42]. This has been attributed to the lack of substances contained in breast milk shown to promote TJ integrity and formula-induced damage of the gut mucosa[42]. Contrarily, BF increases gut integrity[42].

Realizing that consumption of these foods is already prevalent in early life and still on the rise, this information strongly suggests that infants are being exposed to foods that are inappropriate for their stage of development and are, thus, possibly affecting their epigenetic landscape in a way that may promote immune-mediated diseases, and possibly AID, in later life.

IX. Therapeutic Targets and Preventive Strategies in the Epigenetic Era

After the exploration of current evidence of the association of early life nutrition, gut microbiota and permeability with the manifestation of AID, this work aims to identify some nutritional therapeutic targets and preventive strategies, incorporating the latest knowledge of nutriepigenomics.

First, early life epigenetic modifications have shown to be, at least partially, reversible[7]. This paves the way to preventive measures that may hinder autoimmunity in infants who have been exposed to AID-promoting nutritional states[33].

Second, early life undernutrition is the most studied developmental nutritional insult with a possible association to autoimmunity later in life, and several therapeutic and preventive approaches have been described in the currently published literature. Leptin levels has been observed to play a role in the development of AID, and therefore, the possibility to modulate its circulating concentrations presents us with a new instrument in dealing with IUGR-induced alterations[7] caused by both early undernutrition exposure and following overnutrition to catch-up. Folic acid has shown to significantly reverse the reduction of Dnmt1 activity[33] and other developmental effects induced by undernutrition[7][15]. It must be noted, however, that supplementation of folic acid should not be driven to excess, as this may lead to equally undesirable outcomes, such as weight gain and LBW[7][15][36].

Third, vitamin A appears to play a major role in the education of the immune system and prevention of autoimmune responses. Supplementation leads to markedly reduced levels of Th17 and IL-17, as well as an increase of T_{Regs}[25][28]. However, in AID patients, T_{Regs} seem to not fully respond to vitamin A supplementation when compared with healthy subjects[28]. Therefore, vitamin A supplementation might be more useful when used as a preventive measure, calling for more efforts to identify this deficiency, even if subclinical, during early stages of life. It remains to be elucidated whether a deficient vitamin A status could possibly lead to the hypermethylation of LRAT, and as a consequence reduce vitamin A storage and increase the autoimmunity-promoting Th17 and curb T_{Reg} numbers.

Fourth: probiotics. Given the systemic effects of even slight local modifications in the microbiome, probiotics might be of great importance in the prevention of AID. Given the increased plasticity and reactivity of the microbiota in the developing infant gut, the first years of life might represent an ideal moment to prevent autoimmune tendencies[38]. Probiotics have direct epigenetic effects, mainly through suppression of histone acetylation and increasing DNA methylation, inhibiting the production

of IL-17, among other pro-inflammatory cytokines[17][101]. Similar effects are observed as a consequence of maternal probiotic intake, affecting the immediate fetal epigenome[17]. This might make probiotics a good aid in correcting results of unbeneficial maternal nutrition[4]. Probiotics also improve gut barrier function after stress-induced penetrability and decrease levels of permeability-enhancing cytokines[43]. This suggests that an obesity-induced increase in gut permeability by pro-inflammatory cytokines may be counteracted with probiotics. Proposed mechanisms are an upregulation of occluding and cingulin genes, which are proteins contributing to gut barrier integrity[43]. Therefore, the plasticity of the microbiome with its capacity to convert local stimuli into systemic effects, particularly with regards to the immune system, gives health practitioners a potent lever in the prevention of AID already in early life.

Fifth, adipokines play a significant role in autoimmune development. With the drastic rise in early life obesity, elucidating mechanisms allowing regulation of adipokine blood concentrations would be of great significance. Trials evaluating the effects of supplementing globular adiponectin show that it leads to near total suppression of experimental autoimmune encephalitis, partly due to increased differentiation of T_{Reg} cells[16]. Further research in this area might lead to promising results.

Finally, given the substantial role of obesity in the pathogenesis of AID, the simplest and most obvious preventive measure is reducing early life calorie intake when it is found to be excessive. Calorie restriction drops leptin, IL-6 and Th17 levels, ameliorates active AID and increases T_{Reg} numbers[4][16]. Much discussion has taken place over the healthiness of certain foods. Not much has been said about portion sizes, even though calorie intake, via its upregulation of leptin, and not to mention promotion of early life obesity, are visibly contributing factors in the development of AID.

X. Conclusion

Early life nutrition plays a crucial role in the developmental programming of the immune system. Not only macronutrient deficiencies seem to be major determinants of immune health, but maternal and childhood micronutrient deficiencies, formula feeding, and early introduction of processed foods are associated with both obesity, an altered microbiome, as well as increased gut permeability. Despite much of current research focusing mainly on infectious aftermath of an impaired immune system in early life, autoimmune disorders and other immune-related NCDs remain an underreported scope of immune impairments in an early life nutritional context.

Early life nutrition represents a considerable field of investigation and a global opportunity in the prevention of immune disorders like AID. Adaptations of health and nutrional policies at a global scale would not only be a widely accessible and cost-efficient public health measure, but it would have the potential to reach a much larger population than ever planned in former global epidemics[1]. Given the largely reversible features of epigenetic modifications induced in early life, an early identification of infants undergoing nutritional insults and a timely introduction of appropriate preventive measures[7] may provide a highly efficient cost-benefit approach in the prevention of AID worldwide. Furthermore, besides elucidating the precise epigenetic mechanisms, windows of developmental vulnerability/opportunity and specific preventive interventions in the developmental programming of AID, this review highlights the importance of public information on the subject of nutrition[7]. Where people eat so much of what harms them and so little of what would benefit them, nutritional education of large populations about later life consequences of inappropriate early life diets may be a first essential step in the future prevention of autoimmune disorders.

XI. Bibliography

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