Nutritional Influences on Epigenetic Programming

Asthma, Allergy, and Obesity

Debra J. Palmer, PhD[a,b,*], Rae-Chi Huang, MD, PhD[b,c], Jeffrey M. Craig, PhD[d], Susan L. Prescott, MD, PhD[a,b,c]

KEYWORDS

• Nutrition • Early life • Epigenetic regulation • Asthma • Allergy • Obesity

KEY POINTS

- Maternal and infant nutrition play a critical role in determining the subsequent risk of asthma, allergic diseases, and obesity.
- Modern dietary patterns (including less consumption of vegetables, legumes, and fish) result in reduced antiinflammatory nutrient intakes, in particular prebiotics, antioxidants, and omega-3 long-chain fatty acids.
- Antiinflammatory nutrients modulate the developmental programming of metabolic and immune pathways, and increase the risk of the chronic inflammation and immune dysregulation seen in association with asthma, allergic diseases, and obesity.
- Epigenetics is providing substantial advances in understanding how early-life nutritional exposures can affect disease development.

INTRODUCTION

Nutrition in early life, especially from conception until 2 years of age (the first 1000 days), has a major influence on later predisposition to many noncommunicable diseases (NCDs), including cardiovascular, metabolic, and allergic diseases. Barker[1] laid the core foundations by showing the relationships between early-life conditions (particularly nutritional status) and the subsequent risk of cardiovascular and

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[a] School of Paediatrics and Child Health, University of Western Australia (M561), Roberts Road, Subiaco, Western Australia 6008, Australia; [b] Members of '*In-FLAME*' the International Inflammation Network, World Universities Network (WUN); [c] Telethon KIDS Institute, University of Western Australia, Roberts Road, Subiaco, Western Australia 6008, Australia; [d] Department of Paediatrics, University of Melbourne and Early Life Epigenetics Group, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia

* Corresponding author. School of Paediatrics and Child Health, University of Western Australia (M561), Roberts Road, Subiaco, Western Australia 6008, Australia.

E-mail address: debbie.palmer@uwa.edu.au

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metabolic diseases many decades later. This paradigm of developmental programming, now known as developmental origins of health and disease (DOHaD), has been extended to many other organ systems through a large range of cohort studies, mechanistic studies, and animal models. More recently, these have revealed that one of the main mechanisms through which nutrition can influence these long-term health outcomes is via modulation of epigenetic programming. Epigenetic mechanisms can be broadly defined as a network of biological processes that regulate the expression of genes to produce mitotically heritable changes in cellular function without changes in the underlying DNA sequence.[2] These processes include DNA methylation, post-translational modification to histone tails, and regulation through noncoding RNAs. This knowledge has provided new insights into how subsequent patterns of gene expression can be changed by a range of early nutritional and environmental factors to alter the risk of both early-onset and late-onset NCDs, and has become the cornerstone of DOHaD research.[3]

New so-called modern epidemics such as allergic disease, which is an early-onset NCD, provide evidence that the immune system is specifically vulnerable to recent environmental, diet, and lifestyle changes.[4] Over the past 2 decades there has been a dramatic increase in the incidence of allergic disease, especially food allergy, in the first few years of life.[5,6] Over the same period there has been a parallel increase in obesity,[7,8] and there have been suggestions that allergic disease and obesity may be associated.[9] It is also increasingly clear that both immune and metabolic programming are under epigenetic regulation. This article discusses recent evidence focusing on the influence of nutrition on metabolic and immune pathways that are likely to underpin the increasing rates of allergy, obesity, and other inflammatory diseases, with a particular focus on the epigenetic mechanisms.

EPIGENETICS, OBESITY, AND ASTHMA

Epigenetics has provided a substantial advance in understanding of how the early environment, including early-life nutritional exposures, can have effects on disease propensity much later in life. There are now many examples of how nutritional exposures in utero can induce differential effects on epigenetic machinery. These alterations in epigenetic marks are associated with either enhanced or suppressed gene expression with an altered phenotype depending on the nature of the affected biological pathways.[2]

In humans, Fryer and colleagues[10] analyzed the cytosine-guanine dinucleotide (CpG) dinucleotide methylation in 12 cord blood samples using high-resolution genomewide methylation profiling, and levels of plasma homocysteine, a metabolite of folate, correlated with infant DNA methylation patterns and birth weight. In addition, it has been shown that periconceptional maternal folic acid supplementation can lead to a higher methylation level of the differentially methylated region in the *IGF2* gene in children.[11] In this study, DNA methylation was inversely correlated with birth weight. *IGF2* is an important regulator of fetal growth that mediates its effects through the *IGF1* receptor (*IGF1R*), and observed differential methylation patterns in *IGF2* and *IGF1R* in relation to maternal folic acid intake suggest that maternal folic acid intake influences fetal growth and metabolism.

Obesity and Epigenetics

In the context of the development of obesity, experimental evidence shows a causative link between early-life nutritional challenges and the risk of subsequent obesity and metabolic disease.[12–14] In animal models, exposure to maternal obesity and