

Maternal nutrition and metabolic disorder-related mirnas in the offspring

Abstract

Maternal nutrition (particularly, under- and over-nutrition) during pregnancy and lactation is able to modify the foetal programming and epigenetic pattern, influencing in the phenotype of the offspring. The micro RNAs (miRNA) are one of the major important epigenetic determinants and negatively regulate the gene expression at the post-transcriptional level. Thus, in this mini review we focused in the discussion of the effects of maternal diets, including under- and over-nutrition on the miRNA expression and metabolic disorders development in offspring during life. Few recent studies have demonstrated the noxious impact of maternal consumption of protein restriction diets, high-fat diets and high-calorie diets in the miRNA expression pattern of the offspring, accompanied by an increase in the development of metabolic diseases lifelong, especially those related to glucose intolerance, lipid metabolism disruption and chronic low-grade inflammation. However, the available findings are still limited and controversial in the field. Therefore, it is necessary further studies that investigate the underlying mechanisms on the mode of action and specific-tissue functions of miRNAs and the long-term effects of the maternal nutrition, during pregnancy and lactation, on the miRNA expression and future metabolic complications in offspring.

Keywords: maternal nutrition, pregnancy, lactation, mirna expression, metabolic diseases and offspring

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Abbreviations: C/EBP- β , ccaat/enhancer-binding protein- β ; DNA, deoxyribonucleic acid; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin 6; JNK, c-jun n-terminal kinase; MAPK, mitogen-activated protein kinase; miRNA, micro RNA; mRNA, messenger RNA; PPAR- γ , peroxisome proliferator-activated receptor gamma; RNA, ribonucleic acid; TGF- β , transforming Growth factor- β ; TNF- α , tumor necrosis factor alpha

Introduction

Pregnancy and lactation are considered critical periods for the foetal and postnatal development, since in these periods of life the maternal substrates are essential to ensure the nutritional requirements of the offspring.¹

Several evidences have shown that maternal diet (under- and over-nutrition) during pregnancy and lactation may modify the foetal programming and epigenome of the offspring, leading to lifelong phenotypic consequences.¹⁻³ Foetal programming represents a series of adaptive responses of the foetus to adverse environmental conditions during early stages of life, influencing in the gene expression, structures of organs and function of several tissues, likely affecting the susceptibility of the offspring to develop metabolic disorders in adult life, including obesity, type 2 diabetes, cancer and cardiovascular diseases.¹

Epigenetic plasticity and miRNA expression

Epigenetic modification are often used to explain the relationship between maternal nutrition and the predisposition of the offspring to future metabolic complications, since early life periods have shown a strong epigenetic plasticity and ability to respond to environment

factors (e.g., nutrition).³ Epigenetic is based on inheritable changes that regulate tissue-specific gene expression, without altering the DNA sequences.^{4,5} The major epigenetic determinants are DNA methylation, histone modification signatures (e.g. methylation, acetylation and phosphorylation), chromatin conformation and non-coding RNA, including microRNA (miRNA).^{4,5}

MiRNAs are a class of small endogenous non-coding RNA (16-29 nucleotides-long) that negatively regulates the gene expression at the post-transcriptional level. Approximately 2,800 mammalian miRNAs have been annotated and these miRNAs are potentially target up to 60% of protein-coding genes.³ In addition, disturbances in the miRNA expression are linked to aberrant metabolic changes and onset of diseases.⁵

Therefore, this mini review focuses in the effects of maternal diets, including under- and over-nutrition on the miRNA expression and metabolic disorders development in the offspring during life.

Maternal under-nutrition and mirna expression in offspring

Several authors have already reported that maternal malnutrition during pregnancy and lactation can be harmful to the birth weight and metabolic homeostasis of the offspring.⁵⁻⁷ Complementarily, few recent studies have demonstrated the association among maternal diet restriction, disturbances in the miRNA expression and metabolic diseases onset in life.^{6,7}

In fact, Zheng et al.⁶ showed that maternal consumption of low-protein diet during pregnancy and lactation impairs glucose tolerance and regulates the hepatic expression of different miRNAs in the mice offspring at weaning. In this study, four miRNAs (mmu-

miR-615, mmu-miR-124, mmu-miR-376b and mmu-let-7e) were downregulated and two miRNAs (mmu-miR-708 and mmu-miR-879) were significantly upregulated in the 21-day-old pups. Inflammatory pathways (including MAPK, TGF-beta and Toll-like receptor) were associated with all these six differentially-expressed miRNAs and increased mRNA and protein levels of IL-6 and TNF- α were observed in the livers of the offspring exposed to maternal protein restriction during pregnancy and lactation.⁶

Similarly, Pan et al.⁷ evaluated the effects of maternal intake of protein restricted diets during pregnancy and lactation on the lipid metabolism-related miRNA pattern in Meishan pigs. The authors found that maternal low-protein diet induced the expression of miRNA-130b (predicted to target the PPAR- γ gene) and miRNA-374b (predicted to target the C/EBP- β gene) in the subcutaneous fat of piglets at weaning age. In addition, miRNA-130b and miRNA-374b were able to suppress the expression of PPAR- γ and C/EBP- β , respectively. Considering that PPAR- γ and C/EBP- β are transcriptional factors involved in the adipocyte differentiation and fat deposition, this study suggested a post-transcriptional regulation (through miRNA over expression) of the lipid metabolism in the weaning-age offspring exposed to a low-protein diet during pregnancy and lactation.⁷

Taken together, these findings allow suggesting that maternal dietary restriction may induce a programmed perturbation in the expression of some key miRNAs, which can be associated with chronic low-grade inflammation, glucose intolerance and lipid metabolism in the offspring during early life.

Maternal over-nutrition and miRNA expression in offspring

Food consumption patterns have been changed in the population around the world, reflecting a nutritional transition. The high prevalence of under-nutrition was replaced by the predominance of non-communicable diseases, accompanied by an increase in the consumption of unhealthy foods (e.g., high fat diets, processed food and sugar) and incidence of overweight and obesity.⁸ Considering the shift in dietary patterns in many countries, it is extremely necessary to reflect about maternal overfeeding during early life, miRNA expression pattern and metabolic health of foetus and infants lifelong.

In this sense, Zheng et al.⁹ has observed that maternal consumption of high-calorie diet during pregnancy and lactation increases body weight, fasting blood glucose levels and HOMA-IR, suggesting a decrease in the insulin sensitivity of the mice offspring at weaning. Concomitantly, there was a down regulation in the expression of four miRNA (miR-615-5p, miR-3079-5p, miR-124 and miR-101b) and an upregulation of one miRNA (mmu-miR-143) in the liver of pups exposed to high-calorie diet during early life. These differentially expressed miRNAs were mapped to genes in inflammatory signalling pathways (including MAPK, TGF-beta and Toll-like receptor) and an increase in inflammatory markers (IL-6, TNF- α and MAPK1) were observed in the 21-day-old offspring. Taken together, it is suggested that cumulative calorie intake of the dams dysregulates the expression of several hepatic miRNAs, induces an inflammatory state and impairs glucose metabolism in pups at weaning age.⁹

Complementarily, study performed by Benatti et al.¹⁰ showed that the early exposition to maternal high-fat diets during pregnancy and lactation acts harmfully in the body weight, fat depots, food intake, glucose tolerance, insulin resistance, lipid metabolism and hepatic

inflammation (changes in the JNK and Toll-like receptor 4 pathways) of mice pups with 28-day-old. Additionally, the authors associated these results with decreased levels of hepatic miR-122 and increased levels of hepatic miR-370 in the offspring.¹⁰

Taking into consideration the evidences, these data demonstrated that excess in the calorie or nutrient maternal intake was associated with noxious metabolic implications in the pups, accompanied by a disruption in the expression of different miRNAs involved in the adiposity, glucose homeostasis, lipid metabolism and pro-inflammatory responses, which can increase the risk of metabolic chronic diseases development throughout life.

Conclusion

The increase in the obesity incidence and the modification in diet pattern by the population worldwide triggered a growing research interest in the effects of maternal diets during critical time window on the foetal programming, epigenetic inheritable modifications and permanent metabolic adaptations in the offspring. In this sense, the present mini review showed that maternal nutrition (under- or over-nutrition) during pregnancy and lactation actively regulates the miRNAs expression, influencing in the phenotype of the pups throughout life. However, the available findings are still limited and controversial in the literature. Thus, a better understanding about some key points is necessary in future studies: (a) investigation of the underlying mechanisms on the mode of action and specific-tissue functions of miRNAs, and (b) long-term effects of the maternal nutrition, during pregnancy and lactation, on the miRNA expression and metabolic complications in offspring.

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Conflicts of interest

Author declares that there is no conflicts of interest.

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