EVALUATION OF EPIGENETICS IN TERMS OF ENVIRONMENT AND DISEASE ASSOCIATIONS

Munis DUNDAR
Department of Medical Genetics, Erciyes University Faculty of Medicine, Kayseri, Turkey

Abstract

Epigenetics is defined as changes in gene expression that occur through various mechanisms without any change in the DNA sequence. These mechanisms include various modifications such as methylation, acetylation, and sumoylation, and they form a kind of decision-making mechanism on genes by turning on and off the gene expression. The term "environmental epigenetics" has emerged as an epigenetic subtype that deals with the effects of environmental exposures on epigenetic changes, depending on internal factors as well as external factors such as environment and lifestyle. Under this term, the implications of the environment on the development of certain diseases and current approaches to preventing these diseases are aimed to be summarized throughout article. Cancer, obesity, and cardiovascular diseases are the leading health problems worldwide, and new strategies are being developed every day to prevent these diseases before they emerge. Throughout our lifetime, we are familiar with the various pollutants exposed from the intrauterine stage and the habits that make up our lifestyle, such as diet, exercise, smoking and alcohol consumption, have significant effects on the epigenome. This correlation between exposures to epigenetic and environmental factors provides new explanations for how gene expression is regulated, and it is thought that these explanations will lead to significant advances in the field of personalized medicine in the development of effective therapy strategies.
Keyword: Epigenetics, environmental factors, cancer, obesity, cardiovascular diseases

1. INTRODUCTION

Epigenetics is traditionally defined as changes in gene expression that occur through various mechanisms without any change in the DNA sequence. These mechanisms either enable the addition of various chemical compounds

to the DNA sequence by markers called epigenomic marks, or they are responsible for the activation or deactivation of gene expression through several modifications in histone proteins. On the basis of both changes, chromatin conformational alterations determine the gene expression levels, and thus enable the gene to form a kind of decision-making mechanism[1].This decision-making mechanism may be dependent on internal factors as well as external factors including environment and lifestyle. "Environmental epigenetics"term has emerged as a subtype of epigenetics, mainly expressing the effects of environmental exposures on epigenetic changes[2].

Although there are many epigenetic gene regulation mechanisms are existent such as DNA methylation, non-coding RNA, histone modifications including acetylation, phosphorylation, sumoylation, and ubiquitination, in this mini review the associations with the diseases and environment's effect on epigenetics will be discussed. We are already familiar with the fact that various gene polymorphisms are responsible for the basis on predisposition to diseases. Beyond this phenomenon, we can say that the environment has a key role on people's health as its different effects on epigenetics. In fact, current studies guide us on the need to manage the objectives in terms of epigenetics in the formation of allergic reaction sensitivities and drug resistance caused by anticancer drugs.

Due to the recent increase in the world population, some diseases take the first place among people. Cancer, obesity and obesity-related diabetes and cardiovascular diseases are at the top of this list. The implications of the environment on the development of these diseases and current approaches to prevent these diseases will be discussed throughout this article.

2. DISCUSSION

Cardiovascular diseases constitute the largest group of diseases that cause the most death in the worldwide and bring a great economic burden in prevention and treatment of the disease[3]. It is worrying that the emergence of heart diseases at a young age and the complex molecular mechanism underlying the disease constitute the biggest obstacle to solving the root cause of the disease. Undoubtedly, we can convey that the emergence of cardiovascular diseases at a relatively young age is one of the negative impacts of a severely stressful life with the dietary changes brought by today's modern world. Depending on the complexity of the molecular mechanism underlying in cardiovascular diseases, studies revealed the epigenetic dysregulations are being affected recently. In this field the data acquired from twin studies clearly demonstrate that significant results were obtained about the role of epigenetics in the pathogenesis of the disease. With

the determination of epigenetic changes, particularly in the pediatric age, early diagnosis of the disease becomes possible and it is predicted that the route to be drawn in clinical treatment will be more precise. Based on all these implications, it is thought that the incidence of CVD will decrease in the following years [3].

In addition to emphasizing that the environment is the basis for the early development of diseases, it is fundamental to mention the fact that the environmental conditions that the mother is exposed to during the intrauterine period may be a major risk factor for developing disease in the fetus or diseases in the later stages of life. In previous studies conducted, the detection of fatty streak lesions in the arteries of fetuses taken from mothers who are heavy smokers during pregnancy or mothers with hypercholesterolemia, compared to those who are not exposed, support that CVD may originate in the early stages of life [4]. Looking at the epigenetic basis of the environment's impact on cardiovascular disease development, twin studies are the best guiding map for looking at diseases from a new perspective, and they show up distinct effects of genetic, and environmental factors on biomarkers. In some of these studies, it has been shown that the intrauterine environment has a prominent role in terms of CVD risks in parallel with the development of metabolic syndromes such as type 2 diabetes and obesity [5]. Since DNA methylation has been the most frequently studied mechanism in epigenetics for two decades, it has been shown that toxic agents exposed during the intrauterine period contribute a strong connection between epigenome and CVD by changing the methylation profiles[6,7]. In addition, global hypermethylation observed in atherosclerosis has been shown to have an important effect on pathological processes such as inflammation and coagulation [8]. However, due to the reversible potential of these epigenetic modifications, studies on the use of targeted relevant pharmacological agents are ongoing [9].

Apart from cardiovascular diseases, there is bunch of studies in the literature showing that epigenetic mechanisms such as DNA methylation and histone modifications play a role in the development of obesity. It is a well-known fact that exposure to environmental pollutants causes changes in the gut microbiota and is associated with imbalanced food intake such as weight gain with the additional effect of epigenetic mechanisms. As well as in cardiovascular diseases, obesity has an extremely high heterogeneity and involved in metabolism-related diseases, and its underlying mechanisms remain unclear. As the global prevalence of obesity increases every year, it tends to be of high concern for the development of comorbidities, including children and adolescents. Although factors such as environmental pollutants known as obesogens and gut microbiota influence the susceptibility of diseases, focusing on epigenetic mechanisms in studies can be considered

among the treatment strategies that can be applied even before the emergence of obesity [10].Since obesity occurs mainly as a result of the lack of balance between energy intake and expenditure, microRNAs have been shown to take important functions in the regulatory network of adipocyte differentiation. Studies in animals have revealed that miR-26b is involved in the process of adipogenesis and its expression is upregulated gradually during differentiation in mature adipocytes [11]. By clarifying the molecular details of this whole process in further studies, it may be possible to develop new targets for therapeutic interventions in obesity, considering environmental factors.

Sedentary lifestyle brings along another leading disease which has a higher number of mortalities such as cancer besides obesity. Epigenetics has a distinct role in understanding metastatic potentials, and there is a tight correlation between environmental agents affecting the epigenome. Nutrition has proven to play an important role among these environmental factors, and the effect of a diet rich in polyunsaturated fatty acids on mutagenic free radical formation is directly related to epigenetic changes [12]. In another study, differences were demonstrated in gene methylation profiles which promote the regulation of proangiogenic mechanisms in human endothelial cells incubatedwith arachidonic acid [13]. It has also been observed that polyunsaturated fatty acids lead to attenuation of the NF-κB pathway in suppressing tumorigenesis[14].

In conclusion, we aimed to summarize the influence of environment and related epigenetic mechanisms involved in the development of diseases including, CVD, obesity, and cancer. In addition to the genetic background we have, the various pollutants we are exposed to from the in-utero stage and the habits such as diet, exercise, smoking and alcohol consumption that constitute the lifestyle have important effects on the epigenome. Given the correlation between epigenetics and exposure to all these environmental agents, it is expected to help explain how gene expression is regulated depending on these factors. From this point of view, it is thought that it will lead to significant advances in the field of personalized medicine in the development of effective treatments.

REFERENCES

[1] **Tiffon C. 2018.** The impact of nutrition and environmental epigenetics on human health and disease. *International Journal of Molecular Sciences;***19**. doi:10.3390/ijms19113425.

[2] Reamon-Buettner SM, Mutschler V, Borlak J. 2008. The next innovation cycle in toxicogenomics: Environmental epigenetics.*Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis***; 59:**158–65. doi:10.1016/j.mrrev.2008.01.003.

[3] **Sun C, Burgner DP, Ponsonby AL, Saffery R, Huang RC, Vuillermin PJ, Cheung M, Craig JM. 2013**. Effects of early-life environment and epigenetics on cardiovascular disease risk in children: Highlighting the role of twin studies. *Pediatric Research*; **73**:523–30. doi:10.1038/pr.2013.6.

[4] **Napoli C, D'Armiento FP, Mancini FP, Postiglione A, Witztum JL, Palumbo G, W Palinski. 1997**. Fatty streak formation occurs in human fetal aortas and is greatly enhanced maternal, hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atheroeclerotic lesions. *Journal of Clinical Investigation*; **100**: 2680–90. doi:10.1172/JCI119813.

[5] **Dwyer T, Blizzard L, Morley R, Ponsonby AL. 1999.**Within pair association between birth weight and blood pressure at age 8 in twins from a cohort study. *British Medical Journal*, **319:** 1325–9. doi:10.1136/bmj.319.7221.1325.

[6] **Bird A, Tate P, Nan X, Campoy J, Meehan R, Cross S,** Tweedie S**,** Charlton J**,** Macleod D**. 1995**. Studies of DNA methylation in animals. *Journal of Cell Science*; **108**: 37–9. doi:10.1242/jcs.1995.supplement_19.5.

[7] **Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagbooma Lumeye LH. 2008.** Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proceedings of the National Academy of Sciences of the United States of America* **105**: 17046–9. doi:10.1073/pnas.0806560105.

[8] **Libby P, Okamoto Y, Rocha VZ, Folco E. 2010.**Inflammation in atherosclerosis: Transition from theory to practice. C*irculation Journal*; **74**: 213–20. doi:10.1253/circj.CJ-09-0706.

[9] **Weaver ICG, Meaney MJ, Szyf M. 2006.** Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proceedings of the National Academy of Sciences of the United States of America*; **103**:3480–5. doi:10.1073/pnas.0507526103.

[10] **Lopomo A, Burgio E, Migliore L. 2016.**Epigenetics of Obesity. Adipose Tissue Adipokines Heal. Dis., vol. 140, Totowa, NJ: *Humana Pres*, p. 151–84. doi:10.1016/bs.pmbts.

[11] **Song G, Xu G, Ji C, Shi C, Shen Y, Chen L, Chunmei Sh, Lijun Zh, Lei Y, Yaping Zh, Guo X. 2014.** . The role of microRNA-26b in human adipocyte differentiation and proliferation. *Gene*; **533**: 481–7. doi:10.1016/j.gene.2013.10.011.

[12] **Alegría-Torres JA, Baccarelli A, Bollati V. 2011.**Epigenetics and lifestyle. *Epigenomics*; **3:** 267–77. doi:10.2217/epi.11.22.

[13] **Kiec-Wilk B, Razny U, Mathers JC, Dembinska-Kiec A. 2009**. DNA methylation, induced by beta-carotene and arachidonic acid, plays a regulatory role in the pro-angiogenic VEGF-receptor (KDR) gene expression in endothelial cells. *Journal of Physiology and Pharmacology.* **60:** 49–53.

[14] **Nowak J, Weylandt KH, Habbel P, Wang J, Dignass A, Glickman JN, Kang JX. 2007**. Colitis-associated colon tumorigenesis is suppressed in transgenic mice rich in endogenous n-3 fatty acids. *Carcinogenesis* **28:** 1991–5. doi:10.1093/carcin/bgm166.