

Environment, Epigenome & Disease

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EDITORIAL

We are not bewildered as the societies never contemplate to the scientific community's affirmation that genes alone do not determine our well-being, but environment does play the extensive role. The evolution of few genetic variants that proved to be beneficial in the past are detrimental today causing most of the highly prevalent - present day - complex metabolic diseases. Unlike diseases like thalassemia, cystic fibrosis, sickle cell anemia, hemophilia A&B (monogenic/ unifactorial diseases) that rarely affect human population, metabolic diseases involve both susceptible genes and environment. Economic & urban developments, accelerated market globalization have rapidly improved standards of living, expanded food availability and significantly changed our diets and lifestyle. Inappropriate diet patterns associated with decreased physical activity & increased tobacco consumption resulted in corresponding increase in cluster of chronic diseases, together called metabolic syndrome (obesity, type 2 diabetes, hypertension and cardiovascular diseases). Adding to the storyline, deforestation, industrialization, improper agricultural activities and environmental pollution by the exhaustive usage of -carbon fuels, plastics and pesticides have increased the environmental chemical burden leading to the significant raise in diseases due to endocrine disruptors.

Numerous studies have shown that the risk of developing several chronic diseases in adulthood can be affected by conditions experienced *In utero*. David Barker's work defines the effect of maternal nutrition on fetal programming which has come to be known as the "Barker hypothesis," or the developmental origins of adult disease. According to his theory, conditions in the maternal womb have a programming effect on fetal physiology, a phenomenon called fetal programming (1). Nutrients may show their effects on gene expression by epigenetic mechanisms. Any alterations in the methylation status of DNA (one of the epigenetic mechanisms) would alter the gene expression resulting in a different phenotype sometimes that are more susceptible to chronic diseases. Nutrition is known to play a pivotal role in regulating one carbon metabolism and hence epigenome too. Depriving the adequate nutrition for the fetus when in womb will irrevocably program the fetus predisposing it to a host of metabolic diseases, emphasizing developmental plasticity as an etiology of the disease. Thrifty genotype hypothesis proposed that the alterations in metabolic functions of the tissues due to gene environment interaction is the primary element of origin of metabolic syndrome (2). Exposure of this thrifty genotype to profoundly challenging today's "lifestyle" discourse like calorie abundance results in obesity & associated metabolic diseases. Alternatively, inadequate fetal nutrition followed by excessive food availability in postnatal environment may overload the reduced metabolic capacity of the thrifty phenotype leading to obesity due to the storage of surplus energy as fat. In spite of very scanty demographic studies, there are multiple animal studies that link nutrition, fetal environment & poor pregnancy outcomes, possibly due to altered epigenetic profile. This clearly emphasizes the role of good environment together with healthy nutrition for the best pre & postnatal growth.

There is a need to understand the dynamic nature of epigenetic mechanisms and are very often affected by external/ environmental effects. Many studies proved that all the component pathologies of metabolic syndrome and associated CVD, in particular, coronary artery disease have a common backbone called ‘oxidative stress’ associated with decreased antioxidant (enzymatic & non enzymatic) status. Albeit the reactive oxygen species are short lived, they are known to toxify cells and tissues by increasing the unwanted oxidation of macromolecules, affecting the physiological /metabolic process and thus altering signal transductions & gene processing. Researchers have hypothesized that environment induced oxidative stress and associated critical genes’ modification by epigenetic mechanisms as the underlying pathophysiology of both monogenic neurological disorders like Friedreich Ataxia, Huntington’s and complex neurological disorders like Parkinson’s and Alzheimer’s diseases (3). There is growing evidence that most of the cancers are due to disrupted essential cell functions, altered signal transductions & are linked to gene expressions, further associated with activation or repression induced by hypo or hypermethylation of oncogenes or tumor suppressor genes. The regulation of these epigenetic processes are reported to be modulated by increased reactive oxygen species due to oxidative stress (4). Nasser et al interpreted that the environmental stress during brain development causes hypomethylation of promoters of genes associated with Alzheimer’s disease such as the beta- amyloid precursor protein due to inhibition of DNA methyltransferases. The fetal imprint is triggered in later life resulting in increased levels of beta- amyloid precursor protein and beta amyloid, and the latter further promotes reactive oxygen species production that damages DNA and is responsible for Alzheimer’s disease (5).

Impact of the metabolic syndrome and cardiovascular consequences of air pollution, and cigarette smoking is well established. Most of the detrimental effects of either of these are due to the production of reactive oxygen species (with metal complexes through redox cycling of quinone based radicals) and associated oxidative stress due to metal containing inhalable nanoparticles contributing to overall damage by activating inflammatory mediators & pro-apoptotic signal transduction cascades in endothelial cells (6). Metals and aromatic hydrocarbons are known to diminish antioxidants by enhancing electron transport. The epigenetic modification effects of smoking is well illustrated by a molecular pathological epidemiology study by Nishihara et al, demonstrating a protective effect due to cessation of smoking on DNA methylation related carcinogenesis pathway that would otherwise lead to high risk colorectal cancer (7). This study clearly explains the reversible & dynamic nature of epigenetic mechanisms, although heritable.

There is a vast scientific literature that has been discussing the impact of endocrine disrupting chemicals (man-made exogenous chemicals that interfere in some aspects of hormone action) on health and environment. Their role is suspected to be associated with few cancers, infertility, obesity and metabolic syndrome, improper neural development in children and neurodegenerative diseases. The regulatory authorities of Organisation for Economic Co-operation and Development (OECD) countries have prioritized the protection of health and environment from endocrine disruptors. This issue has entered the international chemical policy arena via the Strategic Approach to International Chemicals Management (SAICM). Most of these endocrine disrupting chemicals are known to induce epigenetic transgenerational inheritance of multiple diseases.

There is an obligation for the researchers to further deeply explore the interplay between oxidative DNA damage, DNA repair, environment induced epigenetic modification and disease related genes. Our genes, epigenome and physical environment are deeply entangled and environment is the vital & basic resource of life. There is urgency for the scientific community to demonstrate this theory to a common man and urge the society to abide to the environmental laws for the healthier mankind.

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