Epigenetics – The New Kid on the Block

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What is next for epigenetics in understanding the association to prevention of disease and therapeutic intervention? In addition to classic approaches of compound screening for DNMT and HDAC inhibitors and development of improved stability and delivery of miRNAs, the following issues also play an important role for the impact of epigenetics. Firstly, dietary intake and lifestyle adjustments have been demonstrated to provide a strong influence on the epigenome. For instance, several cruciferous vegetables, green tea and spices have resulted in epigenetic modifications in female cancers [19]. Although some meta-analysis has not provided conclusive results, one study showed that increased consumption of total dairy food, excluding milk, might reduce the risk of breast cancer [20]. Likewise, soy isoflavone intake decreased the breast cancer risk significantly based on a meta-analysis of 4 studies on breast cancer occurrence and 14 studies on breast cancer incidence [21].

Cruciferous vegetables such as kale, cabbage, Brussels sprouts and broccoli contain sulforaphane (SFN) and indol-3-carbinol (I3C), which can act as DNMT and HDAC inhibitors and are also involved in miRNA regulation [22]. Extra virgin olive oil has also showed a positive impact on reduction of cancer risk [23]. For instance, a 4-fold stimulation of type 1 cannabinoid receptor (CB1) expression was observed in the colon of rats receiving 10 days of dietary extra virgin olive oil supplementation. Simultaneously, both miR-23a and miR301a known to be associated to the pathogenesis of colorectal cancer showed a 50% decrease. In relation to prostate cancer, it has been demonstrated that the phytoestrogen genistein demethylates CpG islands in promoter regions leading to enhanced protein expression [24]. Genistein can also enhance the expression of several tumor suppressor genes in prostate cancer cell lines, which has been attributed to demethylation and acetylation events [25] or increased expression of histone acetyltransferases [26]. The polyphenol resveratrol has showed anti-cancer activity both in vitro and in vivo, which could result in applications for both chemoprevention and prostate cancer therapy [27]. Recently, resveratrol analogs with chemical modifications have been designed to improve the low oral bioavailability and rapid metabolism to provide improved pharmacokinetic parameters and superiority in clinical applications [28]. Furthermore, consumption of vegetables and fruits showed a statistically significant inverse association with the risk of stomach cancer [29]. Also, green tea containing high concentrations of antioxidants has demonstrated prevention of esophageal and colon cancer [30].

One interesting but often neglected aspect that plays an important role on epigenetic functions is the composition of the gut microbiome and how it is influenced by dietary intake. Dietary factors and environmental toxins strongly affect the metabolites, which serve as cofactors and allosteric regulators of epigenetic functions and are produced by the gut microbiota [31]. Furthermore, the epigenome of the offspring is influenced by maternal and neonatal nutrition due to
the interaction of consumed food and the composition of the gut microbiota [32]. The link between the epigenetic profile and bacterial predominance was demonstrated in pregnant women, where Firmicutes and Bacteroidetes were the dominant gut microbe groups in obese individuals with differential methylation of gene promoters [33]. It has also been described that the gut microbes are responsible for the conversion of dietary fibers into short-chain fatty acids associated with histone hyperacetylation [34]. Gut bacteria also modulate N-nitroso compounds and heterocyclic aromatic amines derived from fat and red meat and considered as factors elevating the risk of colorectal cancer [35].

Finally, individual genetic and epigenetic differences need to be addressed for therapeutic interventions also for nutritional requirements. For example, in a case-report study a breast cancer patient was not eligible to chemotherapy due to some severe symptoms [36]. Nutritional deficiencies were detected through specialized testing for metabolic, gastrointestinal and immunological functions and after correction allowed to provide treatment to the patients. Nutrigenomics has also played an important role in preparing diets for individual genotypes [37]. In this context, Korean red ginseng has been recommended for the prevention of Helicobacter pylori-associated gastric cancer [38].

In conclusion, epigenetic mechanisms have been demonstrated to play an important role in disease development. The reversible nature of epigenetic functions has made targeting the epigenome attractive. A number of DNMT and HDAC inhibitors have been approved as medicines, either individually or for combination therapy. The rapid and important discovery of the many miRNAs affecting gene expression regulation and their association with human disease has further highlighted the importance of epigenetics in future medicine. The link between epigenetics, diet and disease will further strengthen the potential of developing better treatment for disease, but also most importantly pay serious attention to prevention, which will serve well from social, ethical and economic aspects.

References


