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Editorial

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Nutriepigenetics and Related Topics: From Cell Mechanisms to Possible Therapeutic Relevance

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Nutritional genomics (*nutrigenomics*) is a broad field that relates the genome to nutrition, and includes the effects of dietary components on the expression of genes and on the repair of genetic damage. Bioactive forms of vitamin A (retinoids) and D (calciferols), for example, can modulate gene expression programs and thereby affect reproduction, development, and many other physiological functions, e.g., reviewed in [1-3], discussion below. An individual's genetic and epigenetic uniqueness influences the ability to produce, metabolize, transport or store nutrients, and can result in unique nutritional requirements. Nutrients and other dietary factors can contribute to disease prevention and therapy through several strategies whereby their intake is increased or decreased to

(***a***) help control the effects of genetic mutations that cause diseases or contribute to disease risk, and

(***b***) influence expression of genes that typically lack such genetic mutations but contribute to disease risk.

Nutritional epigenetics (*nutriepigenetics*, a term I use since 2008) is defined as one component of category ***b***, and includes dietary factors that modulate gene expression through some of the covalent modifications of chromatin components. Such modifications create marks or patterns, e.g., DNA methylation, that may be heritable through somatic (mitotic) or germ cell (meiotic) divisions. Category ***a*** is the more classic domain of nutritional genetics (*nutrigenetics*) and this term can also be used to encompass dietary factor-dependent transcriptional modulation of gene expression that is not based on epigenetic patterns. Gene expression modulation through increases in copy number of a given genetic sequence can also be part of category ***b***.

Dietary or other environmental factors (A, B, C or their metabolites, as shown in the figure 1) can influence cellular epigenetic control mechanisms. Figure 1 shows methylation (-CH_3) and other (-X) chromatin modifications, some of which may be heritable. (A) Represents factors such as retinoids and calciferols that bind to nuclear receptors which can recruit enzymes that modify epigenetic marks, or influence the expression levels of modifying enzymes [3]. (B) Represents factors that can participate directly in the action of chromatin modifying enzymes (some examples below). (C) Represents factors that may be directly attached to histones, e.g., biotin [4]. Not shown in the Figure is possible epigenetic control involving ncRNA's. It will be of interest to determine if some dietary factors can also directly influence the actions of these RNA's; I would propose that some of the minerals such as Zn^{2+} which are known to be capable of binding RNA structures [5] and to influence epigenetic regulators [6] are good candidates. Some phytochemicals are known to influence ncRNA expression patterns, e.g., Curcumin [7].

Non-nutrient phytochemicals such as polyphenols can also affect epigenetic marks (or putative codes). The following are a few of many available examples. In some cases, the same compound can either increase or decrease the levels of a given epigenetic mark depending on cell type or experimental conditions. It is also important to note that these compounds typically influence only specific subtypes (isozymes) of the modification enzymes; e.g., over 15 histone deacetylase subtypes are known. Modulation of DNA methylation by inhibiting or lowering the levels of DNA methyltransferases (DNMT's) has been reported for the phytoestrogen genistein [8,9] and some catechins [10], among others. Modulation of various histone chemical modifications by phytochemicals is also well known. Butyrate as well as organosulphur phytochemicals such as diallyl disulfide (and metabolites) can increase histone (H3 and H4) acetylation by inhibiting deacetylases (HDA's) [11,12]. Some catechins can inhibit histone acyltransferases (HAT's) and thereby lower histone acetylation [13]. Phytochemicals that lead to higher HAT activity level are also known e.g., genistein [14].

Nutrition-based therapies have been used for many decades to prevent, treat, or moderate the effects of genetic mutations that lead to metabolic errors, or nutrient/metabolite deficiencies and excesses (nutrigenetics). An example of the latter case is controlling iron intake in those with forms of hemochromatosis (as well as other strategies for iron elimination). Increased folate intake may be recommended for individuals with some mutant forms of the MTHFR enzyme, a folate metabolism enzyme [15]. In cases where there is a metabolic defect that decreases production of a needed metabolite, for example, proper nutrition can help increase levels of that metabolite and decrease levels of potentially toxic accumulation of precursors; a classic case of this involves phenylketonuria [16].

Sometimes nutrigenomics is presented in the context of

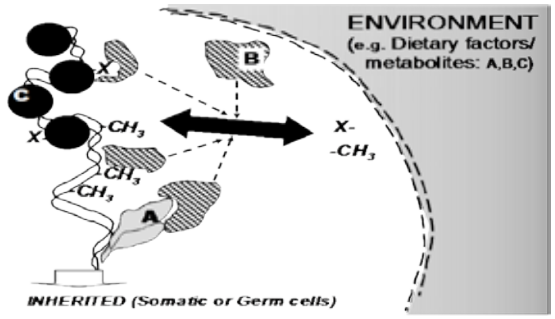

Figure 1: Dietary and other environmental factors (A, B, C, or their metabolites) can effect epigenetic control through covalent chromatin modifications (-CH3, -X).

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nutritional assessment. In terms of nutrigenetics, the presence of a given DNA mutation may have consequences for disease (see above), and such information can then be used for making appropriate dietary recommendations to help in prevention or treatment. In terms of nutriepigenetics, we are now moving toward such diagnostic use: specific patterns of DNA methylation or other chromatin chemical modifications may be used in the future for nutritional counselling and development of preventive or therapeutic dietary strategies. Both genetic and epigenetic tests also have the potential to provide information useful for guiding pharmacotherapy.

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