Journal of Cell Signaling
ISSN: 2576-1471

Haq, J Cell Signal 2018, 3:1
DOI: 10.4172/2576-1471.1000181

Commentary Open Access

DNA Methylation Pattern and their Effect on Ageing

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Received date: February 16, 2018; **Accepted date:** March 05, 2018; **Published date:** March 08, 2018

Abstract

DNA methylation is one of the epigenetic modifications which have been implicated in cellular differentiation, aging, and diseases progression. In this commentary, we discussed the significant role of methylation pattern and imprinting in the cellular differentiation in light of the earlier published work. This is an attempt to highlight the importance of methylation factors in health and disease and explore the potential of various nutritional therapeutic agents directly affecting the methylation pattern of DNA. The role of external dietary chemical and environmental factors contributing towards the epigenetic imprinting has been suggested, but the exact molecular mechanisms through which these dietary and environmental agents mediate their action on genomic methylation pattern require future investigation. One of the possible mechanisms which warrant future investigation is to explore the signalling pathways, directly controlling the DNA methylation pattern through expression of DNMTS. *In vitro* studies on the impact of different therapeutic supplements on the epigenetics and DNA methylation would be useful in the prevention of age-related diseases.

Keywords: DNA methylation; Differentiation; Age-related diseases; Cellular imprinting

Introduction

During embryonic development, a group of cells divide and proliferate and ultimately each one is committed to being a very specialized differentiated cell, performing its niche role in its extracellular environment. This type of differentiation process is strictly regulated and maintained by epigenetic processes; however, the DNA sequence remains unchanged. Early in-depth mechanistic analysis revealed a direct relationship between a gene expression and its repression to its methylation pattern of the promoter regions. Methylation pattern for each differentiated cell type is heritable and stable and maintained throughout successive cell division by mitosis. This methylation pattern also allows faithful and lineage-specific propagation of cells through several cell divisions. Although this journey of a cell towards its differentiating state, thereby allowing only the expression of a subset of genes required for their specialized extracellular matrix is unidirectional *in vivo*, but this pattern of methylation can be reversed or perturbed *in vitro* by treating the cells with the hypomethylating drug such as 5-azacytidine and 5-aza-2´deoxycytidine.

5-azacytidine has the ability to intercalate in both DNA and RNA and non-specific, unlike 5-aza-2´deoxycytidine which has the ability to only intercalate in DNA thus acting as the potent inhibitor for Methylation [1].

In our research project on the effect of 5-aza-2´deoxycytidine on chondrocyte morphology [2], we specifically focussed our attention to the change in DNA methylation pattern during the initial cell division or log phase of cell culture. Initially, when the chondrocytes are plated on the culture plates, they undergo active cell division during their first few hours in culture conditions until they reach confluence. It was very important to note that this initial seeding time was crucial for them to be exposed to the hypomethylating drug, which allowed them to incorporate 5-aza-2´deoxycytidine instead of a cytosine base, preventing it to be methylated, thus ensuring a hypomethylating state of DNA. The key outcome of this research was that it was a brief snapshot of the key events taking place during differentiation of chondrocytes toward its terminal fate. The role of methylation in senescence and aging of cells has been proposed in a number of studies, [3-5]. Recently, with the latest techniques of microarray and next-generation sequencing have enabled the scientist to look at the role of the methylation pattern of DNA more closely and critically. These studies showed that the change in methylation pattern is apparent during the whole lifespan of the human beings and the variability of the methylation pattern with age is imminent. It has been noticed that methylation at certain CpG sites are highly specific for the age, so much so that the age of the donor tissue can be estimated by the methylation pattern [6].

Many lines of evidence have established that Ras signalling pathway triggered by binding of the cell receptor to epidermal growth factor (EGF) and Fibroblastic growth Factor (FGF) are the key modulators of cellular differentiation [7].

Many factors of tissue or cell type may apparently affect their aging methylation pattern, including differences in the rate of cell division, respiration rate and energy expenditure or exposure to environmental factors (**Figure 1**). One of the major contributors to aging is the dis-balance of pro-oxidative and oxidant balance. Increased oxidative stress mediated by the generation of reactive oxygen species can significantly accelerate the aging process by leaving a permanent imprint on the methylation pattern. A current study showed that treatment with the 5-azacytidine to mesenchymal stem cell could reduce oxidative stress, ameliorates superoxide dismutase activity and increases Bcl-2/Bax ratio [8]. The possibility of using demethylation drugs as the future therapeutic interventions to slow down or even

reverse age-related degenerative changes in cells could be very promising. Already a number of food supplements and diets have been demonstrated in a number of studies, [3,4,9] which could potentially change the methylation pattern of tissues. Specific antioxidants active compounds found in dietary phytochemical preparations such as teas, soy products, herbs, grapes and cruciferous vegetables are now generally accepted to defend against the development of many different types of tumours as well as epigenetic modulators that impact not only on the initiation, but also the progression of oncogenesis [10].

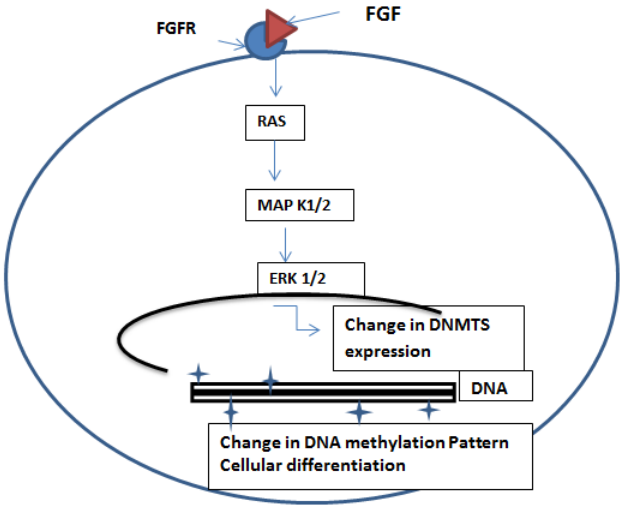

Figure 1: Signalling pathways involved in the cellular differentiation through a change in patterns of DNA methylation by changes in the expression of DNA methyl transferase activity (DNMT). Addition of methyl groups to CpG islands.

Targeting DNA methylations pattern using natural inhibitors of DNA methyl-transferase Enzyme (DNMT) could prove to be an ideal therapy for treating not only cancer but also other age-related diseases. Our increased understanding of DNA methylation pattern and naturally occurring potent inhibitors for DNMT could revolutionize the way we treat diseases.

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