Short Review

Epigenetics-beyond the DNA sequences-current scenario

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Abstract

Epigenetics deals with the phenomenon of altered traits that does not involve any change in the DNA-Genome sequences. This non-DNA sequence based inheritance is very interesting and a main domain of research is to understand the complex interactions between the genome and its surroundings. Many researchers focused on epigenetics to unravel the links of inter and intra cellular environments on DNA during different diseases and traits expression. This short review describes the current scenarios of epigenetics regarding cancers and plants' research.

Keywords: Cancer; Epigenetics; Plants

Epigenetics in cancer

Epigenetics influence is mainly restored by methylation of DNA and histone proteins for regulating metabolic gene expression, which in turn affects different metabolite levels. This leads to the alteration in the cellular metabolite profiles that may have role through oncogenesis for generating a synergetic feedback mechanism promoting the causes of cancer. Once an elaborate picture of the proteins and other molecular components responsible for the crosstalk between epigenetic workers and metabolism is available, researchers may be come enabled to develop new and effective therapeutic options for cancer treatment [1]. Kinnaird *et al.* [2] reviewed in detail the alterations in epigenome linked with metabolism and their effects to facilitate cancer development and progression. They also suggest the presence of significant bidirectional regulatory mechanisms between metabolic changes and the

epigenome (particularly methylation and acetylation of histones) during cancer on progression. This metabolic alteration not only affect the cancer cell differentiation, proliferation and/or apoptosis, but also determines outcomes of therapeutic responses. Recently, Hill *et al.* [3] selected MCF-7 breast cancer cell line to explore the effects of cinnamon based treatments on DNA methylation patterns. They found a potential role for aqueous cinnamon extracts on methylation of the Akt2 gene in MCF-7 cells, possibly declining the expression of this protein. Akt2 signaling can play a main role in different signaling pathways efficiently to prevent cellular apoptosis and thus lead to a prolonged cell life.

Levine *et al.* [4] presented a very good review on the interplay between epigenetics and p53 protein. The p53 protein not only furnish the stability of the genome by the inhibition of genetic modifications in cells, but also performs a role in regulating the epigenetic

modifications that can occur in cells. The full-form p53 protein is mainly inactive in stem cells however in activated form helps these cells in developmental lineages through a series of epigenetic modifications. Just as p53 influences epigenetic alterations, the enzyme activities that carry out epigenetic protein modifications in turn effect the p53 protein and its splice variants in stem and progenitor cells to inactivate or trigger its transcriptional events. Thus, there is a great deal of cross-talk between the p53 protein and epigenetic programs. This realization gives new ideas and directions for the treatment of cancers regarding reactivating developmental pathways for tissue regeneration and responses to the impact of aging.

Abnormal epigenetic alterations, which are sometimes called as “epimutations”, occur at promoters or enhancers sites of tumor-suppressor genes and proto-oncogenes, which are often selected during tumorigenesis. Epimutations are well documented in colorectal cancer (CRC), where many genes (e.g., APC, LKB1, GATA4, p16INK4a, MLH1) and genetic pathways are common targets [5]. Epigenetic controls are also evident in mechanisms that relate food and nutrient availability regarding regulation of gene expression to maintain homeostasis. The basis for this mechanistic link is the fact that most epigenetic enzymes utilize energy metabolites or redox factors as essential co-factors [6]. Thus, all these epigenetics events lead to the CRC development.

Feinberg *et al.* [7] reviewed the presence of ‘tumor progenitor genes’ that are otherwise epigenetically modified at the initial stages of malignancies, even before mutations and thus cause altered differentiation throughout tumor progression. They also suggest an outline for cancer epigenetics which involves three forms of genes: ‘epigenetic mediators’, corresponding to the tumor progenitor genes

suggested earlier; ‘epigenetic modifiers’ of the mediators, which are frequently mutated in cancer; and ‘epigenetic modulators’ upstream of the modifiers, which are responsive to changes in the cellular environment and are often linked to the nuclear architecture. This classification is helpful in devising new diagnostic and therapeutic approaches to counter cancerous proliferations.

Lung cancer is mostly caused by the suppression of tumor suppressor genes (TSG) which is achieved through both genetic and epigenetic approaches, including a repressive chromatin state of the TSG promoter (e.g. aberrant DNA methylation) [8]. Kiehl *et al.* [9] investigated new mechanisms that are indulged in the epigenetic inactivation of TSG, and performed a global DNA methylation analysis for lung cancer cells and found that the downstream genes could be susceptible to epigenetic silencing when organized in a tandem orientation. Diaz-Lagares *et al.* [10] reported nine cancer-specific hypermethylated genes in early-stage lung primary tumors. Four of these nine, linked with transcriptional silencing, showed consistent CpG island hypermethylation compared with nonmalignant lung cells. They also devised a calibrated and cross-validated epigenetic model for predicting with high accuracy the probability to detect cancers through minimally introversive and noninvasive samples. Diaz-Lagares *et al.* [10] also demonstrated that these epigenetic-based markers get more diagnostic efficacy in bronchial fluids as compared with conventional cytology used for lung cancer diagnosis.

The most common cancers are the breast malignancies that causes frequently deaths and account for 20% of all female cancers worldwide. The prevalence of breast cancers is much higher in Western countries compare to Eastern countries [11]. Epigenetic changes

are one of the main causes of the breast cancers where metabolites resulted by foods and drinking water may act as endocrine disruptors causing epigenetic hormonal regulation towards increased breast cancer risk. Romagnolo *et al.* [12] reviewed a working hypothesis regarding the agonists of the aromatic hydrocarbon receptor (AHR), bisphenol A (BPA), and arsenic compounds, that are induced as TSG epigenetic signatures mirroring those often seen in sporadic breast tumors. Recently, Connolly *et al.* [13] used a combination of endocrine and epigenetic therapies having a DNA methyltransferase inhibitor and a histone deacetylase inhibitor, for breast malignancies. These were directed to re-expression of the genes that code vital therapeutic targets, comprising of the estrogen receptor (ER), and found that some women benefit from such therapy along with or without reintroduction of endocrine therapy beyond progression.

Epigenetics in plants

The epigenetic in plants is mostly rendered through regulations by DNA methylation. The plant DNAs cytosine can be modified by methylase, regardless to the sequential order when compared to the advanced animals (mammals) [14]. These cytosines may either be as symmetrical (CG and CHG) or nonsymmetrical (CHH) sequences. The plants' epigenetic has reported role in the regulation of flowering time, flower sex determination, seed development, and fruit ripening [14]. Flowering Locus C (FLC) has a key role in the plant vernalization and very recently, Whittaker and Dean [15] reviewed in detail the FLC of *Arabidopsis thaliana* with respect to the epigenetics by emphasizing how molecular investigation of vernalization pathways has provided significant understandings into antisense-mediated chromatin silencing mechanisms that regulate this locus. The FLC locus has been research focus for deciphering the significant epigenetic molecular events

regulated by noncoding transcription as well as chromatin that affect the gene expression while revealing the processes that can be altered to support adaptation in natural populations.

Brautigam *et al.* [16] studied 13 genes involved in sex determining region (SDR) of balsam poplar (*Populus balsamifera*) for differential methylation through applying whole methylome sequencing of xylem tissue of several plants. They found only SDR gene, PbRR9, having role in cytokinin signaling and it showed a marked pattern of gender-specific methylation. The promoter and the first intron were observed with strongest patterns of differential methylation (mostly male-biased). Banerjee and Roychoudhury [17] reviewed the significance of the plant epigenetics in the stress memory, which is a phenomenon of plants better managing similar stress in future, exposures when pre-exposed to salinity, drought etc. Similarly, Lamke and Baurle [18] reviewed in detail the plants' chromatin modifications, nucleosome positioning, and DNA methylation with respect to the management of both biotic and abiotic stresses, which have evolved with sophisticated adaptations and defense mechanisms. And these potential epigenetic processes may provide a spontaneous basis for a stress memory, enabling plants to cope more proficiently to recurring stress which can even prepare their descendants for potential future stresses.

For worldwide food security, the best option include super hybrid rice varieties with ideal plant architecture (IPA). Zhang *et al.* [19] reported the identification of a QTL, qWS8/ipa1-2D, in the super rice Yongyou12 (YY12) and related varieties which belongs to three distal naturally occurring tandem repeats upstream of IPA1, as being a significant locus and has role to shape rice ideal plant architecture while significantly improving grain yield. Similarly, the qWS8/ipa1-2D is linked with low DNA

methylation and cause an extra open chromatin state at the IPA1 promoter, therefore, easing the epigenetic repression of IPA1 mediated by nearby heterochromatin. Genome-wide approaches to study the hybrid vigor have identified epigenetic changes in the hybrid nuclei in *Arabidopsis* (*Arabidopsis thaliana*), maize (*Zea mays*), and rice (*Oryza sativa*). Similarly, Greaves *et al.* [20] reported the DNA methylation linked with 24-nucleotide small interfering RNAs, showing trans-allelic effects in hybrids of *Arabidopsis* and other species. And these hybrids showed extended leaf size compared to those of the parents and have larger cell size as well as numbers. These larger leaves causes increased photosynthetic performance, which may result in greater vegetative and reproductive yields of the F1 hybrids.

Ornamental plants have more allures due to their flowers and pertaining characters. The shape, size, color, abundance and fragrance of flowers are the most important features of ornamental plants. All these properties of the flowers are regulated by many internal and external factors, including the epigenetics [21]. Therefore, understanding the epigenetic molecular mechanisms for shape, size, color, abundance and fragrance of flowers would enable us to develop better ornamental plants for the industry.

Authors' contributions

Conceived the idea, reviewed the literature and wrote the manuscript: MYK Barozai & AN Aziz.

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