The minimum dna methylation level requirement biology essay

Science, Biology

Abstract

DNA methylation patterns in cancer cell typically express aberrantly that can lead to a malignant transformation. The relationship between cancer cells and these abnormal epigenetic modifications is still limited understood. In this study de carvalho et al identified the genomic regions where DNA methylation is carried out to regulate the survival of cancerous cells. Firstly, the authors observed the minimum level of DNA methylation in cancerous cells by reducing the activity of DNA methyltransferases, then these methylated sites were mapped into 2 different group of tissues, including tumor and normal tissue. Finally, using gene expression meta-analysis to investigate the genomic regions where DNA methylation regulate gene silencing. The result showed that some fundamental genes must be inactive by DNA methylation process for the survival of cancer cell. This finding suggests that these epigenetic alterations open a new approach in cancer therapeutic.

Background description

In the development of a tumor, cancerous cells have the properties to deal with the physiological regulation of body's internal environment. These properties are an ability of unlimited proliferation, self-sufficiency in growth signals, anti apoptosis and resistance to the activation of immune system (Hanahan and Weinberg, 2011). However, these alterations also influence on a process of the stress phenotype of cancer, this include proteotoxic, metabolic, mitotic stress and DNA damage/replication stress. In order to survive cancerous cells modify its genomic circuitry by activating oncogenes

and inhibit nononcogenes. Thus, classic tumor suppressor genes (TSGs) and genes that control nononcogenic signaling pathways, have a vital impact on cancer cell survival (Luo et al., 2009; Weinstein, 2002). The modification of RNA molecules of cancer cell can be regulated by epigenetic genetic and modifications (Jones and Baylin, 2007). One of which is DNA methylation in epigenetic process; the process can change gene expression without altering the DNA sequence. Sharma et al., 2010 proved that in normal somatic cells, CpG dinucleotides within CpG poor sequences are highly methylated, where CpG-rich sequences (CpG islands) are always un-methylated. Many essential mechanism are regulated by DNA methylation, these include embryonic development, genomic imprinting, differentiation, maintenance of pluripotency, gene silencing and X chromosome inactivation De Carvalho et al., 2010). Also, deregulated DNA methylation potentially be a main factor of cancer (Kelly et al., 2010; Portela and Esteller, 2010; Taberlay and Jones, 2011). Sharma et al., 2010 demonstrated that during the development of tumor, hypermethylation of CpG islands and hypomethylation of non-CpG islands are the result by changing in global DNA methylation patterns. In which DNA hypermethylation cause some TSGs abnormal silencing in many cancer types (Jones and Baylin, 2002, 2007). Figueroa et al., 2010 stated that by using utilizing genome-wide techniques, aberrant DNA methylation profiles in cancer are exhibited by a huge of genes . These findings can be utilized to predict cancer outcome and categorized subtypes of cancer (Portela and Esteller, 2010), among other technical. The implication that categorizing which genes is responsible for DNA methylation-mediated gene silencing in cancer development could be extremely beneficial for later

epigenetic therapies (Kelly et al., 2010). But this work is extremely difficult because of a vast quality of differentially DNA-methylated genes in human cancers (Kalari and Pfeifer, 2010). There is no direct evidence for the suggestion that cancer cell may have a tendency appear in an abnormal epigenetic landscape, particularly in DNA methylation. In this study, an approach has been described to deal with this issue.

Main experimental findings

The minimum DNA methylation level requirement for cancerous cell survival

In this study the authors have used Illumina Infinium platform (HumanMethylation27) to identify gene promoters of HCT116, DKO1 and DKO8 cell lines whose DNA methylation is required for their survival in minimum level of DNA methylation. Figure 1 shows the greatest reduction in DKO1 cells compared to DKO 8 and HTC116 cells in global DNA methylation levels. Interestingly, De carvanhol et al also found a set of 566 CpG sites associated with 490 genes are still remain high DNA methylation levels in DKO1 cells(β value > 0. 6); HTC116 and DKO8 cell ((β value > 0. 2) under a high impaired DNA methyltransferase activity . By comparing DNA methylation level of 566 CpG in DKO1 to DNA mythylation patterns of normal colon tissue and primary colon adenocarcinoma and using k means clustering. De carvando also investigated 92 CpG sites associated with 77 genes in normal colon that are unmethylated, but these region in colon adenocarcinoma were hypermethylated (Figure 1). Figure 1 C show that 99Cpg sites associated with 83 genes in somatic tissues cluster are highly

methylated; and 29cpG associated with 25 genes are unmethylated in cell culture specific cluster . By using bisulfite sequencing data of the Infinium-based DNA methylation from somatic and cancer specific DNA methylation clusters, the author observed a high levels of DNA methylation in HCT116 and DKO1 cells (Figure 1D). This support the functional and important role of residual DNA methylation.

The validation of fundamental genes

De carvanho et al demonstrated that the re-expression of genes (from cancer, somatic and cell line cluster) negatively regulate cell viability in HCT116 and RKO gene (figure 5). While NOX4 – control gene is not relevant to DKO1 survival (figure 5). In addition, the author also indicated that the silencing of , interleukin-1 receptor-associated kinase 3 (IRAK3), affects cancer cell survival. The reduction in expression of IRAK3 is present in some types of cancer cells, comparing to normal tissues. This finding implicates that the reduction of IRK3 expression, or IRK3 silencing is regulated the development of tumors. In contract the reduction of IRAK3 is responsible for the increase in expression of SURVIVIN, thus increase cell survival. By re-expressing IRAK3 result in the reduction in protein level of Survivin (figure 5) and the increase in the quality of cell death (figure 5) and reduce the development of cells ($p < 0, 001$; Figure 5).

The significance and future outcomes of the scientific findings

In this study, de carvalho et al has identified the minimal DNA methylation pattern that is regulate cancerous cell survival. Also, by comparing these

DNA methylation pattern with some primary normal tissues and cancer cell types, they found a collection of genes whose de novo methylation in cancerous cell, which is associated with the survival of cancerous cells. The epigenetic silencing of these genes by DNA methylation process is regulate cancerous cell survival in the development of tumor. This finding could promote the new therapies in cancer treatment.