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Short Communication

Prostate Cancer of Epigenome and Genome

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DESCRIPTION

Prediction of prostate cancer clinical outcome remains a major challenge after diagnosis. Several high throughput approaches were applied to analyze the genome abnormalities of prostate cancer. To evaluate whether Copy Number Variation (CNV) of genomes in prostate cancer (T), benign prostate tissues Adjacent to Tumor (AT) and blood of prostate cancer patients predicts biochemical relapse and the kinetics of relapse, 241 samples were analyzed through Affymetrix SNP 6.0 chips. Using gene specific CNV from T, the genome model correctly predicted 73% cases for relapse and 75% for short PSADT. The gene specific CNV model from AT correctly predicted 67% cases for relapse and 77% for short PSADT. Using median size of CNV from blood, the genome model correctly predicted 81% for relapse and 69% for short PSADT [1]. To analyze epigenome abnormalities of prostate cancer, genome wide methylation analyses were performed using both array and whole genome methylation sequencing approaches for 91 human prostate specimens. A gene methylation prediction model was shown to predict prostate cancer relapse with sensitivity of 80.0% and specificity of 85.0%. Through whole genome methylation sequencing, we found both intragene and promoter CpG islands contributed to the suppression of RNA transcription. Most of the differential methylation between T and AT occurred in regions outside the CpG islands. Epigenetic mechanisms such as DNA hyper-or hypomethylation and histone modifications are reversible genetic alterations which allow stable inheritance of cellular phenotypes without any changes in the DNA sequence or quantity. Epigenetic modifications can potentially be used for the molecular classification, detection, and risk assessment in prostate cancer. Chemical inhibitors of DNA methyltransferases and histone deacetylases have been used in different clinical trials and hold promise as novel chemotherapeutics to be effective alone or in combination with other therapeutic interventions in prostate cancer [2]. A major objective of translational cancer research in post-genome era is to discover the repertoire of genetic and epigenetic variations associated with prostate cancer. Genome-wide association studies have been at least partially successful in identifying potential germline polymorphisms and allelic imbalances such as microsatellite instability and loss of heterozygosity associated with prostate cancer susceptibility.

GENOME

Approxmately 23000 gens are contained in those human genome should be expressed in specific cells at specific times. The chromatin is a nucleoprotein complex made of nucleosomes [3]. The nucleosomes are made of DNA, which are wrapped around octamers of globular histone proteins. The changes in the chromatin structure influence the gene expression. When the chromatin is condensed, the gene expression is "switched off" and when it is open, the gene expression is "switched on". The status of chromatin is dynamic and can be controlled by reversible epigenetic mechanisms. The two important, well studied epigenetic mechanisms are DNA methylation and histone modifications such as acetylation. These two processes can act independently and/or together affecting the gene expression and in turn the tumorigenesis.

DNA hypermethylation is a well-established epigenetic abnormality seen in several malignancies, more importantly in prostate cancer. Carcinogenesis is a multi-step process and hypermethylation is hypothesized as an early event in the development and progression of prostate cancer. Hypermethylation of the gene is facilitated by a group of enzymes known as DNA methyltransferases, which includes DNMT1, DNMT1b, DNMT1o, DNMT1p, DNMT2, DNMT3a, DNMT3b and DNMT3L. The hypermethylation involves the CpG islands in the promoter regions that results in the silencing of the genes that are involved in tumor suppressor activity, DNA repair and other critical cellular mechanisms [4]. The two important, well studied epigenetic mechanisms are DNA methylation and histone modifications such as acetylation.

DNA HYPOMETHYLATION

A second type of methylation related aberration seen in variety of prostate cancer. Hypomethylation is facilitated by enzyme group demethylases which includes 5-methylcytosine glycosylase and MBD2b. Methylation of normal genomes act as defensive mechanisms against cancer, for example, the oncogenes can be

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transcriptionally silenced and prevented from propogating by being methylated. The hypomethylation causes breakdown of this defense mechanism and is implicated in the tumor genesis.

EPIGENETIC DIAGNOSTIC

Prostate specific antigen is a less than optimal tumor marker and between prostate cancer and other conditions such as prostatitis, benign prostatic hyperplasia [5]. The false positive results lead to expensive and invasive investigations such as transrectal prostate biopsy. This provides the opportunity to the researchers to identify potential epigenetic markers in the diagnosis of prostate cancer. Epigenetic markers, particularly aberrant DNA methylation, have the potential as an useful diagnostic tumor marker. These markers can be detected in cancer tissues, serum and body fluids. The methylation markers have several advantages over the mutation based genetic markers.

PROGNOSTIC DIAGNOSTIC

Demonstrated that GSTPI hypermethylation is seen in 40% of it aspirate in patients with advanced. They also found evidence of GSTP1 hypermethylation in 90% of PC patients with lymph node involvement whereas in only 11% of lymph nodes in non-cancer group. Genes such as CAV1, CDH1, CD 44 and T1G1 may exhibit specific methylation in high risk and Metastatic tumors that can be used in the molecular staging and predictors of disease progression. Prostate cancers with high Gleason score are correlated with a higher degree of methylation of many genes, such as RARb, RASSF1A, GSTP1 and CDH13. Further studies also indicate that use of panel of multiple methylation makers can be better predictors than individual genes.

HISTONE CODE

Histones have emerged as important regulators of chromatin the nucleosome, two super helical turns of DNA containing around 146 base pairs wrap an octomer of histone core made of four histone partners (an H3-H4 tetramer and two H2A-H2B diamers. Histones consist of a globular domain and a more flexible and charged NH2 terminal called as histone "tail". These tails which are placed peripherally are susceptible for a variety of covalent modifications, such as acetylation, methylation, phosphorylation and ubiquitination [6].

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