INTEGRASI PROFIL EPIGENOMIK DAN GENOMIK UNTUK PENGENALPASTIAN PENANDA GEN DALAM KANSER PAYUDARA

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PENGAKUAN

Saya akui karya ini adalah hasil kerja saya sendiri kecuali nukilan dan ringkasan yang setiap satunya telah saya jelaskan sumbernya.

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ABSTRAK

Metilasi DNA merupakan suatu fenomena epigenetik yang boleh menyebabkan penyenyapan transkripsi pada gen penindas tumor dan menyumbang kepada karsinogenesis. Keterbalikan mekanisme ini boleh menyebabkan pengekspresan semula gen dan membawa kepada regulasi gen yang normal. Objektif kajian ini adalah untuk menentukan profil metilasi DNA dan pengekspresan gen dalam sel-sel kanser payudara berbanding dengan tisu bukan kanser. Gen pemandu dan tapak jalan molekul yang menghubungkan gen-gen tersebut boleh dikenalpasti dalam kanser payudara dengan menggunakan pendekatan integrasi. Profil metilasi DNA telah dijalankan ke atas 76 keratan segar beku tisu tumor payudara primer dan 25 tisu payudara bersebelahan yang bebas daripada sel kanser dengan menggunakan cip Illumina Infinium® HumanMethylation27 BeadChip. Validasi profil metilasi dijalankan ke atas tujuh gen sama ada dengan menggunakan MLPA yang spesifik metilasi atau tindak balas berantai polimerase yang spesifik untuk metilasi. Profil pengekspresan gen telah dilakukan ke atas 15 tisu tumor payudara dan lima tisu payudara bersebelahan yang bebas daripada sel kanser dengan menggunakan tatasusunan Affymetrix GeneChip® Human Gene 1.0 ST. Pengkelasan hierarki berselia menunjukkan 1255 tapak CpG mengalami hipermetilasi dan 15 tapak CpG mengalami hipometilasi. Dengan menggunakan perubahan gandaan sekurang-kurangnya 1.5 dan *False Discovery Rate* dengan nilai $p < 0.05$, sebanyak 404 gen beregulasi menaik dan 463 gen beregulasi menurun telah dikenalpasti daripada analisis mikroatur bagi pengekpresan gen. Analisis berintegrasi daripada kedua-dua set data telah mengenalpasti sebanyak 64 gen pemandu. Daripada jumlah tersebut, 51 gen mengalami hipermetilasi dengan tahap ekspresi yang rendah (hubungan negatif) dan 13 gen mengalami hipermetilasi dengan tahap ekspresi yang tinggi (hubungan positif). Daripada 51 gen yang mengalami hipermetilasi dengan tahap ekspresi yang rendah, 14 gen telah dikaitkan dengan kanser payudara, termasuk *DAB2IP, NDRG2, AGTR1, CXCL2, CCND2, DKK3, FGF2, KLK10, NRG1, PTN, PTPRZ1, SFRP1, RELN* dan *KIT*. Bagi 13 gen yang mengalami hipermetilasi dengan tahap ekspresi yang tinggi, empat gen iaitu *COL1A2, FBN1, THBS2* dan *COL4A1* telah dilaporkan dalam kanser payudara. Gen yang bertindih di antara profil metilasi DNA dan pengekspresan gen seterusnya telah dipetakan kepada pangkalan data Kyoto Encyclopedia of Genes and Genomes (KEGG) untuk mengenalpasti tapak jalan molekul yang berkaitan dengan gen tersebut. Dua tapak laluan yang diperkaya telah dikenalpasti daripada pangkalan data KEGG iaitu lekatan fokus dan interaksi reseptor ektrasel matriks. Terdapat tujuh gen (*PAK7, COL4A1, CCND2, COL1A2, RELN, COL1A1* dan *THBS2*) yang terlibat dalam lekatan fokus manakala lima gen (*COL4A1, COL1A2, RELN, COL1A1* dan *THBS2*) yang terlibat dalam interaksi reseptor ektraselular matriks. Kedua-dua tapak jalan ini penting untuk mengawal motiliti, migrasi, proliferasi dan pembezaan sel. Kesimpulannya, analisis integrasi data genomik hasil daripada profil metilasi DNA dan pengekpresan gen membolehkan kami menyenarai pendekkan senarai gen-gen yang signifikan dan tapak jalan yang penting dan berkemungkinan menyumbang kepada karsinogenesis kanser payudara. Gen-gen ini berpotensi untuk dijadikan sebagai penanda biologi dan sasaran terapi untuk kanser payudara.

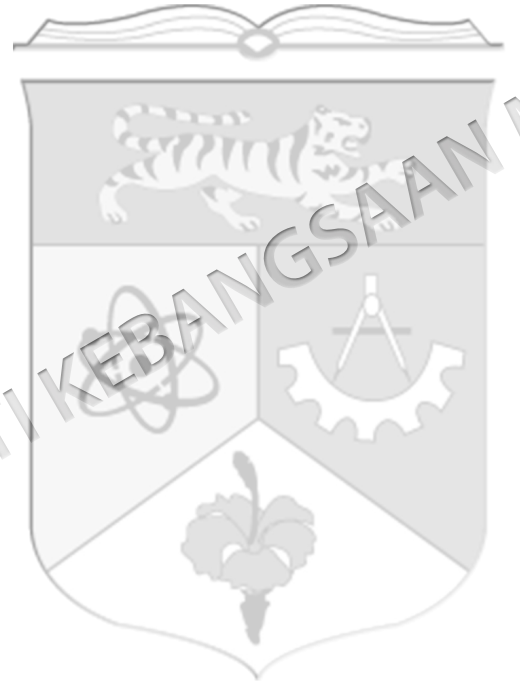
AN INTEGRATIVE EPIGENOMIC AND GENOME WIDE PROFILING IDENTIFY GENE SIGNATURES IN BREAST CANCER

ABSTRACT

DNA methylation is an epigenetic event which could lead to transcriptional silencing of tumour suppressor genes and may contribute to carcinogenesis. Reversibility of this mechanism can result in gene re-expression that leads to normal gene regulation. The objective of this study was to determine the DNA methylation and gene expression profiles in breast cancer cells as compared to non-cancerous tissues. Driver genes and molecular pathways that linked these genes in breast cancer can be identified using an integrative approach. DNA methylation profiling was carried out on 76 representative fresh frozen primary breast tumour tissues and 25 adjacent non-cancerous breast tissues using the Illumina Infinium® HumanMethylation27 BeadChip. Validation of methylation profiling was performed on seven selected genes using either methylation specific-MLPA or methylation specific quantitative polymerase chain reaction. Gene expression profiling was done on 15 breast tumours and five adjacent non-cancerous breast tissues using the Affymetrix GeneChip® Human Gene 1.0 ST Array. Supervised hierarchical clustering analysis revealed 1255 hypermethylated and 15 hypomethylated CpG sites. Gene expression microarray analysis using fold-change of at least 1.5 and False Discovery Rate with p value < 0.05 identified 404 up-regulated and 463 down-regulated genes. Integrated analysis of both datasets identified a total of 64 driver genes. Of these, 51 genes were hypermethylated with low expression (negative association) and 13 genes were hypermethylated with high expression (positive association). Of the 51 hypermethylated genes with low gene expression, 14 genes were associated with breast cancer, including *DAB2IP*, *NDRG2*, *AGTR1*, *CXCL2*, *CCND2*, *DKK3*, *FGF2*, *KLK10*, *NRG1*, *PTN*, *PTPRZ1*, *SFRP1*, *RELN* and *KIT*. For the 13 hypermethylated genes with high expression, four genes, namely *COL1A2*, *FBN1, THBS2* and *COL4A1*, were previously reported in breast cancer. The overlapped genes between DNA methylation and gene expression datasets were further mapped to Kyoto Encyclopedia of Genes and Genomes (KEGG) database to identify the molecular pathways that linked these genes. Two of the enriched pathways identified from the KEGG database were the focal adhesion and extracellular matrix-receptor interaction. There were seven genes (*PAK7, COL4A1, CCND2, COL1A2, RELN, COL1A1* and *THBS2*) involved in focal adhesion while five genes (*COL4A1, COL1A2, RELN, COL1A1* and *THBS2*) were involved in extracellular matrix-receptor interactions. Both pathways were crucial in controlling cell motility, migration, proliferation and differentiation. In conclusion, the integrated analysis of genomic data from DNA methylation and gene expression profiling has enabled us to narrow down the list of significant genes and the key pathways that may contribute to breast carcinogenesis. These genes could serve as potential biomarkers and therapeutic targets for breast cancer.

KANDUNGAN

SENARAI JADUAL



SENARAI RAJAH

SENARAI LAMPIRAN

SENARAI SINGKATAN

ANOVA	Analysis of variance
bp	Pasangan bes
CpG	Cytosine/phosphate/Guanine
Ct	Cycle threshold
DNA	Deoksiribonukleik asid
EDTA	Ethylene diamine tetra acetic acid
et al.	dan pengarang-pengarang lain
g	Gram
GC	Guanine/Cytosine
IDC	Invasive ductal carcinoma
M	Molar
mL	Mililiter
Mw	Megawatt
PCR	Tindak balas rantaian polimerasi
PKB	Protein kinase B
A	ribonukleik asid
RRPA	Reverse phase protein array
Rpm	Revolutions per minute
SPIA	Single Primer Isothermal Amplification
TBE	Tris/Borate/EDTA
TpA	Thymine/phosphate/Guanine
TpG	Thymine/phosphate/Adenine
µl	Mikroliter
µm	Mikrometer
xg	Centrifugal force in gravities

BAB I

PENGENALAN

1.1 LATAR BELAKANG

Kanser payudara merupakan kanser yang paling kerap berlaku di kalangan wanita (Lim et al. 2008; Jemal et al. 2011). Kejadian kanser payudara semakin membimbangkan dan ia merupakan punca utama kematian di kalangan wanita (Jemal et al. 2011). Kajian terdahulu menunjukkan kanser payudara boleh disembuhkan jika dikesan pada peringkat awal (Boutayeb & Boutayeb 2005) dan cara yang paling berkesan untuk mengurangkan kadar kematian adalah melalui pengesanan awal (Moore et al. 2003).

Terdapat beberapa jenis kaedah saringan yang telah digunakan secara meluas untuk mengesan kanser payudara. Kaedah-kaedah ini termasuklah mamografi, pemeriksaan sendiri payudara dan pemeriksaan klinikal payudara. Walau bagaimanapun, kaedah saringan ini tidak berkesan untuk mengurangkan kadar kematian di kalangan pesakit kanser payudara (Hackshaw & Paul 2003; Weiss 2003; Gøtzsche et al. 2011). Oleh itu, penanda biologi seperti metilasi DNA telah digunakan untuk pengesanan awal.

Metilasi DNA merupakan salah satu fenomena yang berlaku pada peringkat awal kanser dan merupakan suatu proses yang berbalik (Das & Singal 2004; Mascolo et al. 2012). Ubat seperti *5 aza-2'-deoxycytidine* dapat digunakan untuk menterbalikkan proses metilasi di kawasan penggalak dan memulihkan pengekpresan gen yang disenyapkan oleh metilasi DNA (Qu et al. 2010). Kelebihan dan sifat-sifat yang ada pada metilasi DNA ini menyebabkan ia sesuai dijadikan sebagai sasaran

terapeutik dan penanda biologi bagi kanser payudara.

Metilasi DNA berlaku apabila satu kumpulan metil ditambahkan kepada kedudukan 5' sitosina cincin pirimidin (Jones 2005; Richards 2006). Secara ringkas, terdapat dua jenis gangguan metilasi iaitu hipermetilasi dan hipometilasi. Hipermetilasi pada penggalak telah dikaitkan dengan penurunan tahap ekspresi gen atau penyenyapan gen (Esteller 2008). Sebagai contoh, hipermetilasi pada penggalak *ARID1A* (*AT Rich Interactive Domain 1A*) telah mengakibatkan penyenyapan gen tanpa dijejaskan oleh variasi bilangan salinan DNA, mutasi dan pengubahsuaian pada histon (Zhang et al. 2013).

Selain itu, hipermetilasi juga melibatkan sebahagian besar kawasan pada kromosom yang seterusnya membawa kepada ***L**ong **R**ange **E**pigenetic **S**ilencing* (LRES) (Novak et al. 2008). Dalam LRES, metilasi pada gen tertentu akan menyebabkan gen-gen yang berdekatan dengannya menjadi senyap walaupun gen-gen tersebut tidak mengalami sebarang gangguan metilasi (Coolen et al. 2010). LRES yang berlaku dalam gen *HOXA* terletak pada kromosom 7 manakala untuk gen *PCDH* pula terletak pada kromosom 5 merupakan dua kluster gen spesifik yang ditemui dalam kanser payudara (Novak et al. 2006; Novak et al. 2008). Gangguan metilasi yang berlaku di pulau CpG bagi gen *HOXA1, HOXA5, HOXA7* dan *HOXA 9* mengakibatkan penyenyapan gen *HOXA1* hingga *HOXA10* manakala hipermetilasi pada pulau CpG bagi gen *PCDH* menyebabkan penurunan tahap ekspresi gen dalam kluster gen tersebut (Novak et al. 2006; Novak et al. 2008).

Hipometilasi sejagat juga telah dikenalpasti sebagai salah satu faktor yang menyumbang kepada kanser (Jones 2005). Hipometilasi sejagat biasanya berlaku pada elemen berulang-ulang seperti jujukan DNA satelit (Ehrlich 2002). Sebagai contoh, hipometilasi pada *SATR-1* yang melibatkan kehilangan kumpulan metil pada jujukan DNA satelit telah ditemui dalam kanser payudara (Costa et al. 2006). Kajian terdahulu menunjukkan bahawa hipometilasi *long range,* fokus hipermetilasi dan domain berkait lamina nukleus telah terlibat dalam penyenyapan gen dan memainkan peranan penting dalam kanser kolon (Berman et al. 2012). Keadaan ini berkemungkinan berlaku dalam kanser payudara.

Baru-baru ini, beberapa gen yang mengalami hipermetilasi telah dilaporkan sebagai penanda DNA yang berpotensi untuk kanser payudara, gen-gen ini termasuklah *TUSC5, DOK7, KLF11, SIM1, NT5E* dan *OTP* (Bubnov et al. 2012; Faryna et al. 2012; Kim et al. 2012; Lo Nigro et al. 2012; Heyn et al. 2013). Walau bagaimanapun, kebolehpercayaan, sensitiviti dan spesifisiti penanda biologi ini masih dipertikaikan.

Untuk lebih memahami peranan metilasi DNA dalam pengekpresan gen dan menerokai lanskap metilasi DNA dalam kanser payudara, data daripada mikroatur metilasi DNA telah diintegrasi dengan data daripada mikroatur pengekspresan gen. Ini bertujuan untuk mengenalpasti gen-gen yang berpotensi sebagai sasaran terapeutik dan penanda biologi untuk kanser payudara. Di samping itu, tapak jalan bagi gen-gen telah ditentukan untuk lebih memahami patofisiologi kanser payudara.

1.2 OBJEKTIF UMUM

Untuk menentukan gen-gen yang berkemungkinan terlibat di dalam patogenesis kanser payudara.

1.3 OBJEKTIF KHUSUS

1. Untuk menentukan profil metilasi DNA di dalam tisu kanser berbanding dengan tisu normal.
2. Untuk menentukan profil pengekspresan gen di dalam tisu kanser berbanding dengan tisu normal.
3. Untuk mengesah sahihkan keputusan mikroatur metilasi DNA.
4. Untuk menentukan hubungan di antara profil metilasi DNA dan pengekspresan gen.
5. Untuk menentukan tapak jalan yang terlibat di dalam kanser payudara.

1.4 HIPOTESIS

1. Hipermetilasi lebih kerap berlaku pada tisu kanser berbanding dengan tisu normal.
2. Tahap ekspresi gen penindas tumor adalah rendah pada tisu kanser berbanding dengan tisu normal manakala tahap ekspresi onkogen adalah tinggi pada tisu kanser berbanding dengan tisu normal.
3. Tahap metilasi yang tinggi pada promoter gen mengakibatkan ekspresi gen tersebut rendah.

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