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Differential Gene Expression Profile in Essential Hypertension

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1. Introduction

Essential hypertension affects 20-30% of the population worldwide and contributes significantly to mortality and morbidity[1] from cerebrovascular diseases, myocardial infarction, congestive heart failure and renal insufficiency. Essential hypertension is a prevalent disorder that leads to significant morbidity and mortality. Essential hypertension is defined as chronically elevated arterial pressure resulting from an unknown etiology. Intrinsically, it is a complex, heterogeneous, multifactorial syndrome to which environmental factors are partly responsible for. A lineup of aberrant environmental factors, including dietary salt intake[2,3,4], body weight[5,6], physical inactivity[7.8], physical stress[9.10], cigarette smoking [11-14], alcohol consumption[15-18] and inadequate potassium consumption[19,20] contribute to essential hypertension, possibly by infuriating genetically programmed susceptibilities. Results from twins, adoptive and population studies suggest high degree of similarity of blood pressure values, thus indicating the importance of genetic variables in essential hypertension etiology[21-25]. It is assumed that blood pressure is under the control of a large number of genes each of which has only relatively mild effects.

Despite progress in genomic and statistical tools, identification of genes involved in complex cardiovascular traits such as hypertension remains a major challenge. Several strategies have been developed so far. Of these approaches developed, gene expression techniques hold vast promises as functional roles of gene products are determined among diverse biological processes[26]. Gene expression profiling has become an overshadowing tool for discovery in medicine. Genes have additive function of working together; therefore expression levels of these groups of gene can be monitored through gene expression studies.

At present, differential gene expression between two sets of biological samples is carried out by utilizing techniques such as Northern blot analysis, serial analysis of gene expression (SAGE), differential display reverse transcription-PCR (DDRT-PCR) and Dot Blot analysis [26,27]. The drawback of these techniques is that large numbers of genes cannot be analyzed simultaneously. What's more, with Northern blot limited number of mRNAs may be examined simultaneously and quality and quantification of expression are negatively affected[28]. Although the strengths of SAGE are remarkable, extensive DNA sequencing is technically difficult and formidable. With DDRT-PCR, simultaneous discovery of multiple differences in gene expression is possible; however, screening is not based on identity but in

mRNA length[29]. Dot blot analysis is less time consuming, however, no information on the size of the target biomolecules is offered.

DNA microarray technology has the potential to overcome these limitations, as it has allowed unprecedented analysis of thousands of genes in a high-throughput form. On account of its high-throughput expression profiling, DNA microarray technology has become the predominant assay of choice in clinical medicine. This review, to a great extent looks at studies that used gene expression microarray technology in hypertension research to provide information on the disease specific risk profiles and pathology.

2. Methods

A literature search of the PUBMED database, using the medical headings "hypertension," "blood pressure," "gene expression," and" microarray analysis," will be conducted. The search will include published studies in human beings and as well as experimental models. Additionally, a search will be performed using references cited in original study articles and reviews and if copies of articles cannot be accessed, authors will be contacted.

2.1 Methods for the study of gene expression

Methods used to profile gene expression include Northern blot analysis, serial analysis of gene expression, differential display, dot blot analysis, subtractive hybridization and microarray hybridization.

2.2 Northern blot analysis

Although more sensitive gene expression techniques have emerged over the last decade, Northern blot analysis remains the standard for detection and quantitation of mRNA. Northern blotting has proven very effective in evaluating the expression levels of troponin c in chicken skeleton and cardiac muscles[30], arterial natriuretic factor mRNA and peptide in the human heart during development [31], myosin heavy chain and actin[32]. It is remarkable in that it allows a direct relative comparison of message abundance between samples on a single blot. Regrettably, this technique requires large quantities of RNA and is prone to significant experimental manipulation for each of the genes examined. Taniguchi et al compared Northern blotting analyses with DNA microarrays and discovered Northern blotting to be more sensitive and consistent than DNA microarrays[33]. Despite the fact large-scale transcriptome analysis experiments are not performable with Northern blotting, it is however, conveniently used in studies focused on analysis of small numbers of genes.

2.3 Serial analysis of gene expression (SAGE)

Serial analysis of gene expression method was recently discovered at John Hopkins University with the intention to create a global picture of cellular function. SAGE enables tagged short sequences of reverse transcribed cDNA to be prepared and identified by DNA sequencing[34]. The SAGE technique can be used to obtain large-scale cardiac gene expression[35,36]. Even supposing the quantitative and cumulative data this technique presents, one limitation is the identification of the genes reported by the SAGE.

2.4 Differential Display (DD)

Differential display was first introduced by Liang and Pardee in 1992[37]. This technique involves the identification and analysis of differentially expressed genes at the mRNA level. The basic principle of differential display is to use short primers in combination with oligo-dT primers to amplify and visualize mRNA in a cell. DD has been a powerful and successful method due to its inherent simplicity to detect changes in mRNA profiles among multiple samples without any prior knowledge of genomic information of the organism studied.

2.5 Dot blot analysis

Dot blot is an immunological technique and is a simplification of northern blotting, southern blotting, or western blotting methods[38,39]. This method identifies a known protein in a biological sample. Dot blot differs from western blotting in that protein samples are separated electrophoretically but are spotted through circular templates directly onto the membrane or paper substrate. The characteristic of dot blot is the use of immunodetection to identify a specific protein.

2.6 Subtractive hybridization

Subtractive hybridization is a powerful technique that was first described by Sargent and Dawid for creating cDNA libraries and generating probes of genes expressed differentially [40]. This technique is based on the principle that nucleic acid sequences in common with the two populations can form hybrids. It is the first tool used for identifying differentially expressed genes on a global scale. With Subtractive hybridization, the isolation of genes does not require prior knowledge of their sequence or identity.

2.7 Microarray hybridization

Microarray analysis, is a high through-put technique that provides an important tool to study the global patterns of gene expression. Two of the most commonly used microarrays for gene-expression measurements are oligonucleotide GeneChip expression arrays by Affymetrix and cDNA microarrays. Oligonucleotide microarrays contain sets of multiple 25 mer oligonucleotide probes specific for each gene or expressed-sequence tag (EST), whereas cDNA microarrays generally contain longer oligonucleotide probes (usually 25 to 60 bases) or cDNA probes (usually 500 to 1,000 bases) that stand for the specific gene, so cDNA microarrays are more commonly used. It permits quantitative analysis of RNAs transcribed from both known and unknown genes. Microarray analysis is based on the principle of complementary, single-stranded, nucleic acid sequences forming double-stranded hybrids. This technology can simultaneously measure the expression levels of thousands of genes within a particular mRNA sample in a high-through put manner[42,43].

2.8 Research objects

For the DNA microarrays, we could study human or animal models. The spontaneously hypertensive rats (SHR) are the most popular used animal models for essential hypertension, and the Lyon hypertensive rats[44] follows behind, compared to normotensive Wistar Kyoto rats (WKY).

2.9 Samples

We mainly use peripheral blood samples[45] in human and vascular smooth muscle cell (VSMC) [46,47], adrenal[44], heart[2,48,49] and kidney[2,44,53-56,58] in animal models.

2.10 Software tools

The large amount of information generated from microarrays has been a great strength, but is sometimes seen as a frustrating weakness because of the inability to process experimental data easily, assess the data quality, manage multiple data sets and mine the data with user-friendly tools. Most of the microarrays have the suite of software to deal with the results, such as the Affymetrix software for the Affymetrix microarrays. The related software is listed as follows. The software was not designed to do complex statistical analyses and visualization. Rather, it was designed to help the researcher narrow their search from tens of thousands of gene candidates to several hundred or fewer that meet specific, but adjustable criteria.

2.11 Altered gene expression in blood

Peripheral blood gene expression has the potential to provide information on underlying pathologic states. Several authors have used whole blood as a surrogate tissue for gene expression in patients with essential hypertension. In their study, Korkor et al identified 49 differentially expressed genes; 31 up regulated and 18 down regulated genes. Amongst genes found to be altered include CD36, SLC4A1, NET1, SESN3, ZNF652, PRDX6, HIP1, FOLR3, ERAP1, CFD[45]. Most of the genes that were differentially expressed were related to immune/inflammatory responses. In a study conducted by Chon et al, gene expression patterns of hypertensives revealed 680 genes that were upregulated as compared to patients who were normotensive on medication [52]. Timofeeva AV et al reported that 22 genes were up-regulated and 18 genes down-regulation in atherosclerotic aorta compared with normal vessel through cDNA microarray, among these, CD53, SPI1, FPRL2, SPP1, CTSD, ACP5, LCP1, CTSA and LIPA genes are up-regulated both in peripheral blood leukocytes from EH patients and in atherosclerotic lesions of human aorta. The majority of these genes significantly positively correlated with hypertension stage as well as with histological grading of atherosclerotic lesions[53].

2.12 Altered gene expression in the tissues and organs

Koo et al reported altered gene expression in the kidneys of adults of spontaneously hypertension rats[54]. Analyzing mRNA from 8-week-old female SHR and age-matched female WKY, 43 up-regulated and 31 down-regulated genes were revealed. The upregulation of stearoyl-COA desaturase-2 gene and downregulation of taurine/beta-alanine transporter gene in SHR compared with WKY rat were reported and in the SHR group, dysregulations of several genes involved in lipid metabolism was also revealed. Seubert et al investigated renal gene expression profiles in SHR and WKY animals at prehypertensiive (3 wk of age) and hypertensive (9 wk of age) stages and identified 22 genes at 3 wk of age and 104 genes at 9 wk of age that were differentially expressed in SHR compared with WKY[55]. There are some other studies identified differential gene expression in animal models of essential hypertension that are listed in table 2.

Results	References
49 genes were found differentially expressed in essential hypertension, 31 up regulated and 18 down regulated.	Korkor et al. (45)
680 genes were found differentially expressed in untreated hypertensives compared to normotensive controls. On the other hand, only 7 genes were differentially expressed in treated hypertensives compared to normotensive controls.	Chen et al. (52)
22 genes were up-regulated and 18 genes demonstrated down-regulation in atherosclerotic aorta compared with normal vessel, CD53, SPI1, FPRL2, SPP1, CTSD, ACP5, LCP1, CTSA and LIPA genes are up-regulated in peripheral blood leukocytes from EH patients and in atherosclerotic lesions of human aorta. The majority of these genes significantly ($p<0.005$) positively ($r>0.5$) correlated with AH stage as well as with histological grading of atherosclerotic lesions.	Timofeeva AV et al (53)

Table 1. Differential gene expression profiling in human blood in essential hypertension.

Animal model and the control group	Tissue	Microarray platform	Software	Observations	References
SDR, SHR and WKY	Area postrema	Rat Genechip 230 2.0 microarrys	GeneSpring GX11	'hypertension-related' elements revealed genes that are involved in the regulation of both blood pressure and immune function	Hindmarch CC et al. (46)
eET-1 and wild-type (WT) mice	mesenteric arteries	Ilumina microarray, validation by qPCR of 4 genes	Flexarray software for the microarray results, and Ingenuity Pathway Analysis for the gene lists.	increased endothelial ET-1 expression results in early changes in gene expression in the vascular wall that enhance lipid biosynthesis and accelerate progression of atherosclerosis.	Simeone SM et al. (47)
SHR and BNR for the control	Kidney	Affymetrix U34A-C microarrays, validation by RT-PCR, DNA sequencing and RFLP analyses.	Solexa Tag analysis	88 transcripts are identified to be differentially expressed between SHRs and BN rats.	Johnson MD et al. (2)

Animal model and the control group	Tissue	Microarray platform	Software	Observations	References
normal (normotensive) Wistar rats, DOCA–salt hypertensive (DH) rats, DH rats treated with AG1478, and DH rats treated with FPTIII	kidney	Codelink Uniset Rat 1Bioarrays	Affymetrix Scanner 428, Imagene and Genowiz softwares by Ocimum Biosolutions (India) and subjected to arsinh transformation	2398 genes were upregulated and only 50 genes were downregulated by more than 2-fold in hypertensive rat kidneys compared to non-diseased controls.	Benter IF et al. (44)
SHR	aorta	GeneChip® Affymetrix Rat Genome Rat Genome 230 2.0 Array	GeneChip®Operating Software Version 1.4, Affymetrix analyzer.	Thirty-nine genes that showed more than a 2-fold increase in expression after administration of VPP and IPP, Fourteen genes that showed less than a 0.5-fold decrease in expression	Yamaguchi N et al. (48)
SHR and WKY	brain, heart, kidney and liver	UniSet Rat I Expression Bioarray, validation by RT-PCR of 9 genes	F-test and unpaired t test. CodeLink Expression Analysis Software, GenePix Pro 6.0 Software, GeneSpring software	60 genes were differentially expressed in the heart of SHRSP rats. Of these, five genes were up-regulated and 55 genes were down-regulated.	Kato N et al. (51)
SHR, LHR, heterozygous TGR(mRen2)27 rat, and their respective controls	heart	Affymetrix GeneChip Rat Expression Array RAE230A, validation by qPCR of 6 genes.	Affymetrix Microarray Suite 5.0 software, significance analysis of microarrays (SAM) 1.21 software	Only four genes had significantly modified expression in the three hypertensive models among which a single gene, coding for sialyltransferase 7A, was consistently overexpressed	Cerutti C et al. (49)
WKY	Kidney and aorta.	Affymetrix rat genome 230A array, validation by RT-PCR	software R together with its bioinformatics packages collected in the Bioconductor project	Six functionally known genes (Igfbp1, Xdh, Sult1a1, Mawbp, Por, and Gstm1) and two expressed sequence tages (BI277460 and AI411345) were significantly upregulated	Westhoff TH et al. (56)

Animal model and the control group	Tissue	Microarray platform	Software	Observations	References
Female C57Bl/6J mice	Blood, heart and liver	Mouse NIH 15K cDNA microarrays	Expression Profiler tool EPCLUST	L-NNA and BSO both caused hypertension. Gene expression was regulated in cytoskeletal components in both models, protein synthesis in L-NNA-treated mice, and energy metabolism in BSO-treated mice.	Chon H et al. (41)
SHR and WKY	kidney	Affymetrix rat RG-U34A array	Normalisation and scaling using GeneChip suite.	20 genes were down-regulated and 7 genes were up-regulated in SHR	Hinojos CA et al. (50)
SHR and WKY	heart	Affymetrix Rat Genome U34A GeneChips	Affymetrix software, GeneSpring software	Comparison of LV RNA profiles from 20- and 12-month-old SHR identified 61 known genes and 20 ESTs, whose expression was upregulated >1.5-fold, and 31 known genes and 15 ESTs, whose expression was downregulated >1.5-fold.	Rysä J et al. (57)
Sabra rat	kidney	Affymetrix Rat Genome RAE230 GeneChip, validation by RT-PCR of 7 genes.	Affymetrix software	2470 transcripts were differentially expressed between the study groups. Cluster analysis identified genome-wide 192 genes that were relevant to salt-susceptibility and/or hypertension, 19 of which mapped to chromosome 1.	Yagil C et al. (58)
Nppa+/+ and *Nppa*−/- mice	Heart, Lung, kidney, brain, liver, and spleen	mouse microarray membranes (GeneFilter GF-400 membranes)	software package	Expression of 80 genes was elevated >2-fold and expression of 10 was reduced to <0.5 in 7-day TAC *Nppa*+/+ compared with control	Dajun Wang et al. (59)

Animal model and the control group	Tissue	Microarray platform	Software	Observations	References
SHR and WKY	Kidney, spleen, and liver	Affymetrix Rat U34 array set validation by qRT-PCR	Affymetrix MAS 5.0	There was a significant reduction in expression of glutathione S-transferase mu-type 2, a gene involved in the defense against oxidative stress	Martin W. McBride et al. (60)
SHR	kidney	Affymetrix Rat Genome U34A arrays	Software packge	Of the 8,799 known genes and expressed sequence tag (EST) clusters of Affymetrix Rat Genome U34A arrays, 74 differentially expressed transcripts, of which 43 were up-regulated and 31 were down-regulated in SHR.	Koo et al. (54)
SHR and WKY	kidney	cDNA Rat version 2.0 Chip, validation by Northern blot and RT-PCR	ArraySuite version 2.0	22 genes at 3 weeks of age and 104 genes at 9 weeks of age were differentially expressed in SHR compared with WKY in renal gene expression.	Seubert et al. (55)

SHR, spontaneously hypertensive rats. WKY, Wistar-Kyoto rats, usually used for the control the experimental group. WTR, wild-type rats. BNR, Brown Norway rats. LHR, Lyon hypertensive rats. SDR, Sprague-Dawley rats.

Table 2. Animals' microarray studies utilizing target organ tissue.

3. Summary and conclusions

Gene expression profiling provides a phenotypic resolution not feasible with standard clinical criteria. Differences in the gene expression profiles found in these studies identify markers useful for diagnostic, prognostic and therapeutic purposes. These findings emphasize the utility of whole blood and target organs as surrogate tissues for gene expression profiling. Gene expression profiling of different animal models of essential hypertension, and comparison of these profiles with human essential hypertension, will assist in determining the complex pathways that comprise the pathobiology of essential hypertension and help with the diagnostic, prognostic and therapeutic purposes in the future.

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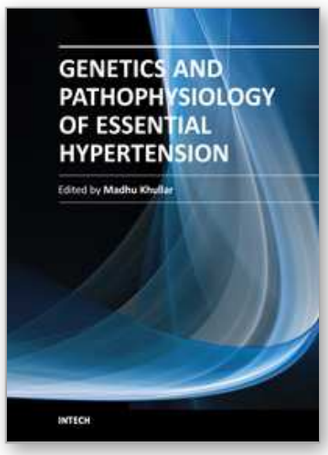

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This book, authored by renowned researchers in the field of Hypertension Research, details the state of the art knowledge in genetics, genomics and pathophysiology of Essential hypertension, specifically the genetic determinants of hypertension and role of gene variants in response to anti-hypertensive therapy. Two chapters describe mitochondrial mutations in Essential hypertension and in hypertension associated Left ventricular hypertrophy, one chapter reviews in detail the global gene expression in hypertension, and an up to date treatise on pathophysiology of resistant hypertension is detailed in another chapter. Other topics included in the book are end organ damage, baroreceptor sensitivity and role of music therapy in essential hypertension.

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