Global Gene Expression Profiling in the Failing Myocardium

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Heart failure (HF) is a syndrome that involves multiple cellular mechanisms leading to a common phenotype of reduced ventricular contraction and cardiac chamber dilation. To clarify the mechanisms, a number of microarray analyses of the failing myocardium have been conducted. Gene expression profiles are usually compared between opposing pairs of samples, such as non-failing vs failing hearts, ischemic vs non-ischemic hearts, male vs female failing hearts or atria vs ventricles of failing hearts. Apart from these conventional methods, a different novel approach identified cardiac myosin light chain kinase (MLCK) as a HF-related gene by the comprehensive search for the genes that had an expression level that strongly correlated with the severity of HF; further investigations proved the important role of cardiac MLCK in HF. Moreover, a robust gene expression signature composed of 27 genes was revealed on analysis of 4 independent microarray data sets from the failing myocardium of dilated cardiomyopathy. The authors newly demonstrate 107 HF-related genes that were listed in 2 or more of 7 microarray data sets previously reported. Among these genes, many were observed to be involved in mitochondrial dysfunction and oxidative phosphorylation and 3 extracellular molecules, including periostin, pleiotrophin, and SERPINA3, which might become novel diagnostic and therapeutic targets for HF. These novel strategies warrant the new identification of specific genes that are linked to the pathophysiology of HF. (Circ J 2009; 73: 1568–1576)

Key Words: Dilated cardiomyopathy; Genes; Genetics; Heart failure

Diverse Pathogenesis of Heart Failure (HF)

HF is a multifactorial syndrome that shows an increasing prevalence in Japan as well as other Western countries. It is increasing because of (1) the aging of society, (2) the increased prevalence of metabolic syndrome culminating in HF, and (3) the decreased hospital death rate of patients with acute myocardial infarction owing to the development of reperfusion therapy. Because HF has a high morbidity and mortality, its increased prevalence results in enormous economic and social affects. HF can be caused by a variety of cardiovascular diseases, including ischemic heart disease, valvular heart disease, hypertrophic cardiomyopathy, dilated cardiomyopathy (DCM), viral myocarditis, hypertension, anemia, hyperthyroidism, and diabetes. However, progressive HF features common symptoms and outcomes based on cardiac dilation and the reduced contractility of the ventricles.

The onset and progression of HF is closely associated with several molecular and cellular alterations, including abnormal calcium handling, neurohumoral activation, increased oxidative stress, and abnormal cytokine signaling. The molecules with most relevance for calcium handling are the ryanodine receptor, phospholamban, sarco-endoplasmic reticulum-type Ca\(^{2+}\)-ATPase, and the Na\(^{+}\)-Ca\(^{2+}\) exchanger. Activation of the sympathetic nervous system and the renin-angiotensin system exacerbates the pathophysiology of HF. This is the major reason that medications for HF include angiotensin-converting enzyme inhibitors, \(\beta\)-blockers, and treatment has advanced markedly over the past 20 years, and the prognosis of patients with HF has improved as a result. However, it is a fact that there are limitations on the benefits of medical therapy for patients with refractory end-stage HF. Patients with severe HF may need mechanical support, such as cardiac resynchronization therapy or a left ventricular assist device (LVAD), and finally heart transplantation may be the only option if the severity of HF does not improve or worsens. There is thus an urgent need to develop novel and revolutionary treatments for HF. To achieve this objective, we must understand the pathogenesis of HF in more detail and uncover novel mechanisms associated with this condition.

Approaches to New Findings in the Cardiovascular Field

There are various unknown, unresolved and essential factors in the cardiovascular field as well as in other fields. How will we be able to discover such important unknown factors in the field of HF? It seems to be difficult to do so based only on our current knowledge, because there are various unknown facts that are beyond our comprehension.

How do we discover a novel substance or mechanism? One possible approach to making new findings is to identify a novel substance related to a certain disease or a known substance with a novel function. There are 3 approaches to hunting for novel substances (Figure 1). The first classic approach is to search for a new protein or peptide by using column chromatography or a yeast 2-hybrid system.

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Recently, it has been made easier to identify the protein related to some diseases by the use of mass spectrometry. The second approach is to hunt for novel genes by genomic analysis. This approach was able to elucidate the etiology of familial hypertrophic cardiomyopathy. Mutations in cardiac genes in the cardiac myosin heavy chain genes can cause familial hypertrophic cardiomyopathy, and to date, more than 450 different mutations of 13 genes encoding cardiac structural proteins (β-myosin heavy chain, myosin-binding protein C, troponin T, and troponin I) have been identified in patients with hypertrophic cardiomyopathy.

The third approach is to find novel genes by evaluating gene expression with SAGE and differential display. The DNA microarray technique was developed in the 1990s for examining the expression level of many genes. The first report of a DNA microarray was published in 1995 and the technique became commercially available around the year 2000. This method of analysis has 3 major advantages. The first is that it is an easier and faster technique than protein purification or genomic analysis. The second advantage is that the expression of tens of thousands of genes can be analyzed simultaneously. The third advantage is the high reliability and reproducibility of the results and this is the most important advantage. Consequently, the number of studies using microarray analysis has increased rapidly (Figure 2).

**Microarray Analysis**

HF is not classified as a disease, but is a syndrome that involves multiple processes leading to a common phenotype of reduced ventricular contraction and cardiac chamber dilation. Changes in the expression of common genes should occur in relation to the development of HF. Both atrial natriuretic peptide (ANP; mainly secreted from the atria) and brain natriuretic peptide (BNP; mainly produced from the ventricle) are widely used in the clinical setting for the diagnosis and treatment of HF. Human ANP (carperitide) is frequently used for the treatment of acute HF in Japan. It was recently reported that infusion of human ANP reduced the infarct size and improved cardiac function in patients with acute myocardial infarction. BNP is used for the diagnosis of HF and for evaluating the severity of failure. It is also used in eastern countries as a drug for treating acute HF. These facts suggest that both ANP and...
BNP may be critical genes for HF and global gene expression analysis of the failing myocardium using a microarray has clarified that both genes were included in the cluster of genes that showed significant changes of expression. If ANP and BNP had been unknown genes, we could have cloned them as novel genes related to HF by performing microarray analysis of the failing myocardium. Thus global analysis of gene expression in failing myocardium seems to be a useful method of hunting for novel genes related to HF.

Microarray Analysis of the Failing Myocardium

A number of microarray analyses of failing myocardium have been conducted already and researchers have analyzed microarray data in various ways to search for genes associated with the pathogenesis of HF. They have usually compared gene expression between opposing pairs of samples, such as non-failing vs failing hearts, ischemic vs non-ischemic hearts, hypertrophic vs failing hearts, atria vs ventricles or male vs female failing hearts.

Gene Expression Profile of DCM

Yang et al performed microarray analysis of 4 human myocardial samples harvested from 2 patients without HF, 1 patient with DCM and 1 patient with ischemic cardiomyopathy (ICM) using the Affymetrix Hu6800 GeneChip microarray. They reported 12 genes with altered expression in both failing hearts compared with the normal hearts and 5 genes that were only detectable in the failing hearts. These genes were categorized into 5 clusters: (1) cytoskeletal and myofibrillar genes (FH1, MYOM1, MRCL3, and ACTB), (2) genes responsible for metabolism and disassembly of myocardial proteins (SERPINA3, UBB, and GSN), (3) genes involved in metabolism (ATP5A1, SDHA, AKR1B1, and TIMM17A), (4) genes related to protein synthesis (EEF2, EIF4A2, and NFE2L1), and (5) genes encoding stress proteins (CRYAB and CRYM). The researchers confirmed the levels of protein expression for FH1, SERPINA3, GSN, CRYAB, and UBB.

Barrans et al developed the CardioChip, a nonredundant 10,848-element expressed sequence cDNA microarray on a glass slide. They analyzed gene expression in the hearts of 7 patients with DCM undergoing transplantation and 5 non-failing hearts, finding 111 genes that were differentially expressed between the non-failing and failing hearts. ANP was the most markedly upregulated gene in the failing hearts (19-fold compared with non-failing hearts). They observed that genes encoding sarcomeric and cytoskeletal proteins (cardiac troponin, α- and β-actin, and tropomyosin) and stress proteins (heat shock protein 40 kd and 70 kd) were also upregulated. Genes involved in the regulation of transcription and translation (elongation initiation factor 1, elongation factor-1α, and elongation factor-2) were upregulated as well. Conversely, there was striking downregulation of genes involved in Ca2+ signaling and homeostasis (inositol 1,4,5-triphosphate receptor, sarco-endoplasmic reticulum Ca2+-ATPase3, and Ca2+/calmodulin-dependent protein kinase kinase 2).

When the microarray analysis is done, it is important to narrow down the candidate genes related to HF. Tan et al investigated the gene expression fingerprint of human HF using the Affymetrix HuFl 6800 GeneChip microarray. They selected 229 genes for which expression was significantly different between non-failing and failing myocardium. Next they chose 191 genes with a >1.7-fold change of expression, followed by 127 genes with a mean average difference >200. Finally, they selected 103 genes filtered on the basis of being present or marginally present. The upregulated genes with the most significant changes of expression between non-failing and failing hearts included periostin with a 12-fold change (12 FC), BNP (7.9 FC), type I collagen (4.9 FC), and ANP (4.2 FC), whereas the downregulated genes included phospholipid transfer protein (-35 FC), S100 calcium binding protein A9 (-13 FC), nuclear transport factor 2 (-7.8 FC), and phospholipase A2 (-5.1 FC). They divided the 103 genes into 10 clusters using GeneSpring software and identified novel pathways related to HF.

Yung et al used the Affymetrix HG-U133A GeneChip microarray to identify genes with statistically significant changes of expression in the ventricular myocardium harvested from 6 patients with DCM vs samples from 5 non-failing patients. In their study, the changes in ANP and BNP were not found to be statistically significant. They identified 165 genes with differential expression between non-failing and failing myocardium, including several apoptotic genes (AOP2, MAP1, and PLAGL1) and the plakin family of cytoskeletal linker proteins, which had not been reported before.

Grzeskowiak et al performed a large-scale expression screening study of cardiac biopsy specimens from 10 patients with DCM at various stages of the disease. They identified 364 nonredundant, differentially expressed genes among 30,336 cDNA clones. They observed strong activation of several enzymes implicated in lipid catabolism and fatty acid oxidation, indicating that a chronic switch of the cardiomyocyte energy processes towards lipid oxidation occurred in DCM. They also suggested that the balance between hypertrophic and apoptotic programs may determine whether or not ventricular dilation occurs in these patients. They speculated that the genes involved in intracellular signaling are linked to the early stage of DCM, whereas genes involved in muscle contraction are important at the middle stage, and genes for apoptosis and cell cycle regulation become prominent in the late stage. It is hoped that these results can be applied clinically for the diagnosis of DCM.

Colak et al used ABI high-density oligonucleotide microarrays containing 27,868 annotated genes to investigate differential gene expression in DCM. The ABI microarray platform they used allows analysis of more genes and has greater ability to detect rare mRNAs than most microarray platforms. They found 626 and 654 genes that were respectively upregulated and downregulated in the failing myocardium of patients with DCM compared with non-failing myocardium. They newly identified HTRA1 (6.9 FC), ODCD8 (5.2 FC), and PRDX2 (4.4 FC) among the upregulated genes, as well as NR4A2 (4.8 FC), MX1 (4.3 FC), LGALS9 (4 FC), IFNA13 (4.3 FC), UNC5D (3.6 FC), and HDAC2 (3 FC) among the downregulated genes, none of which had been previously reported as related to HF. They also found that the most significantly altered pathways were the TCA cycle, asparagine and aspartate biosynthesis, apoptotic signaling, Parkinson’s disease, cell cycle, and salvage pyrimidine ribonucleotide pathways among those related to the upregulated genes, as well as the TGF-β signaling, p53, apoptotic signaling, Ras, integrin signaling, and Alzheimer’s disease presenilin pathways among those related to the downregulated genes. Furthermore, they demonstrated undeciphered genes and pathways associated
with HF in patients with DCM using a different microarray platform.

These findings identified a number of genes that were differentially expressed in failing hearts compared with non-failing hearts. The lists of genes could help to identify new diagnostic and therapeutic strategies for HF. However, the HF-related gene clusters obtained in those studies do not fully overlap, so it remains unclear which genes are really associated with the pathogenesis of HF in patients with DCM and it will be necessary to perform further microarray analyses of the failing myocardium.

**Chamber-Specific Gene Expression**
Ellighaus et al analyzed gene expression in human left atrial and ventricular myocardium from 6 patients with HF undergoing heart transplantation and identified 125 genes that were differentially expressed between the left atrial and ventricular myocardium among 22,215 genes on the Affymetrix GeneChip HG-U133a microarray. They found that several potassium channels, including TWIK-1, TASK-1, and Kv1.5, were more highly expressed in the atrium than in the ventricle of HF patients, whereas they observed higher expression of potassium channel Kir2.1 in the ventricle than in the atrium. In recent investigations, the global gene expression profile of the atria has been generated using a microarray in patients with atrial fibrillation. Several genes, including those for ion channels, are known to be involved in the pathogenesis of atrial fibrillation. Barth et al found that the gene expression profile of the fibrillating atrial myocardium has a ventricular-like pattern. These findings imply that ion channels may represent novel therapeutic targets for cardiac arrhythmia and HF.

**Sex-Specific Gene Expression**
It is well known that the clinical presentation of DCM differs between men and women. Intriguingly, Haddad et al reported sex-differences in the gene expression profile of the failing myocardium. They found deregulation of genes involved in energy metabolism and regulation of those related to transcription and translation in the failing myocardium of female patients with DCM, whereas genes related to muscle contraction were deregulated in the failing myocardium of male patients.

**Changes in the Gene Expression in the Failing Myocardium After LVAD Support**
Mechanical support with a LVAD leads to regression of morphological and functional abnormalities in patients with cardiomyopathy. Microarray analysis has been performed on paired human myocardial samples harvested at the time of device implantation and removal. Hall et al revealed that 85 genes were upregulated and 22 genes were downregulated in response to mechanical unloading of failing hearts. This gene set included some of those involved in vascular signaling networks, such as neuropilin-1, FGFR9, CXCL12 (SDF-1), and endomucin.

Blaxall et al performed global gene expression analysis with the Affymetrix GeneChip HuGeneFL Array before and after LVAD support and found 295 upregulated genes and 235 downregulated genes among 6,800 genes following implantation of the device. Among the genes that were altered, microarray analysis revealed a high percentage of genes involved in metabolism. They also noted different changes in the gene expression profile among different patients treated with a LVAD. Much more extensive changes in gene expression were observed in patients with non-ICM than in patients with ICM.

Margulies et al performed a global transcription analysis of 199 human heart samples using the Affymetrix GenChip HG_U133 Array and observed 3,088 genes with expression that was significantly different between 113 failing hearts and 6 non-failing hearts. Interestingly, of these 3,088 genes, only 238 showed a consistent response to support with a LVAD. These findings indicate that cardiac function may be improved by mechanical support without widespread normalization of abnormal transcriptional changes, and also suggest that some of the genes with dysregulated expression because of HF play a limited role in the reverse remodeling of failing hearts.

Recently, Hall et al performed a microarray analysis of 6 paired human heart samples before and after a novel combination therapy of LVAD and a selective β2 agonist, clenbuterol. They found a significant association between recovery and the integrin signaling pathway, and identified several novel targets that included EPAC2, a guanine nucleotide exchange factor that binds to cAMP. These findings could assist with future investigations into the mechanism of reverse remodeling following support with a LVAD.

**Different Approach to Finding HF-Related Genes**
Most researchers have simply compared gene expression levels between samples of normal and failing myocardium. However, the severity of HF varies between patients, so we consider it important for the severity of HF to be taken into account when performing microarray analysis. We have therefore tried a novel way to identify new genes related to HF.

We collected cardiac tissue samples from 12 patients with severe HF who underwent the Batista or Dor operation. It should be noted that the severity of HF varied markedly because the serum BNP level ranged from 80 to 2,710 pg/ml. We then searched for genes showing expression that correlated with parameters of HF such as the pulmonary artery pressure and left ventricular ejection fraction (Figure 3). We subsequently selected the genes that were most highly expressed in cardiac tissue and of these, we identified cardiac-specific myosin light chain kinase (MLCK3) as a novel HF-related gene. Cardiac MLCK only
exists in the myocardium, whereas skeletal muscle MLCK only exists in skeletal muscle and smooth muscle MLCK is expressed ubiquitously. Cardiac MLCK phosphorylates myosin light-chain protein and plays a role in sarcomere assembly. Investigation of a zebrafish model revealed ventricular dilation and reduced contractility in MLCK3-knockdown fish. Thus, we succeeded in finding a novel HF related gene by using microarray analysis with a clinical parameter.

Meta-Analysis of Gene Expression Profiling Studies

A number of microarray analyses have been performed to determine the global gene expression profile of the failing myocardium from patients with DCM and these analyses have revealed a plethora of deregulated genes that are associated with HF. However, the gene sets detected by each microarray analysis of failing myocardium do not necessarily correspond. It is still unclear which genes have an important role in the pathogenesis of HF among the many deregulated genes that have been identified by previous global gene expression analyses of failing myocardium. To determine the genes that are important for HF, it seems to be necessary to re-arrange and integrate the gene sets identified by each analysis.

For example, Barth et al. revealed a robust gene expression signature of DCM based on analysis of 4 independent microarray data sets. They analyzed tissue samples from non-failing (n=20) and failing (n=20) human hearts using 2 different microarray platforms (RZPD Unigine 3.1 cDNA and Affymetrix U133A arrays). They detected 1353 upregulated genes and 384 downregulated genes in the failing myocardium using the Unigine cDNA array, whereas there were 399 upregulated genes and 75 downregulated genes identified by the Affymetrix array. Using both microarrays, 76 transcripts, including BNP and chemokine (C-C motif) ligand 2, were found to be consistently deregulated. Furthermore, they identified a robust set of 27 genes (Table 1).

Table 1. Gene Set in the Failing Myocardium of Patients With Dilated Cardiomyopathy

| Adipocyte enhancer binding protein 1 | Alanine-glyoxylate aminotransferase 2-like 1 | Asporin | Activating transcription factor 3 | Chemokine (C-C motif) ligand 2 | Complement factor H-related 3 | Corin | Connective tissue growth factor | Ets variant gene 5 | Ficolin 3 | Frizzled-related protein | Putative lymphocyte G0/G1 switch gene | Inhibitor of DNA binding 4 | Kelch-like 3 | Myosin, heavy polypeptide 6, cardiac, α | Myosin, heavy polypeptide 10, non-muscle | Natriuretic peptide precursor A | Natriuretic peptide precursor B | Ornithine decarboxylase 1 | Procollagen C-endopeptidase enhancer 2 | Pleckstrin homology-like domain, family A, member 1 | Retinoic acid receptor responder 1 | S100 calcium binding protein A8 | Secreted frizzled-related protein 4 | Synuclein, α | Sparc/osteonectin proteoglycan | Zinc finger and BTB domain containing 16 |

Meta-Analysis of Gene Expression Profiling Studies

| Table 2. Global Gene Expression Profiles of the Failing Myocardium of Patients With DCM

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Year published</th>
<th>No. of patients</th>
<th>Microarray platform</th>
<th>Total genes</th>
<th>Selected genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang J et al.</td>
<td>2000</td>
<td>2 NF vs 1ICM/1 DCM</td>
<td>Affymetrix Hu6800 (A-D) GeneChip</td>
<td>6,606</td>
<td>19</td>
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<tr>
<td>Barrans DJ et al.</td>
<td>2002</td>
<td>5 NF vs 7 DCM</td>
<td>CardioChip</td>
<td>10,848</td>
<td>111</td>
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<tr>
<td>Tan FL et al.</td>
<td>2002</td>
<td>7 NF vs 8 F</td>
<td>Affymetrix Hu6800 GeneChip</td>
<td>6,606</td>
<td>103</td>
</tr>
<tr>
<td>Yung CK et al.</td>
<td>2004</td>
<td>5 NF vs 6 DCM</td>
<td>Affymetrix GeneChip HG-U133A</td>
<td>22,283</td>
<td>165</td>
</tr>
<tr>
<td>Grzeskowiak R et al.</td>
<td>2003</td>
<td>4 NF vs 10 DCM</td>
<td>UniGene RZPD cDNA</td>
<td>30,336</td>
<td>364</td>
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<tr>
<td>Kittleson MM et al.</td>
<td>2004</td>
<td>6 NF vs 21 NICM</td>
<td>Affymetrix GeneChip HG-U133A</td>
<td>22,283</td>
<td>216</td>
</tr>
<tr>
<td>Colak D et al.</td>
<td>2009</td>
<td>4 NF vs 5 DCM</td>
<td>ABI high-density oligonucleotide</td>
<td>27,868</td>
<td>1,262</td>
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</tbody>
</table>

DCM, dilated cardiomyopathy; NF, non-failing; ICM, ischemic cardiomyopathy.
from their own 2 microarray data sets and 2 public data sets that was able to classify 108 myocardial samples into non-failing and failing samples with >90% accuracy. This molecular signature has the potential to be useful for the diagnosis of HF in patients with DCM.

Gene nomenclature is constantly changing with updating of the genomic database. Published microarray data sets that were obtained by evaluation of gene expression in the failing myocardium of patients with DCM tend to select approximately 1% of deregulated genes among all genes analyzed by the microarray, although the ABI-density oligonucleotide array found deregulation of approximately 5% of all genes. However, the designations of gene clusters published previously have shown considerable changes over time. We re-examined the designation of each gene associated with HF in lists that were obtained by 7 studies using microarray analysis of the failing myocardium in patients with DCM, and we searched for the genes that were present in at least 2 of the 7 different gene sets (Table 2). The gene encoding ANP was found in 4 of the 7 gene sets; 15 other genes (ACTB, ACTC1, ACTN2, ATP2A2, ATP5A1, CRYAB, CRYM, HMGN2, NDUFB5, POSTN, PTN, SERPINA3, TCF4, TP1, UBB) were found in 3 of the 7 gene sets, and 91 genes (including NPPB, CXCL12, MYOM1, and TXNIP) were found in 2 of the 7 sets (Table 3). It is thought that the genes included in multiple lists are more likely to have a stronger association with the pathogenesis of DCM. ANP was listed in 4 gene sets and is widely accepted as linked with HF. Among the 15 genes found in 3 of 7 gene sets, there were several involved in cell structure regulation (including ACTB, ACTC1, and CRYM) and cell growth (including POSTN and PTN). Among the 91 genes observed in 2 of 7 gene sets, we detected some that are involved in oxidative phosphorylation and mitochondrial dysfunction, including ATP5B, ATB5H, ATP6V1D, COX6B1, COX7A2, CYC1, CYP2J2, DCN, DMD, DST, DZIP3, EIF4A2, ETV1, FABP3, FBXO3, FCN3, FHL1, FN1, FOS, FRZB, GATM, GI1A, HMGCL, HTRA1, IMMT, LMNA, LUM, MDH2, MRPS5, MSI2, MT1X, MYOM1, NBN, NCOA2, NDUFA10, NDUFB1, NDUFB2, NPPB, NR2F2, NR3C1, ODC1, PCCB, PDE7A, PHKB, PIK3R1, PI3CL1, PLCE1, PNN, POPDC2, PRDX2, PSD3, PTCD3, PTGDS, RABGAP1, RGS2, RPS16, RPS28, SDHA, SFRS7, SLC25A11, SMARCA2, SORBS2, STARD7, STAT1, SULCL1, TAF6L, TGER1L, TIA1, TNN3, TXNIP, VARS, WEE1.

Table 3. Genes Identified in at Least 2 of 7 Gene Sets From Previous Microarray Analyses

<table>
<thead>
<tr>
<th>Category</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 gene in 4 of 7 gene sets</td>
<td>NPPA</td>
</tr>
<tr>
<td>15 genes in 3 of 7 gene sets</td>
<td>ACTB, ACTC1, ACTN2, ATP2A2, ATP5A1, CRYAB, CRYM, HMGN2, NDUFB5, POSTN, PTN, SERPINA3, TCF4, TP1, UBB</td>
</tr>
<tr>
<td>91 genes in 2 of 7 gene sets</td>
<td>ACAP2, ACSL3, AK3, ANXA4, APP, ASMTL, ATF4, ATP5B, ATP5H, ATP5O, ATP6V1D, C6, CALU, CCND1, CDKN1B, CKB, COL1A1, COL3A1, COX6B1, COX7A2, CS, CXCL12, CYC1, CYP2J2, DCN, DMD, DST, DZIP3, EIF4A2, ETV1, FABP3, FBXO3, FCN3, FHL1, FN1, FOS, FRZB, GATM, GI1A, HMGCL, HTRA1, IMMT, LMNA, LUM, MDH2, MRPS5, MSI2, MT1X, MYOM1, NBN, NCOA2, NDUFA10, NDUFB1, NDUFB2, NPPB, NR2F2, NR3C1, ODC1, PCCB, PDE7A, PHKB, PIK3R1, PI3CL1, PLCE1, PNN, POPDC2, PRDX2, PSD3, PTCD3, PTGDS, RABGAP1, RGS2, RPS16, RPS28, SDHA, SFRS7, SLC25A11, SMARCA2, SORBS2, STARD7, STAT1, SULCL1, TAF6L, TGER1L, TIA1, TNN3, TXNIP, VARS, WEE1</td>
</tr>
</tbody>
</table>
NDUFAB1, NDUFB2, and SDHA (Figure 4). Among the products of these genes, extracellular molecules have more potential for use in the diagnosis of HF. Among the 16 genes listed in 3 or 4 gene sets, we found a network with a role in lipid metabolism, molecular transport, and small molecule biochemistry by using ingenuity pathway analysis software: 13 genes were part of this network linked to the oncprotein p53, follicle stimulating hormone, and ERK (Figure 5). We also demonstrated the deregulation of 4 extracellular molecules (NPPA, POSTN, PTN, and SERPINA3) in the failing myocardium from patients with DCM. NPPA (ANP) has already been used clinically for the diagnosis and treatment of HF.

POSTN (peristin) is a molecule that has received considerable attention in recent years. It is a secreted protein that is not detectable in the normal adult ventricular myocardiun, but is expressed in the myocardium following events such as myocardial infarction and HF. Mice with mutant peristin show increased susceptibility to cardiac rupture after myocardial infarction. Moreover, peristin has been suggested to possibly induce reentry of differentiated cardiomyocytes into the cell cycle. Because peristin has been proposed as a regulator of cardiac remodeling, it might be a marker for diagnosis of the severity of HF, and especially for diagnosis of the severity of cardiac fibrosis. Peristin might also be a therapeutic target for HF. PTN (pleiotrophin) is a growth factor that seems to be a possible molecule for the diagnosis of HF. Pleiotrophin is also reported to increase apoptosis of cardiomyocytes. SERPINA3 (serpin peptidase inhibitor, clade A (a-1 anti- protease, antitrypsin), member 3) is a protease inhibitor and may be potential pharmacological target for treating HF.

Conclusions

Global gene expression analysis of the failing myocardium using several microarray platforms has continued for 10 years and a variety of gene sets have been clarified. These gene sets do not overlap completely because of diversity in the severity of HF and microarray platforms. In this review, we newly demonstrate 107 genes related to HF that are listed in 2 or more of 7 gene sets previously reported. This new gene set contains many genes involved in mitochondrial dysfunction and oxidative phosphorylation. We also found 3 extracellular molecules, POSTN, PTN, and SERPINA3, and it is possible that these molecules might become diagnostic and therapeutic targets for HF.

References


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