

Pathogenesis of Axial Spondyloarthritis in a Network Perspective

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Abstract—Complex chronic diseases are usually not caused by changes in a single causal gene but by an unbalanced regulating network resulting from the dysfunctions of multiple genes or their products. Therefore, network based systems approach can be helpful for the identification of candidate genes related to complex diseases and their relationships. The Axial spondyloarthritis (SpA) is a group of chronic inflammatory joint diseases that mainly affects the spine and the sacroiliac joints, yet, the pathogenesis of SpA remains largely unknown. In this paper, we conducted a networked systems study on the pathogenesis of SpA. We integrated data related to SpA, from the OMIM database, proteomics and microarray experiments of SpA, to prioritize SpA candidate disease genes in the context of human protein interactome. Based on the top ranked SpA related genes, we constructed a PPI network and identified potential pathways associated with SpA. The PPI network and pathways reflect the well-known knowledge of SpA, i.e., immune mediated inflammation, as well as imbalanced bone modeling caused new bone formation and bone loss. This study may facilitate our understanding of the SpA pathogenesis from the perspective of network systems.

Keywords- spondyloarthritis, disease gene, protein-protein interaction network, pathway, microarray expression, proteomics

I. INTRODUCTION

Axial spondyloarthritis (SpA) is a family of chronic inflammatory joint diseases of the spine and the sacroiliac joints, and ankylosing spondylitis (AS) is one of the major prototypes of SpA. The two central features of SpA are inflammation and new bone formation, especially in the spine [1]. Inflammation first occurs around the sites where ligaments attach to bone. As the inflammation heals, there is new bone formation in the ligament, causing the thickening or hardening of the underlying bone, and eventually the fusion of the vertebral bodies and even the spinal stiffness. It is known that SpA is associated with multiple genes, such as HLA-B27, TNF and IL23R [2].

However, the pathogenesis of SpA remains largely unknown. The complexity of the disorder indicates a multifactorial etiology involving multiple biological processes or pathways. In this work, we integrated SpA-associated genes from different resources (known disease genes in the OMIM database, proteomic and microarray experiments) and proposed an approach to prioritize candidate genes in the context of human interactome. We then took out the genes most likely associated with SpA to construct a protein-protein interaction (PPI) network of SpA and identified potential pathways involved in SpA. The PPI network and pathways could facilitate our understanding of the pathogenesis of SpA.

II. MATERIALS AND METHODS

A. Collection of SpA-active genes

We collected genes active in SpA from three resources as follows:

- (1) the Online Mendelian Inheritance in Man (OMIM) database [3]: we searched the OMIM database with a keyword “Spondyloarthritis” and found 8 causal genes: HLA-B, TNFA, IL23R, CYP2D6, TNFSF13, TNFSF13B, B2M and COL2A1.
- (2) Proteomic experiment results: quantitative proteomics approaches were applied to investigate changes in protein expression in AS (the most common prototype of SpA) monocytes in comparison with healthy controls [4]. We used the 43 genes whose encoded proteins were differentially expressed [4] as active genes in SpA.
- (3) The NCBI Gene Expression Omnibus (GEO) database: we searched the GEO database and found two microarray experiments related to SpA: GSE1402 (Affymetrix U95Av2) and GSE18781(Affymetrix HG_U133_Plus2). The GSE1402 experiment included a comparison of peripheral blood mononuclear cells (PBMC) from

juvenile SpA with that of normal individuals, and the GSE18781 experiment was an investigation of peripheral blood cells from 18 subjects with SpA and 25 normal individuals. Samples in the GSE18781 experiment were proceeded as two separate sets at different times: 11 SpA + 12 control subjects in Set 1 and 7 SpA + 13 control subjects in Set 2. We treated the results of these two experiments as three separate datasets.

To integrate gene expression data from the two different platforms, we mapped the probe sets of the platforms to Entrez Gene ID. This process yielded a set of 9448 genes common to the two platforms. For each gene in a dataset, we calculated the average expression level for probe sets associated to this gene, and filtered out genes whose mean expression ratios (SpA over control) in the two samples are greater than .67 (1/1.5) and less than 1.5. In the next step, we converted the expression value to its rank in the common genes [5]. Thereafter, a nonparametric two sample test, the Wilcoxon rank-sum test, was used to test if a gene is differentially expressed in the SpA and control samples and the p-value of the Wilcoxon rank-sum test was obtained. For such a large number of genes being simultaneously tested, the FDR [6] corrected p-values were used for screening differentially expressed genes. Given FDR level of 0.10, we found genes that are differentially expresses in the two samples for each of the three datasets. We then combined differentially expressed genes in the three datasets and identified 119 distinct genes potentially active in SpA. Finally, the combination of genes from the three recourses yielded a total of 168 SpA-active genes. These 168 potentially SpA-active genes were used in a subsequent analysis (see Section III A).

B. Protein-protein interaction data

Weighted protein-protein interactions (PPI) of human beings were downloaded from version 8.3 of STRING [7]. STRING includes both physical and functional interactions integrated from numerous sources, including experimental repositories, computational prediction methods and public text collections; uses a scoring system to weigh the evidence of each interaction; and includes the interactions between 14532 proteins (Entrez gene ID) of human genome. We normalized the interaction scores in STRING to the area [0, 1] and represented the weighted PPI network as a matrix \mathbf{W} .

Innate immunity-relevant human proteins and their interactions were downloaded from the InnateDB database [8] on April 25, 2011. Till the day we downloaded the data, this database includes 2310 human genes and 4819 interactions manually collected by literature review.

C. Pathway data

We downloaded pathway data from the FTP service of KEGG [9] (Kyoto Encyclopedia of Genes and Genomes) on April 11, 2011. The KEGG PATHWAY section is a collection of manually drawn pathway maps representing the information on the molecular interaction and reaction networks. The "hsa_pathway.list" file in this section includes a list of known proteins encoded by *H. sapiens*'s genome and the corresponding pathways in which these proteins are involved.

D. Scoring and ranking genes

Having a group of SpA-active genes as seeds, we developed a Katz' centrality based index [10] to prioritize genes in the protein-protein interaction network. The starting point from the derivation is the observation that disease genes are typically close, in the associated protein network, to other disease genes [11-13]. Given a weighted human interactome represented as a matrix \mathbf{W} corresponding to the interaction strength between genes, and a set D of k known disease-active genes as seeds, we define vector $\mathbf{x} = (x_1, x_2, \dots, x_n)^T$ as initially known activity of genes in the disease, with $x_i=1$ if gene i is in the set D , $x_i=0$ otherwise. It should be noted that our SpA-active gene set is a combination of OMIM, proteomics and microarray data, each of which actually has different confidence level for the study of disease pathogenesis. A good way is to set different weights for them. But determining the value of each weight makes the solution much more difficult. For simplicity, we just give them the same weight.

Let $\mathbf{s} = (s_1, s_2, \dots, s_n)^T$ be our score vector over the set of genes (where s_i indicates how strong i is as a disease-gene candidate),

$$s_i^{t+1} = x_i + \phi \sum_j w_{ij} s_j^t \quad (1)$$

where t indicates iteration time, and ϕ is a parameter that sets the relative contributions of the activity \mathbf{x} and links in protein interaction networks \mathbf{W} to the score. If ϕ is small, the known activity is more important; if ϕ is large, the coupling to the protein neighbors is more important. ϕ needs to be calibrated with real data. The score could be obtained by performing the iteration until the algorithm converges, and then all genes in the protein-protein interaction network could be ranked according to their s -scores.

Equation (1) can be represented as matrix form as follows:

$$\mathbf{s} = \mathbf{x} + \phi \mathbf{W} \mathbf{s} \quad (2)$$

which can be solved by matrix algebra:

$$\mathbf{s} = [\mathbf{I} - \phi \mathbf{W}]^{-1} \mathbf{x} \quad (3)$$

where $[\mathbf{I} - \phi \mathbf{W}]^{-1}$ represents the inverse of the matrix $\mathbf{I} - \phi \mathbf{W}$. We solved (3) by Jacobi iteration algorithm.

The known k disease-active genes were used to determine the parameter. For different values of ϕ , we performed leave-one-out cross-validation on the known disease-active gene set D . Then ϕ was taken as the value that resulted in the highest average rank of known disease genes.

E. k -core and k -core layer

The k -core of a graph is the maximal subgraph such that all its nodes has at least k links within the subgraph [14, 15]. The k -core layer l_k is defined as the set of nodes that belong to

k -core but not to $k+1$ -core, i.e., k -core is the union of $k+1$ -core and k -core layer. A k -core subgraph of a graph can be generated by recursively deleting the vertices from the graph whose present degree is less than k . This process can be iterated to gradually zoom into the more connected parts of the network. The higher-level core corresponds to more densely connected part of the network. See Fig. 1 for an explanation.

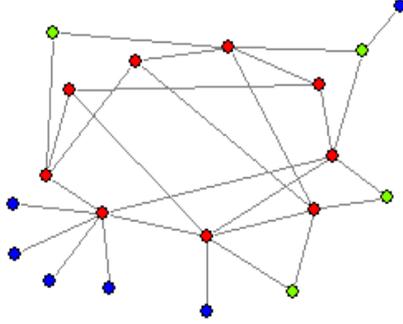


Figure 1. Illustration of k -core and k -core layer. The 1-core layer are the blue nodes, the 2-core layer are green. The 1-core is the whole graph, the 2-core is subgraph consisting of green and red nodes and the 3-core is the subgraph consisting of red nodes.

F. P-value

If we randomly draw n samples from a finite set, the probability of getting i samples with the desired feature by chance obeys the hypergeometric distribution with the following probability mass function:

$$f(i) = \frac{\binom{K}{i} \binom{N-K}{n-i}}{\binom{N}{n}} \quad (4)$$

where N is the size of the set, K is the number of items with the desired feature in the set. Then the probability, defined as the P-value, of getting at least k samples with the desired feature by chance can be obtained as the following, using the hypergeometric cumulative distribution function (CDF),

$$P = 1 - \sum_{i=0}^{k-1} f(i) = 1 - \sum_{i=0}^{k-1} \frac{\binom{K}{i} \binom{N-K}{n-i}}{\binom{N}{n}} \quad (5)$$

Given a significance level α , a P-value smaller than α demonstrates a low probability that the items with the desired feature are chosen by chance. Hence this P-value can be used to measure whether the n samples drawn from the set is more enriched with items of the desired feature than would be expected by chance [16].

III. RESULTS AND DISCUSSION

A. Ranking genes in the PPI network

We integrated OMIM data with the results of the proteomics and microarray experiments and obtained 168 genes potentially active in the axial spondyloarthritis disease. A total of 128 of the 168 genes were found present in the STRING PPI network, and these genes were used as seeds to construct the disease gene activity vector \mathbf{x} in (3). For all the genes in the PPI network, we calculated the s -score vector by (3) and ranked the genes accordingly. We first determined the parameter ϕ by leave-one-out cross-validation. Specifically, applying different values of ϕ in the area (0, 1/100), we successively took out one disease active gene and used the left genes as input to rank this one and checked the average ranks of all the seed genes. In this way, ϕ was taken as 5/1000, which resulted in the highest average rank 4272 of seed genes. Then we set ϕ as 5/1000 and scored all the genes in the human PPI network according to (3).

B. PPI network of SpA

The s -score of a gene indicates its possibility associated with the disease. Setting 10% as a cut-off, we took out the genes whose s -scores were top 10% of all genes in the PPI network. We identified a total of 379 genes. Then we limited interactions in the STRING database to weights of at least 0.5, which corresponds to a medium-confidence human genome PPI network [7], and constructed a subnetwork spanned by these 379 genes. Finally, we obtained a PPI network associated with SpA, which included 367 nodes and 10906 edges.

Including 10906 interactions with strength at least 0.5 between only 367 gene-coded proteins, the PPI network of SpA is densely connected. To understand its topology, we conducted k -core decomposition on the network. A so-called k -core decomposition is a way to visualize both of the connectivity of neighborhoods of nodes and their centrality [15]. In short, a k -core decomposition is obtained by iteratively deleting low-degree nodes to achieve a sequence of k -cores (maximal subgraphs with minimal degree k , see the Methods section). By and large, following the k -core decomposition is similar to zooming into the more central and more interconnected parts of the network. For the PPI network we studied, the innermost core is the 45-core, which includes 197 nodes. In Fig. 2, we illustrate the node distribution in the hierarchical k -core layers of the PPI network and the number of seed genes in the core layers. This figure suggests that the network topology exhibits a core-periphery dichotomy [17, 18] - about two thirds of nodes in this network interact frequently and are thus interconnected densely to form an inner 41-core, while others communicate with fewer nodes and scatter in different outer core layers to form the periphery of the network. Fig.2 also shows that most seed genes locate at the periphery part whereas the inner core includes most of the non-seed genes. Specifically, a total of 116 seed genes appear in this network, in which only 14 are located in the inner core. All nodes in the core layers 1~20 and about half nodes in the core layers 21~40 are seed nodes. Therefore, as shown in

Fig.3, we partition the network into three parts accordingly—the inner core is the 41-core, and the medium and outer layers correspond to core layers 21~40 and 1~20, respectively. It can be seen that seed genes in the outer and medium layers tend to interact with genes in the inner core, indicating that the inner core could be the modulating center of the network.

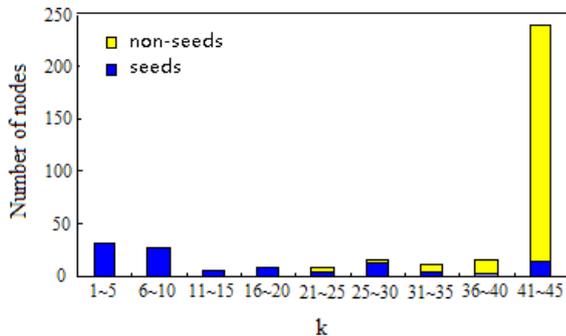


Figure 2. Distribution of k -core layers and seed nodes in the SpA PPI network.

Furthermore, we searched the DrugBank database [19] for drugs treating SpA and their protein targets. We mapped the protein targets onto the SpA PPI network and found 6 targets in this network, *i.e.*, PTGS2, MMP2, MAPK3, HRAS, EGF and ALB. They are drug targets for the two main classes of AS drugs [1]: non-steroidal anti-inflammatory drug such as Aspirin, Celecoxib and Sulindac; and disease-modifying antirheumatic drug such as Thalidomide and Methotrexate. As shown in Fig.3, five of the six targets are located in the inner core of the SpA PPI network, and only ALB situates at the medium layer, suggesting that the drugs may interfere with the disease by acting on proteins in the core.

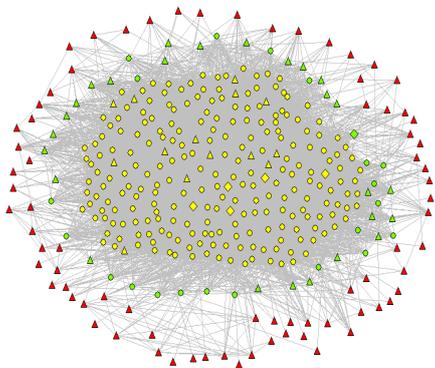


Figure 3. Core-periphery topology of the SpA PPI network. Yellow, green and red nodes represent the inner core, the medium and outer core layer, respectively. Triangles are seed genes, and diamonds are targets of drugs for SpA.

To explore the implications of this PPI network to SpA, we conducted gene ontology (GO) analysis. We used the P-value to quantitatively measure whether this PPI network is statistically significantly enriched with genes of a specific Gene ontology (GO) term. In Table I we listed the most

significantly enriched GO terms presented in the network, with p -values smaller than 10^{-40} . It can be seen that proteins in this network are significantly involved in biological processes of immune system, such as the regulation of granulocyte macrophage, natural killer cell proliferation, as well as the activation of leukocytes, lymphocytes and T cells, in consistent with the immune-mediated feature of SpA.

TABLE I. SELECTION OF THE MOST SIGNIFICANTLY ENRICHED GO TERMS IN THE SPA PPI NETWORK

GO ID	GO Term	Total genes	Mapped genes
0032725	positive regulation of granulocyte macrophage colony-stimulating factor production	5	5
0032819	positive regulation of natural killer cell proliferation	6	6
0002376	immune system process	1429	124
0006950	response to stress	2520	155
0051716	cellular response to stimulus	3999	186
0010941	regulation of cell death	1034	99
0042127	regulation of cell proliferation	939	92
0002694	regulation of leukocyte activation	288	53
0051249	regulation of lymphocyte activation	261	51
0050863	regulation of T cell activation	207	46

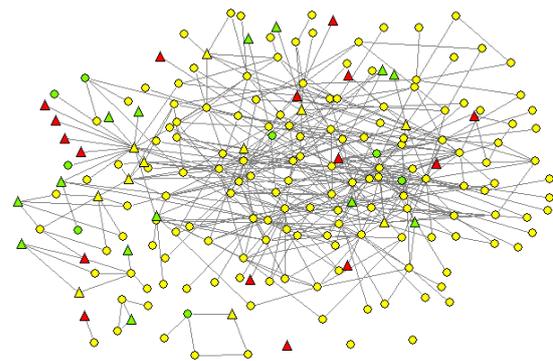


Figure 4. A subnetwork of the SpA PPI network involved in innate immune response. Yellow, green and red nodes represent the inner core, the medium and outer core layer of the SpA PPI network in Fig.3, respectively. Triangles are seed genes in Fig. 3.

The immune system process protects human beings against diseases with increasing specificity. The innate immune system provides an immediate, but non-specific response to invading pathogens; and the adaptive immune system, which is activated by the innate response in case that pathogens successfully evade the innate response, adapts its response to improve its recognition of the pathogen. The innate immune response is important in the initiation of and interplay with the adaptive immune response. To investigate the association between the innate immune response and SpA, we constructed a subnetwork of the SpA PPI network involved in the innate immune response, by mapping proteins of the SpA network onto the PPI network of human innate immune response constructed from the InnateDB database (see Fig.4). This subnetwork includes more than half nodes of the SpA network, suggesting that the dysfunction of the innate immune system could be associated with the development of SpA. As can be seen in Fig.4, the innate immune subnetwork is significantly

enriched with core nodes and non-seed nodes of the SpA PPI network (p-values are 7.01×10^{-12} and 2.14×10^{-7} , respectively). This observation indicates that a very large fraction of proteins identified by our algorithm (non-seed nodes) are involved in the innate immune response, suggesting that in the human genome PPI network, the known SpA active proteins (seed nodes in our study) are close to a common group of innate immune proteins. Thus our approach reveals the important role of innate immune system in the initiation and development of SpA.

C. Pathways associated with SpA

To identify SpA-relevant biological processes, we mapped the 379 SpA associated genes onto the KEGG and Biocarta pathways, respectively. Given significance level $\alpha = 0.05$, we found that a total of 27 KEGG pathways are significantly enriched with genes in this group (see Table II). Similar pathways in the Biocarta database are also enriched with SpA associated genes. In Table III we just list four SpA gene enriched pathways included in the Biocarta database but not in the KEGG database.

A central feature of SpA is inflammation, one of the first responses of the immune system to infection or irritation. As listed in Table II, SpA is related to a large fraction of pathways in immune system. Some other pathways, although not classified into immune system in the KEGG database, have been known to be highly associated with the function of immune response, such as apoptosis [20], MAPK signaling pathway [21], and cell adhesion molecule interactions [22]. Specifically, Table II includes several pathways related to pathogen recognition and inflammatory signalling in innate immune defences, in which the most important one is the Toll-like receptor (TLR) signalling pathway. The innate immune system relies on pattern recognition receptors (PRRs) to detect distinct pathogen-associated molecular patterns (PAMPs). Upon PAMP recognition, PRRs trigger a number of different signal transduction pathways. The pathways induced by PRRs ultimately result in the expression of a variety of proinflammatory molecules, such as cytokines, chemokines, cell adhesion molecules, and immunoreceptors, which together orchestrate the early host response to infection, mediate the inflammatory response, and also bridge the adaptive immune response [22] together. The family of TLRs is the major class of PRRs [22]. The association of TLR2 and TLR4 with SpA has been reported [23]. It was noticed that three major signalling pathways are responsible for mediating TLR-induced responses including NF- κ B, mitogen-activated protein kinases (MAPKs), and IFN regulatory factors (IRFs) [22], while we found that the two pathways, MAPKs and NF- κ B, which play central roles in induction of a proinflammatory response, are involved in SpA. Tumor necrosis factor α (TNF α) is an important upstream protein of the NF- κ B pathway, which binds to its receptor to recruit TNF receptor death domain (TRADD) and thus activates NF- κ B. TNF inhibitors have been proven highly effective for the treatment of SpA [1]. In addition, we also found that SpA is associated with some proinflammatory molecule involved pathways, such as the chemokine signaling pathway, natural killer cell mediated cytotoxicity, Fc epsilon RI signaling pathway, and cell adhesion molecules interaction. These

pathways indicate the process of innate immune response in the progress of SpA. On the other hand, it is known that B and T lymphocytes are responsible for the adaptive immune response [24]. Table II shows the association of B and T cell receptor signalling pathways with SpA, implying their function in the adaptive immune response in SpA. In fact, it has been known that both the innate and adaptive immune responses are involved and interdependent with each other in SpA [25].

TABLE II. KEGG PATHWAYS SIGNIFICANTLY ENRICHED WITH SPA-ASSOCIATED GENES.

Pathway class	Pathway name	Total genes	Mapped genes
Cell Communication	Focal adhesion	206	57
	Adherens junction	80	25
	Gap junction	93	18
Cell Growth and Death	Apoptosis	89	30
	p53 signaling pathway	69	16
	Cell cycle	119	20
Cell Motility	Regulation of actin cytoskeleton	219	45
Endocrine System	Insulin signaling pathway	138	35
	Adipocytokine signaling pathway	67	20
	GnRH signaling pathway	108	23
	Melanogenesis	105	16
Immune System	Chemokine signaling pathway	198	60
	T cell receptor signaling pathway	110	47
	B cell receptor signaling pathway	75	31
	Leukocyte transendothelial migration	122	37
	Fc epsilon RI signaling pathway	79	34
	Natural killer cell mediated cytotoxicity	138	43
	Toll-like receptor signaling pathway	102	44
	Hematopoietic cell lineage	88	33
	Jak-STAT signaling pathway	155	51
Signal Transduction	VEGF signaling pathway	77	27
	ErbB signaling pathway	87	37
	TGF-beta signaling pathway	87	18
	MAPK signaling pathway	276	57
	Wnt signaling pathway	152	18
Signaling Molecules and Interaction	Cell adhesion molecules (CAMs)	136	20
	Cytokine-cytokine receptor interaction	263	69

Another prominent feature of SpA is new bone formation; meanwhile bone loss is also a common finding in SpA [26]. As can be seen in Table III, SpA is associated with bone remodeling, a process that maintains bone density and structure through a balance of bone resorption by osteoclasts and bone deposition by osteoblasts. Both ossification and osteoporosis symptoms of SpA are consequences of an imbalance in the regulation of these two sub-processes of bone remodelling. It is known that the WNT pathway regulates the balance between osteoclast and osteoblast function [27], verifying our result that SpA is associated with the WNT pathway (see Table II).

TABLE III. SELECTION OF BIOCARTA PATHWAYS SIGNIFICANTLY ENRICHED WITH SPA-ASSOCIATED GENES.

Pathway name	Total genes	Mapped genes
Bone Remodelling	13	6
Cytokines and Inflammatory Response	26	17
NF- κ B Signaling Pathway	22	13
TNFR2 Signaling Pathway	17	8

IV. CONCLUSIONS

We have extracted data related to SpA—known SpA causal genes from the OMIM database, proteomic experiments from literature, and microarray experiments from the GEO database. Using these genes as seeds, we developed a Katz' centrality based index, *s*-score, to rank genes in the human PPI network. This score has only one parameter that needs to be calibrated by real data. The parameter has a clear biological interpretation so that its optimum value can give us some further insights. And the computation of *s*-score is easy implemented. Then we considered 379 top ranked genes as associated with SpA with high possibility. Based on these genes, we constructed a PPI network and identified potential pathways associated with SpA. The PPI network exhibits a core-periphery topology, in which most seed genes are located at the periphery part, while the inner core aggregates the non-seed genes enriched with innate immune genes and drug targets for SpA, suggesting that the core could be the modulating center of the network. The pathways represent the well-known knowledge of SpA, i.e., immune mediated inflammation, as well as imbalanced bone modeling caused new bone formation and bone loss. This network approach represents an alternative method for analyzing the complex effects of candidate genes related to complex diseases. It may shed new lights on the pathogenesis of axial spondyloarthritis from the perspective of network systems.

ACKNOWLEDGMENT

This research was supported by the National Natural Science Foundation of China (10971227); the Special Program for New Drug Innovation of the Ministry of Science and Technology, China (2009ZX09311-001, 2008ZX09101-Z-029); the Swedish Foundation for Strategic Research, the Swedish Research Council and the WCU program through NRF Korea funded by MEST R31-2008-10029-0.

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