

Databases and ontologies

dbNEI2.0: building multilayer network for drug–NEI–disease

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ABSTRACT

Summary: The neuro-endocrine-immune (NEI) system plays a critical regulatory role in modulating host homeostasis and optimizing health. We created the dbNEI 2 years ago to collect NEI molecules and interactions. For transferring the conceptual NEI to the systematic NEI network and uncovering the NEI's medical function, we updated the dbNEI 2.0 in three ways: (i) extended NEI molecules to 2242 genes and 7657 chemical compounds by using gene ontology-based (GO-based) data mining strategy, (ii) added multilayer interactions of NEI molecules including KEGG signal transduction and metabolic pathways, HPRD protein–protein interactions (PPI), transcription factor and microRNA regulations and (iii) connected 611 drugs and 823 diseases through multilayer NEI interactions. The reconstructed drug–NEI–disease network will facilitate the systematic study of NEI system.

Availability: <http://bioinfo.au.tsinghua.edu.cn/dbNEIweb/>**Contact:** shaoli@mail.tsinghua.edu.cn**1 INTRODUCTION**

The neuro-endocrine-immune (NEI) network, first proposed by Besedovsky and Sorkin (1977), plays a pivotal role in regulating homeostasis and optimizing health and makes great contributions to various complex diseases including aging (Fabris, 1990), inflammation (Luger and Schwarz, 1995), rheumatic diseases (Wilder, 2002) and cancer (McEwen *et al.*, 1997). With the rapid progress of the cross-disciplines such as neuroendocrinology, neuroimmunology and neuroimmuno-endocrinology, the shift from the conceptual NEI to the systematic NEI network is required for deeply understanding the molecular basis of mutual interrelationships among nervous, endocrine and immune systems. On the basis of our previous version (Zhuang *et al.*, 2006), dbNEI2.0 (Fig. 1A) updated NEI molecules, integrated multilevel interactions such as pathway information, protein–protein interaction (PPI), transcriptional regulation and microRNA, and then explored the NEI-based relationship between drug and disease, which will facilitate establishing the knowledge base for an integrative view of future systematic medicine.

2 DATABASE AND UTILITIES**2.1 NEI molecules updates**

The NEI system regulates body homeostasis by producing or secreting a variety of cellular mediators known as regulatory peptides or chemical compounds (Besedovsky and Sorkin, 1977). dbNEI1.0 collected 946 molecules of NEI messengers accounting for the communication and regulation among NEI from different data resources (Zhuang *et al.*, 2006). dbNEI2.0 extends NEI molecules to 2242 NEI genes and 7657 NEI compounds. NEI genes refer to genes categorized as neurotransmitters, neuropeptides, hormones, cytokines and growth factors in 'Gene Ontology' and they were retrieved from GenBank. NEI compounds refer to substance fallen into these five categories in 'MeSHTerm' and they were retrieved from NCBI PubChem database. Many molecules are multifunctional and classified into more than one category according to the NEI classification system. For example, ADCYAP1 encodes adenylate cyclase activating polypeptide 1, which activates adenylate cyclase and subsequently increases the cAMP level in target cells. This product is not only a hypophysiotropic hormone, but also functions as a neurotransmitter or neuromodulator (Nakata and Yada, 2007).

We extracted all human NEI genes' tissue information from the UniProt database. There are 246 kinds of tissues and each gene can be found expressed in 2.5 different tissues on average. NEI molecules are distributed in a diverse range of tissues besides NEI anatomic tissues, indicating that NEI molecules function as messengers and regulators among the body. The brain contains many more NEI genes than the other tissues, which has been confirmed by studies in isolated-cell systems (Guillemin, 1978). Tissue information regarding to three typical regulation subnetworks of NEI, namely hypothalamic–pituitary–adrenal axis, hypothalamic–pituitary–gonadal axis and hypothalamic–pituitary–thyroid axis, is also illustrated in dbNEI2.0. As our future direction, we will extend the NEI system from human to other model species.

2.2 NEI multilayer network reconstruction

NEI interaction is achieved through gene transcription, post-transcription regulation, PPI as well as metabolic reaction. dbNEI2.0 reconstructs NEI multilayer network by integrating all such interactions among NEI genes and compounds (Table 1) from databases of KEGG, HPRD (the 7th release), and TRANSFAC (the release 7.0), respectively. Moreover, microRNA, a kind of small non-coding regulatory element that commonly represses or degrades mRNA by binding the 3' UTR region, has recently been found

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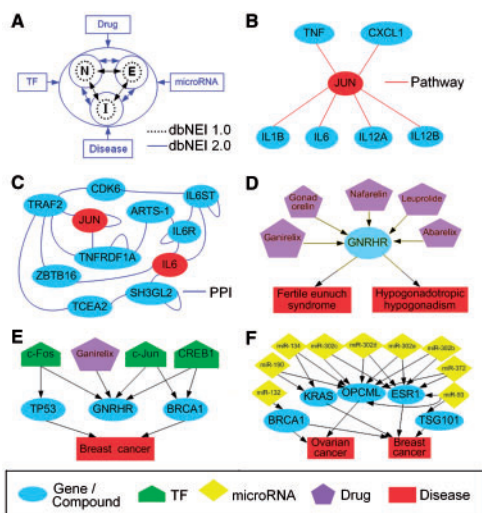


Fig. 1. (A) dbNEI 2.0 versus 1.0. (B) NEI gene network. (C) Module between two query NEI genes. (D) Drug–NEI–disease network. (E) Drug–disease relation in TF network. (F) Disease–disease relation in microRNA network.

Table 1. NEI molecules and four types of interactions

Category	Number ^a			Description
	Gene	Compound		
NEI molecule	Neuropeptide	137	1414	Nervous system
	Neurotransmitter	208	2701	
	Hormone	444	4744	Endocrine system
	Cytokine	572	279	Immune system
	Growth factor	881	215	
NEI interaction	Signaling/metabolic pathway	5008		From KEGG
	PPI	12 454		From HPRD
	TF-gene	1287		From TRANSFAC
	microRNA-gene	5199		Prediction

^aOne gene/compound can be categorized to more than one N, E or I system.

to execute an important post-transcription regulatory function. We chose two popular methods, miRanda (John et al., 2004) and PicTar (Krek et al., 2005), to predict the microRNA targets. These two methods predicted 1787 and 3612 microRNA–NEI gene binding relations, respectively. Besides, 22 microRNA–NEI gene relations recorded in TRANSFAC were also deposited in dbNEI2.0.

dbNEI2.0 integrates and supports many search categories, such as gene ID, gene name, compound ID, KEGG ID, Mesh term, tissue, transcription factor (TF) and microRNA in its webpage. We provide a brief explanation of all kinds of search categories on the ‘Help’ menu. Once given a NEI gene, the background program can return its basic information and find all the related genes, compounds, TFs and microRNAs and draw different types of networks around

the query gene. The searched gene will be highlighted in red as shown in Figure 1B. By default, we search the molecules which are directly related to the given genes. If user wants to see indirectly related genes, he can change the parameter ‘level’, which means how many steps the molecules can connect to the query gene. User can also search NEI compound, NEI-related TF and microRNA in the webpage and the server will return the related NEI genes. For addressing the multi-relations between two NEI molecules, we provide a ‘module’ searching scheme, which can access to the module between two given NEI molecules in the KEGG pathway or PPI network within the given steps (Fig. 1C).

2.3 Drug–NEI–disease network

dbNEI2.0 further constructs network for 611 drugs from DrugBank and 823 diseases from OMIM through NEI multilayer interactions to facilitate the study of complex disease and therapy. NEI plays a key function in bridging genetic and environmental interactions in complex disease (Tolle and Low, 2004). Aberrations of NEI system may critically modulate vulnerability to various diseases (Marchetti et al., 2005). In dbNEI2.0, we provide three kinds of search methods. The given query can be a drug, a NEI gene or a disease and the server will return the corresponding drug–NEI–disease network around the query (Fig. 1D). A useful tool to search a sub-network between two drugs or diseases is also available and the network type could be KEGG, HPRD, TRANSFAC or the microRNA target network. When given the names of two drugs or diseases, the program searches two groups of NEI genes related to two queries and results in a sub-network containing these NEI genes in a given type. Examples are illustrated in Figure 1E and F, respectively. Figure 1E denotes the relationship between a given drug (e.g. ganirelix) and a given disease (e.g. breast cancer) bridged by common transcription factors. User will find that the drug ganirelix and three TFs target on the same gene. These TFs could also regulate the other two genes, TP53 and BRCA1, which are associated with breast cancer. Figure 1F describes a microRNA–NEI network related to two given diseases (e.g. breast cancer and ovarian cancer), from which user could find that two diseases have common NEI genes as well as the upstream microRNAs. This result may give a clue on the molecular association of two different diseases.

In summary, dbNEI2.0 not only gives a multilayer layout on the drug–NEI–disease interactions, but also helps detect the potentially novel connections between drug and disease.

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Conflict of Interest: none declared.

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