

dbNEI: A specific database for neuro-endocrine-immune interactions

YongLong Zhuang, Shao Li* & YanDa Li

MOE Key Lab of Bioinformatics, Department of Automation, Tsinghua University, Beijing, 100084, P. R. China.

Correspondence to: Shao Li, PhD, MD, Associate Prof.
MOE Key Lab of Bioinformatics, Department of Automation
Tsinghua University, Beijing, 100084, P. R. CHINA
TEL: +86 10 62797035
FAX: +86 10 62786911
EMAIL: shaoli@tsinghua.edu.cn

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Abstract

OBJECTIVES: To construct a specific database for the neuro-endocrine-immune (NEI) interactions.

METHODS / RESULTS: Version 1.0 database for neuro-endocrine-immune (dbNEI) serves as a web-based knowledge resource specific for the NEI systems. dbNEI collects 1,058 NEI related signal molecules, their 940 interactions and 72 affiliated tissues from the Cell Signaling Networks database, manually selects 982 NEI papers from PubMed, and gives links to 27,848 NEI related genes from UniGene database. NEI related information, such as signal transductions, regulations and control subunits, is integrated. Especially, dbNEI represents as graphic visualization, by which control subunits can be automatically obtained according to the inquiring issues, the combinative queries and the NEI related diseases respectively.

CONCLUSIONS: dbNEI, which can be accessed at <http://bioinfo.au.tsinghua.edu.cn/dbNEIweb/>, provides a knowledge environment for understanding the main regulatory systems of NEI in a molecular level.

Abbreviations:

HPA – hypothalamo – pituitary – adrenal;
JNK – Jun kinase;
MAPK – mitogen-activated protein kinase;
NEI – neuro-endocrine-immune;
PGSM – proteins, genes, or small molecules;
RA – rheumatoid arthritis.

1. Introduction

The neuro-endocrine-immune (NEI) interactions play a pivotal role in modulating host homeostasis and optimizing health naturally. Since the doctrine of the network of immune-neuroendocrine interac-

tions was put forward in 1977 [1], new interdisciplinary fields such as neuroimmunoendocrinology [2], neuroimmunology [3], psychoneuroimmunology [4], and neuroendocrinology [5] have been developed rapidly in recent decades. The interactions among the nervous, the endocrine, and the immune systems have been a focus that provides a better understanding for physiological homeostasis in a molecular level. The system of NEI regulation of inflammatory, immune responses is extremely complex, which is beyond the scope of any individual researcher. However, the lack of the integrated methods is still a nodus to recognize the functional

structures and the systemic regulations of NEI. Thus, it is an important orientation for NEI that integrates NEI related information from genes, proteins to the multi-levels of cells, tissues, organs, physiologies and pathologies.

Up till now, databases such as the Cell Signaling Networks database (CSNDB) [6,7], the Kyoto Encyclopedia of Genes and Genomes (KEGG) [8,9], the Gene Network database (10), the Signaling Pathway database (SPAD), and the Online Mendelian Inheritance in Man (OMIM) database, which based on sequences and structures of either genome or protein, have applied to various fields of life sciences. The scattered discoverings in free-formatted text compose the knowledge of the whole scientific community. Specific databases, however, have definite subjects, concentrated contents and multipartite categories with a smaller scale. They can further improve the dependability and usability of the stored data by combining the professional knowledge.

Here, a database for neuro-endocrine-immune (dbNEI) is developed to unite the knowledge about NEI related proteins, genes, or small molecules (PGSM) and their interactions among three major regulatory systems: nervous, endocrine, and immune. With a standardized inquiry platform, dbNEI smoothes the disunion of selections, structures and information of NEI related data among different databases. Through the unified inquiry interface offered by a searching system, users can make a uniformed inquiry that facilitates the information mining.

2. Database description

2.1. Construction and content

The construction of version 1.0 dbNEI is based on several public databases and manually selected literatures. dbNEI consults the data structure of CSNDB (<http://geo.nihs.go.jp/csndb.html>), syncretizes the useful information from both databases of CSNDB and UniGene (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=unigene>), and gathers literatures from PubMed database (<http://www.ncbi.nlm.nih.gov/>). It is known that CSNDB contains signal transduction descriptions, structure-function data, and references to extracellular chemicals and biomolecules as well as various graphical representations such as pathway diagrams, images and pictures [6,7]. UniGene is an experimental system for automatically partitioning GenBank sequences into a non-redundant set of gene-oriented clusters. Each UniGene cluster contains the sequence that represents a unique gene, as well as the gene expressed and mapped tissue types [11]. While PubMed includes links to many sites providing full text articles and other related resources.

dbNEI collects and integrates NEI related information such as signal transductions, regulations and control subunits from public databases and the prior information of NEI. dbNEI makes freely available the data for the 1,058 signal molecules, 940 interactions, 72 related

tissues, 982 related papers and gives links to 27,848 genes generally related to NEI in UniGene database.

2.2. NEI related PGSMs

Literature data, including titles, journals, publishing years, volumes, pages, authors and types (such as Article and Review), are manually selected from PubMed. The available molecule and signal in each reference are also presented. The basic descriptions include the name, the category (such as Endogenous and Exogenous), the type (such as Hormone, Cytokine, Neurotransmitter, Receptor, Ion channel, Messenger, Enzyme, Transcription factor, and Regulatory sequence), the family, and the alias.

dbNEI describes the characters of signal molecules, the basic elements of signal transduction networks, which including basic descriptions, tissue descriptions and links. Specific tissue information includes synthesis tissues and target tissues. Links include the locus of UniGene database and article references in dbNEI. The upstream and downstream information around a molecule in regulated procedure for each signal molecule is also provided, so that researchers can find more information around a signal molecule.

2.3. Signal transductions

The section of signal transductions involves intracellular signals and extra signals. "Extra Signal" contains originated tissues, reached tissues, molecules, functional descriptions of signal transductions and related literatures. While "IntracellularSignal" is divided into two patterns, direct and indirect. The direct pattern includes Polymerization Reaction, MetabolicReaction, and Standard Reaction. The indirect pattern is Gene Expression. Other effects include activations and suppressions, interaction sites, functions, and interaction tissues.

2.4. Tissue distributions

To store the name, the alias, the subjection, and the affiliated system of tissues, dbNEI contains signal molecules and signal transductions expressed in various tissues. Expression loci of a signal molecule and its signal transduction are important for building signal regulated network. However, the same molecule always make use of different ways of signal transduction in different tissues. dbNEI unites and standardizes the tissue information according to CSNDB and the gene expression related tissues according to UniGene database, then divides them into the nervous, the endocrine and the immune systems, as illustrated in Figure 1.

2.5. Graphic visualization

For a network of biological molecules, the relationships among components are more pivotal than components themselves. The gene regulatory network [12], metabolic network [13], and signal transduction network [14] are developed rapidly in recent years to model the complex interactions among mass biological molecules. And several approaches for modeling such complex

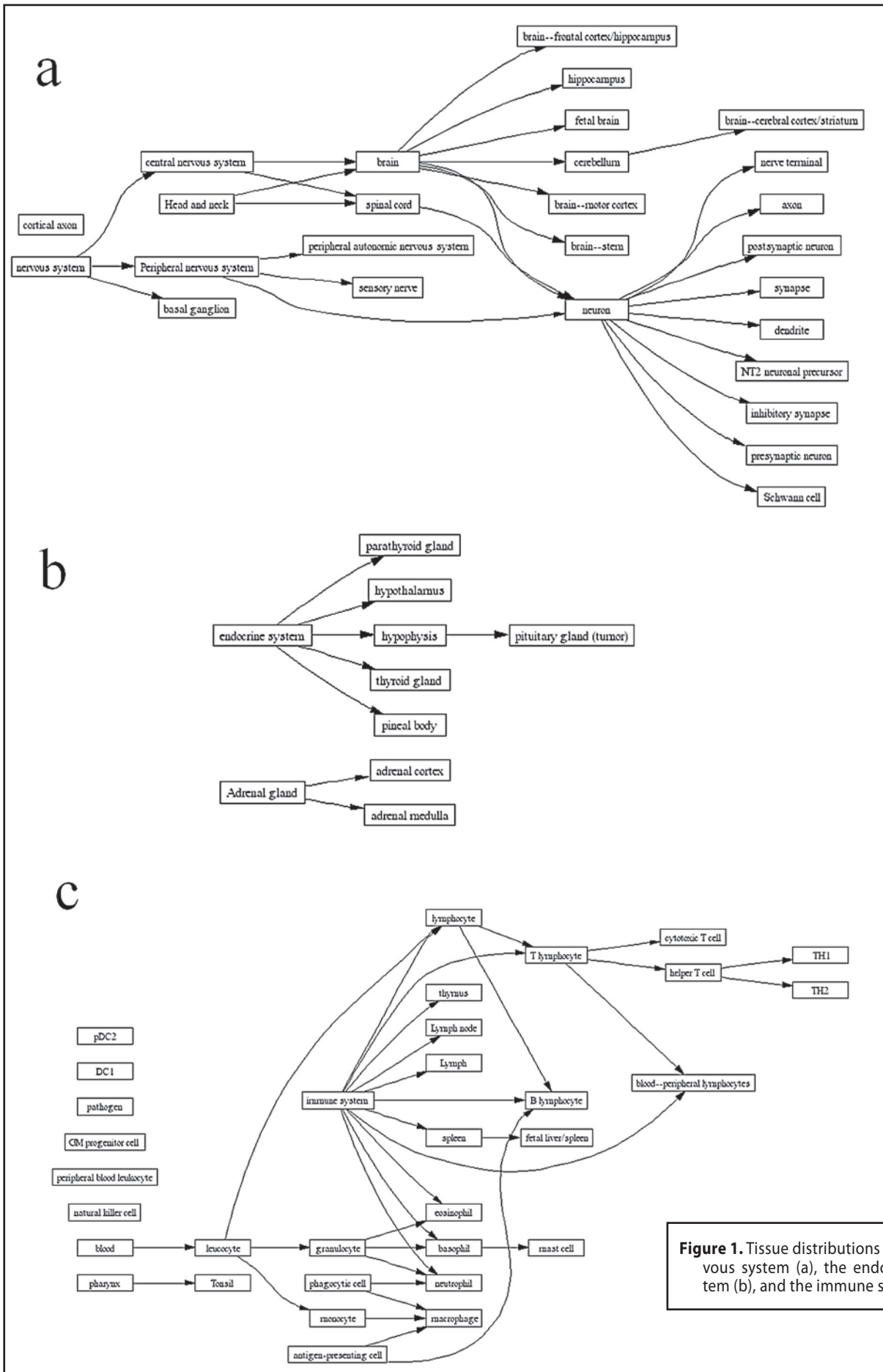


Figure 1. Tissue distributions of the nervous system (a), the endocrine system (b), and the immune system (c).

biological networks have been addressed. For example, Karp et al [15] developed automatic software for visualizing the metabolic network from binary relations within reactants, products and biological enzymes. Moreover, Kolpakov et al [16] established an automatically visualized software of metabolism by using JAVA from the known pathways of biological molecules. Based on the interrelated nodes, graphics can be automatically created for further modeling regulated pathways. dbNEI adopts the graphic visualization for NEI designed as the following sections.

2.6. Graphics of cellular signal transductions

Several modes of cellular signal transductions such as the polymerization reaction, the metabolic reaction, the standard reaction, and the gene expression are presented before automated visualization. This method has advantages for directly expressing types of reactions and interactions. Modes of interactions are expressed with different arrow headed notations, while the symbol “-” refers to suppressions, the symbol “+” refers to activations, and non-interactions refer to no expressions. Different types of reaction are expressed with different colors. For instance, the “metabolic approach” is marked with the red color, “standard reaction” with the black color, “gene expression” with the blue color, “association” and “disassociation” with the green color. If the number of reactants or products in a reaction is more than 1, or there is a metabolic reaction, we add an intermediate connection with a broken line.

2.7. Visualization for the network around a signal molecule

The search strategy is as follows: Give a node at first, set up its maximal upstream or downstream steps, lay this node in stack, and set the corresponding step as 0. Next, take out the front element as a new node. Suppose that the node corresponding to steps is not beyond the prescriptive maximum steps, we need to find out new upstream or downstream elements around this node. The upstream element represents the reactant for the reaction in which this node participates, and the downstream element represents the product for the reaction in which this node participates.

Mitogen-activated protein kinase (MAPK) as an example, the dynamic display of the MAPK relating signaling network is divided into two ways. Around a certain molecule, the platform finds out steps from upstream or

downstream signal and expression in a special tissue system. In searching it can set up whether input molecule is case sensitive, whether the same grade nodes are ranked in the same height while drawing nodes; restrict functional types for searching, i.e., metabolism, standard reaction, association/disassociation, gene expression are compounded randomly; set up masking molecules; select special tissues expressed, e.g., select the genes expressed in the tissue of “brain” but not expressed in “head and neck” (Figure 2).

2.8. Finding pathway between two molecules

According to the searching rules to restrict maximum approaches, functional type, and tissue information, we can find pathway between two factors by the search strategy as follows: First, node 1 is regarded as the beginning node, and the beginning step is set as 0. Next, with the same strategy above mentioned, if a new element of the return node consists with node 2, the pathway of finding a link is saved. The search procedure will exit when exceeding the maximum steps, and all available links between two elements are marked clearly via graphic ways. Finally, the Graphviz software (<http://www.research.att.com/sw/tools/graphviz/>) and the breadth-first algorithm are used for the arrangement of nodes and the evaluation of protein interactions. The graphs are generated with the adjustable parameters that determined by the size of the gene neighborhood. The breadth-first algorithm prioritizes the links with higher weight. The Neato program in the Graphviz software is used to create the two-dimensional layout. Taking example for the functional interactions between CD4 and Jun kinase (JNK), two signal pathways are available and visualized in Figure 3.

2.9. NEI-related disorders

Cytokines, peptide hormones, and neurotransmitters, as well as their receptors/ligands act as a common chemical language for communication within NEI system [17]. The defects of NEI may result in various kinds of dysregulatory pathologies including autoimmune disorders such as rheumatoid arthritis (RA) [2, 18]. dbNEI contains the information about the NEI network and the NEI related diseases [19]. OMIM contains 1,782, 326 and 201 records about the nervous system, the endocrine system and the immune system respectively. dbNEI selected various NEI related diseases from OMIM records. Among them we further analyze the data deriving from RA and its rela-

Figure 2 (right). Searching networks around a certain molecule. (a) Searching upstream or downstream signal pathways around a certain molecule. Here “Input molecule” denotes a molecule around which the platform can construct the related network, “Preceding steps” denotes the upper limited steps, “Succeeding steps” denotes the lower limited steps, “Node mapping” denotes the setting of node mapping, “Signaling type” denotes the related signaling type, “Masking molecules” denotes the shielded molecule, and “Tissue selected” denotes the expressive tissue that being restricted. (b) Expressive tissues in dbNEI. “Brain” as an example, possesses 13,213 expressed genes storing in UniGene. Here the mark “/” denotes no relations, the mark “+” denotes expressions, and the mark “-” denotes no expressions. (c) The graphic visualization of a network by searching a molecule MAP-kinase (in the red rhomboidal box). The black, blue, and green lines show the standard reaction, gene expression, and association/ disassociation interactions, respectively.

a

2. construct signaling network around a molecule:

Input molecule : case sensitive

preceding steps:(<4)

succeeding steps:(<4)

Node Mapping : ranked not ranked

Signaling TYPE: metabolism standard reaction association/disassociation gene expression

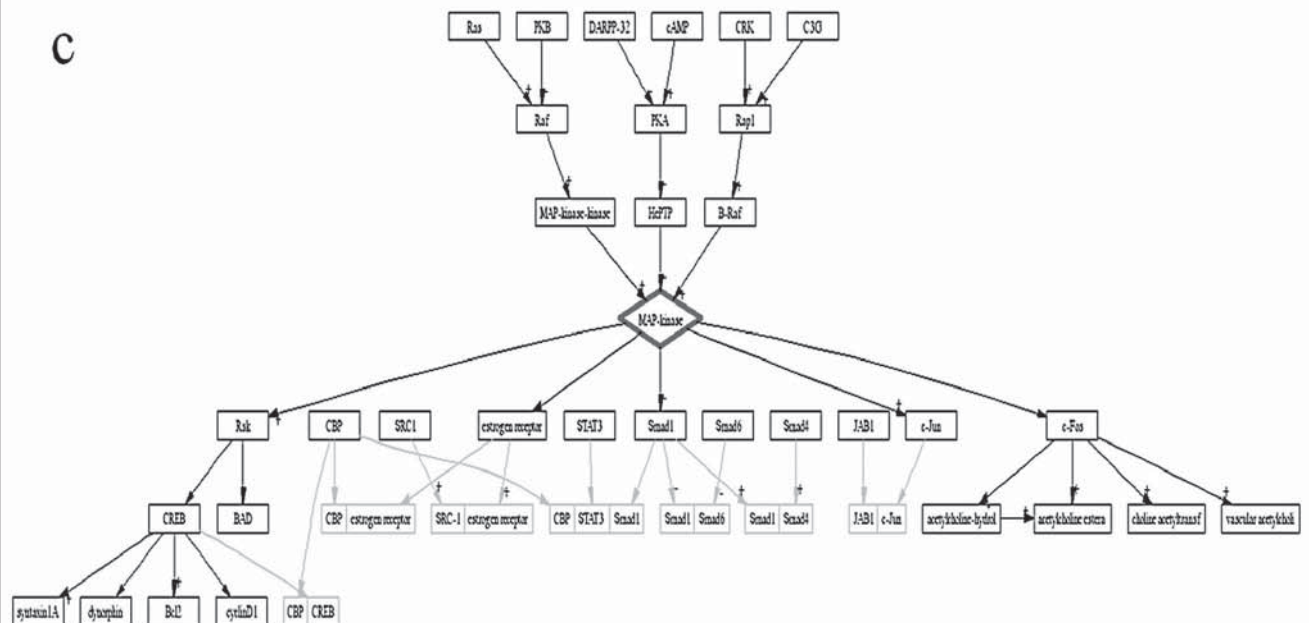
Masking molecules:

Tissue selected:

b

nervous system				endocrine system				immune system			
brain [13213]	/	⊙	+ ⊙ - ⊙	Adrenal gland [1022]	/	⊙	+ ⊙ - ⊙	Tonsil [1506]	/	⊙	+ ⊙ - ⊙
Head and neck [11430]	/	⊙	+ ⊙ - ⊙	parathyroid gland [50]	/	⊙	+ ⊙ - ⊙	T lymphocyte [1821]	/	⊙	+ ⊙ - ⊙
peripheral autonomic nervous system [4081]	/	⊙	+ ⊙ - ⊙	hypothalamus [5394]	/	⊙	+ ⊙ - ⊙	thymus [2334]	/	⊙	+ ⊙ - ⊙
hippocampus [6785]	/	⊙	+ ⊙ - ⊙	thyroid gland [2239]	/	⊙	+ ⊙ - ⊙	Lymph node [1749]	/	⊙	+ ⊙ - ⊙
fetal brain [2311]	/	⊙	+ ⊙ - ⊙	pineal body [2760]	/	⊙	+ ⊙ - ⊙	Lymph [11802]	/	⊙	+ ⊙ - ⊙
Peripheral nervous system [5368]	/	⊙	+ ⊙ - ⊙	adrenal medulla [4541]	/	⊙	+ ⊙ - ⊙	spleen [11406]	/	⊙	+ ⊙ - ⊙
cerebellum [2326]	/	⊙	+ ⊙ - ⊙	pituitary gland [2690]	/	⊙	+ ⊙ - ⊙	fetal spleen [1344]	/	⊙	+ ⊙ - ⊙
basal ganglion [3911]	/	⊙	+ ⊙ - ⊙					natural killer cell [2205]	/	⊙	+ ⊙ - ⊙
spinal cord [336]	/	⊙	+ ⊙ - ⊙					B lymphocyte [10417]	/	⊙	+ ⊙ - ⊙
brain--cerebral cortex [1788]	/	⊙	+ ⊙ - ⊙					peripheral blood leukocyte [13]	/	⊙	+ ⊙ - ⊙
brain--frontal cortex [37]	/	⊙	+ ⊙ - ⊙					lymphocyte [10981]	/	⊙	+ ⊙ - ⊙
cerebrum [12]	/	⊙	+ ⊙ - ⊙					leucocyte [4412]	/	⊙	+ ⊙ - ⊙
neuroglia [1575]	/	⊙	+ ⊙ - ⊙					macrophage [2783]	/	⊙	+ ⊙ - ⊙
								liver [9423]	/	⊙	+ ⊙ - ⊙

c



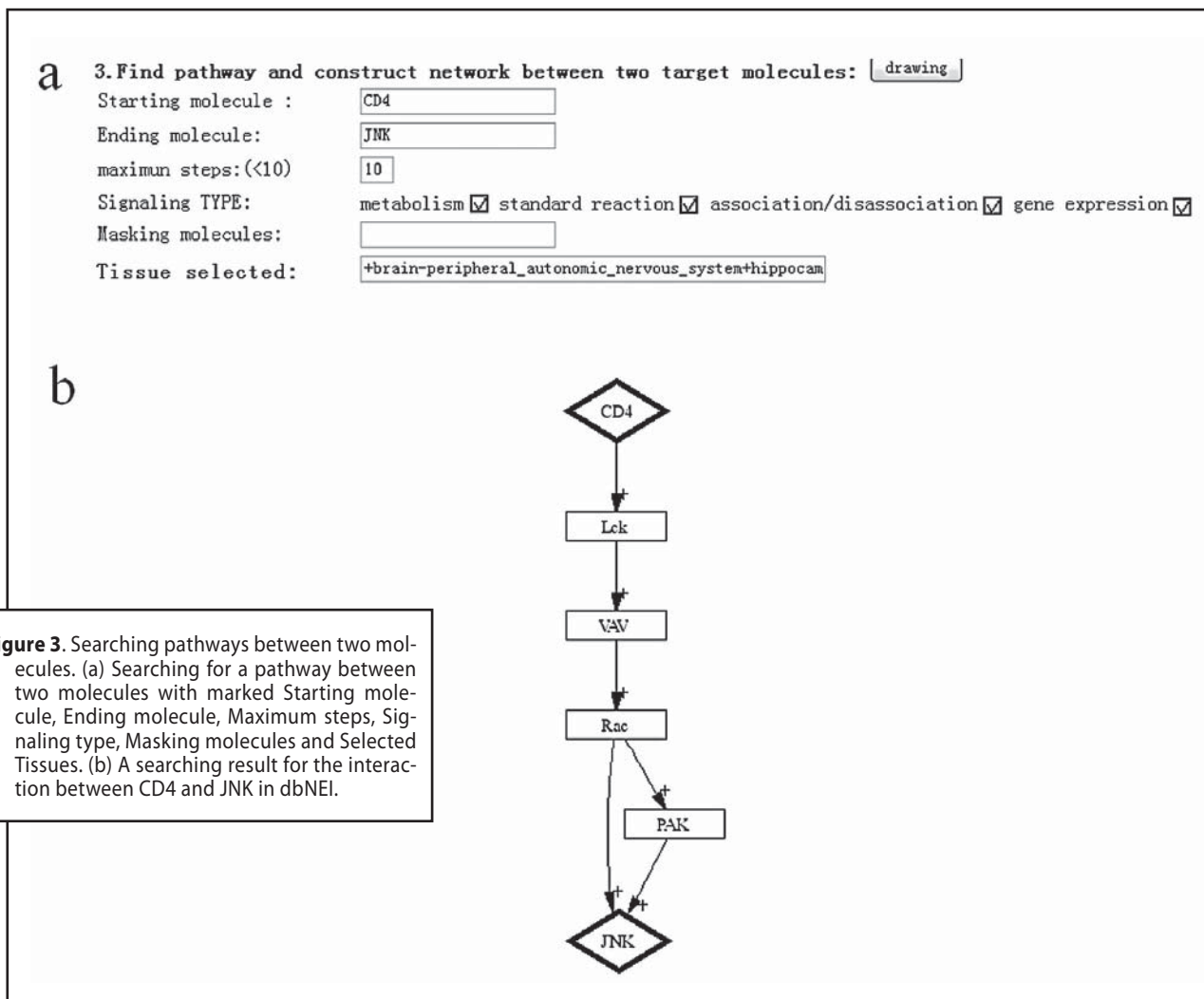


Figure 3. Searching pathways between two molecules. (a) Searching for a pathway between two molecules with marked Starting molecule, Ending molecule, Maximum steps, Signaling type, Masking molecules and Selected Tissues. (b) A searching result for the interaction between CD4 and JNK in dbNEI.

tion to NEI network, and extract corresponding twenty-six records from OMIM database. Future work includes constructing these NEI related disorders and their relationship with the typical sub-networks and control subunits of NEI such as hypothalamo – pituitary – adrenal (HPA) axis by combined with prior knowledge.

3. Utility

Version 1.0 of dbNEI is a fully searchable web-based system designed to automatically extract, store, catalog and describe a broad range of available NEI related molecules, tissues and interactions. It also tracks the flexible links to other databases and provides more information associated with NEI. By submitting information, annotations or queries in a standardized format, users can reach such information as the parent tissues and the child tissues, the involving molecules, the signaling patterns, the interactions or the related reference links by clicking the button of each tissue, each molecule, each signaling, and each reference respectively.

4. Conclusions

dbNEI deposits NEI-related productions, proteins, genes, their interactions and the related information from public databases including CSNDB, UniGene and OMIM. The references are also restricted to the citation in those cases from PubMed. Especially, dbNEI automatically visualizes the corresponding network according to the needs of users, which will be helpful for the integration of the main physiological regulatory systems of nervous, endocrine and immune, as well as their relationship with dysregulatory diseases.

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