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KEGG: integrating viruses and cellular organisms

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ABSTRACT

KEGG (https://www.kegg.jp/) is a manually curated resource integrating eighteen databases categorized into systems, genomic, chemical and health information. It also provides KEGG mapping tools, which enable understanding of cellular and organism-level functions from genome sequences and other molecular datasets. KEGG mapping is a predictive method of reconstructing molecular network systems from molecular building blocks based on the concept of functional orthologs. Since the introduction of the KEGG NETWORK database, various diseases have been associated with network variants, which are perturbed molecular networks caused by human gene variants, viruses, other pathogens and environmental factors. The network variation maps are created as aligned sets of related networks showing, for example, how different viruses inhibit or activate specific cellular signaling pathways. The KEGG pathway maps are now integrated with network variation maps in the NETWORK database, as well as with conserved functional units of KEGG modules and reaction modules in the MODULE database. The KO database for functional orthologs continues to be improved and virus KOs are being expanded for better understanding of virus-cell interactions and for enabling prediction of viral perturbations.

INTRODUCTION

Systems and perturbations have been used as a conceptual framework for developing the KEGG (Kyoto Encyclopedia of Genes and Genomes) database resource (1). Since 1995 the primary objective of KEGG has been to enable computational reconstruction of biological systems, including the cell, the organism and the ecosystem, from genome information. Current knowledge of such biological systems is captured from experimental data published in literature, represented in terms of molecular interaction and reaction networks, and accumulated in the KEGG PATHWAY database. The nodes of molecular networks are linked to functional orthologs of the KO (KEGG ORTHOLOGY) database so that experimental evidence observed in specific organisms can be generalized for use in other organisms. This architecture has made KEGG into a generic database with predictive power. The KEGG mapping, a method to reconstruct biological systems and to infer high-level functions, can be applied to any cellular organism once its complete genome sequence is available.

In 2010 the health information category of KEGG was introduced to promote genome-based medical and industrial innovations using the concept of perturbations. Diseases are associated with perturbed states of molecular networks caused by perturbants including human gene variants, viruses, other pathogens and environmental factors. Drugs are treated as different types of perturbants affecting perturbed molecular networks. In 2017, we started developing the KEGG NETWORK database (2) as a collection of disease-related network variants, which are experimentally observed perturbed molecular networks. While KEGG PATHWAY has a predictive power of ‘systems’, the question we ask is whether KEGG NETWORK can have a predictive power of ‘perturbations’. At least for a special class of perturbations, namely those caused by human viruses, we wish to establish better links from viral genomes to viral perturbations and then to human systems, which would enable better understanding of viral diseases.

NEW DEVELOPMENTS IN KEGG

Overview

KEGG is an integrated database consisting of eighteen original databases in four categories as shown in Figure 1. The databases in the health information category together with two outside databases of drug labels are collectively called KEGG MEDICUS. The original databases are all manually curated except the computationally generated SSDB database. The content covers wide-ranging biological objects, including genes and proteins (genomic information), chemical substances and reactions (chemi-

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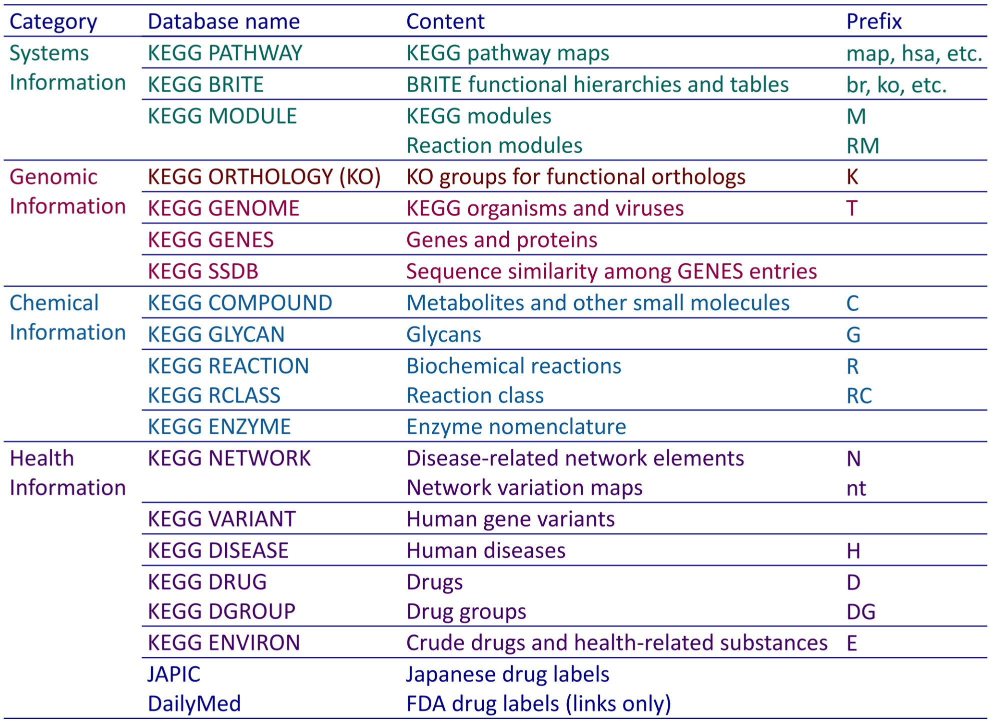


Category	Database name	Content	Prefix
Systems Information	KEGG PATHWAY	KEGG pathway maps	map, hsa, etc.
	KEGG BRITE	BRITE functional hierarchies and tables	br, ko, etc.
	KEGG MODULE	KEGG modules Reaction modules	M RM
Genomic Information	KEGG ORTHOLOGY (KO)	KO groups for functional orthologs	K
	KEGG GENOME	KEGG organisms and viruses	T
	KEGG GENES	Genes and proteins	
	KEGG SSDB	Sequence similarity among GENES entries	
Chemical Information	KEGG COMPOUND	Metabolites and other small molecules	C
	KEGG GLYCAN	Glycans	G
	KEGG REACTION KEGG RCLASS	Biochemical reactions Reaction class	R RC
	KEGG ENZYME	Enzyme nomenclature	
Health Information	KEGG NETWORK	Disease-related network elements Network variation maps	N nt
	KEGG VARIANT	Human gene variants	
	KEGG DISEASE	Human diseases	H
	KEGG DRUG KEGG DGROUP	Drugs Drug groups	D DG
	KEGG ENVIRON	Crude drugs and health-related substances	E
	JAPIC DailyMed	Japanese drug labels FDA drug labels (links only)	

Figure 1. KEGG consists of eighteen original databases in four categories. The health information category, called KEGG MEDICUS, is supplemented with two outside databases of drug labels: Japanese drug labels obtained from JAPIC (http://www.japic.or.jp) and FDA drug labels linked to the DailyMed database (https://dailymed.nlm.nih.gov). The identifier of each entry in the KEGG database generally takes the form of a prefix followed by a five-digit number and is called, for example, map number, M number and K number for the PATHWAY, MODULE and KO databases, respectively.

cal information), molecular interaction/reaction/relation networks (systems information) and human diseases and drugs (health information). Each biological object, when represented in KEGG, is given a unique identifier mostly in the form of a prefix followed by a five-digit number, such as hsa05010 for the pathway map of Alzheimer disease in the PATHWAY database and K04505 for the functional ortholog of presenilin 1 in the KO database. For the GENES, SSDB, ENZYME and VARIANT databases, the identifier takes the form of db:entry, such as hsa:5663 for human presenilin 1 (PSEN1) in the GENES database and hsa_var:5663v1 for PSEN1 mutation in the VARIANT database.

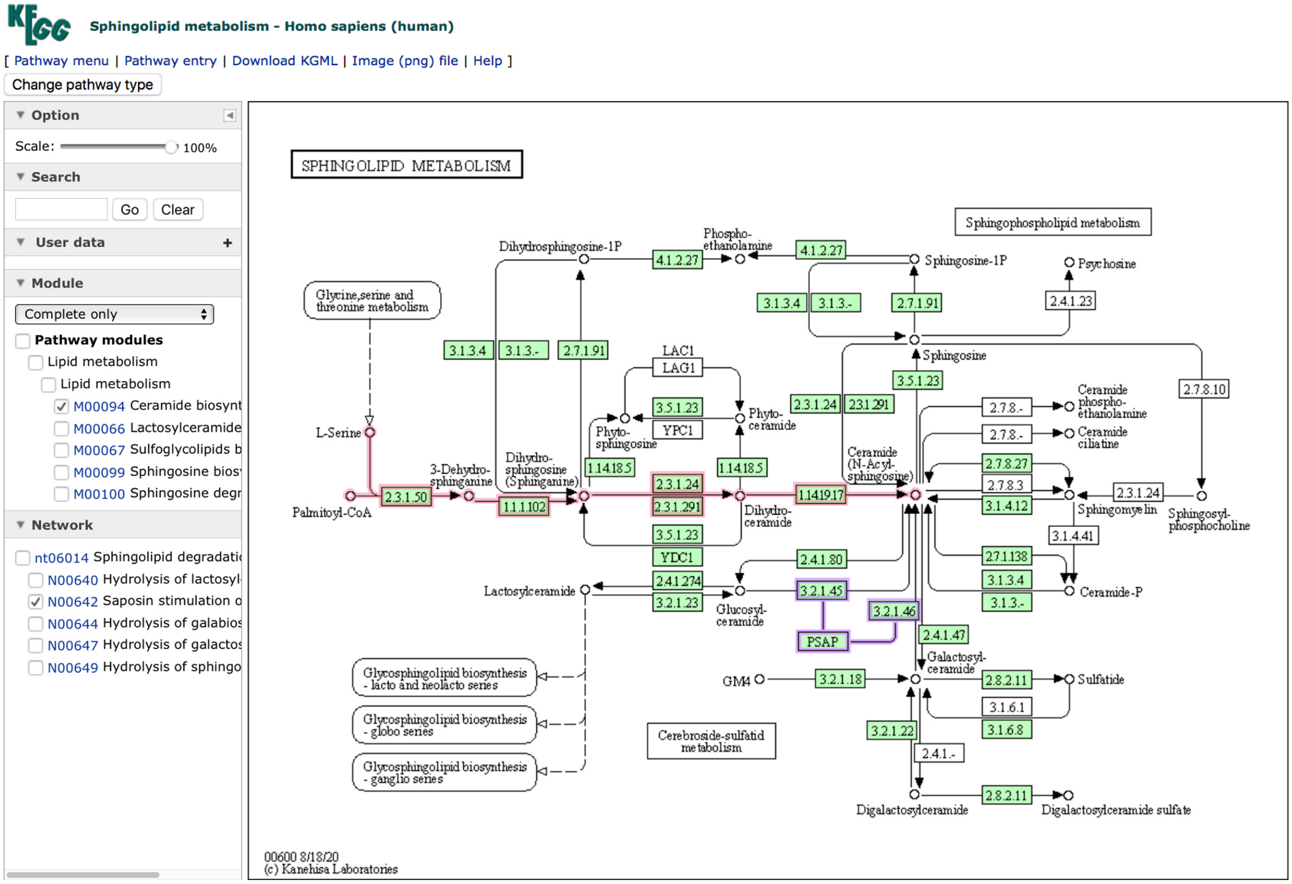
One important principle of organizing biological objects in the KEGG database is the distinction of reference data (classes) and variation data (instances). For example, K04505 is a class of presenilin 1 and hsa:5663 is an instance in human. The pathway map for Alzheimer disease is manually drawn as a reference pathway, map05010, where nodes (boxes) are linked to KO identifiers (K numbers). The human pathway map hsa05010 is an organism-specific pathway computationally generated from the reference pathway by converting KO identifiers to human gene identifiers and by coloring nodes (boxes) in green.

Pathway, module and network

The PATHWAY database is the central database in KEGG, consisting of manually drawn KEGG pathway maps, each identified by a five-digit number preceded by 'map' (for the reference pathway), three- or four-letter organism code (for an organism-specific pathway) or one of the other defined prefixes. The pathway maps represent the molecular wiring diagrams of the biological systems, categorized into metabolism, genetic information processing, environmental information processing, cellular processes, organismal systems and human diseases. The MODULE database is a collection of manually defined functional units in metabolic pathways, both in terms of conserved enzyme gene sets as KEGG modules and of conserved biochemical reaction steps as reaction modules. The identifiers of modules and reaction modules are M numbers and RM numbers, respectively.

The NETWORK database is a human-specific database consisting of network elements, simply called networks, defined as functionally meaningful segments of signaling and other pathways and identified by N numbers. There are three types of networks: reference networks, disease-related variant (perturbed) networks and drug-target relations. Variant networks are further divided into three types of perturbants: human gene variants, pathogens and environmental factors. The NETWORK database may also be viewed as a collection of network variation maps (see below) identified by nt numbers, displaying aligned sets of both reference and variant networks. Reference networks are linked to reference (non-disease) pathway maps and variant networks are linked to disease pathway maps.

The new KEGG pathway map viewer released in July 2020 comes with a side panel for client-side operations and integrates modules, reaction modules and networks into pathways. Figure 2 shows an example of the human pathway map hsa00600 for sphingolipid metabolism. The side



Sphingolipid metabolism - Homo sapiens (human)

[Pathway menu | Pathway entry | Download KGML | Image (png) file | Help]

Change pathway type

Option

Scale: 100%

Search

Go Clear

User data +

Module

Complete only

☐ Pathway modules
☐ Lipid metabolism
☐ Lipid metabolism
☑ M00094 Ceramide biosynt
☐ M00066 Lactosylceramide
☐ M00067 Sulfoglycolipids b
☐ M00099 Sphingosine bios
☐ M00100 Sphingosine degr

Network

☐ nt06014 Sphingolipid degradati
☐ N00640 Hydrolysis of lactosyl
☑ N00642 Saposin stimulation o
☐ N00644 Hydrolysis of galabios
☐ N00647 Hydrolysis of galactos
☐ N00649 Hydrolysis of sphingo

Figure 2. The new pathway map viewer with a side panel for client-side operations. Here the human pathway map hsa00600 for sphingolipid metabolism is shown with the module M00094 for ceramide biosynthesis in red and the network N00642 for saposin (PSAP) stimulation of GBA (3.2.1.45) and GALC (3.2.1.46) in purple. The saposin node and regulatory links are not present in the original map and are displayed only when this network is selected.

panel can be used to change the scale of the map, to search map objects of boxes (genes and KOs) and circles (chemical substances) by identifiers or aliases, and to selectively display the locations of modules and networks in the map. In Figure 2, the module M00094 for ceramide biosynthesis and the network N00642 for saposin stimulation of GBA and GALC are selected and displayed. PSAP (prosaposin) is known to be a causative gene for sphingolipidosis, but in KEGG metabolic pathway maps such a regulatory element is not usually included. The new pathway map viewer allows additional elements to be displayed and additional links to be enabled when the selection of certain networks are made. In Figure 2, the selection of N00642 displays the additional node of PSAP and regulatory links to 3.2.1.45 (GBA/GBA2) and 3.2.1.46 (GALC), which are not present in the original map.

For the global maps (map numbers 01100s) and the overview maps (01200s), the new map viewer allows additional options to be selected. The coloring option in the global map distinguishes whether to use multiple coloring according to the color codes of pathway categories or single coloring of green when displaying an organism-specific pathway. The link option in the global and overview maps is whether to use the normal mode or the module mode, the latter treating the map as consisting of modules rather than individual genes or KOs. The module link mode is useful to characterize metabolic capacity of a genome or a metagenome, for modules are defined as functional units of enzyme genes for specific metabolic processes, enabling automatic evaluation of whether the units are complete. Figure 3 shows the global map of metabolic pathways in the module link mode for an environmental sample (T30798_01100) from the Tara Oceans project (3), where complete modules displayed in brown indicate the presence of specific metabolic processes. The module link mode is also implemented in the Reconstruct Pathway tool of KEGG Mapper (4).

Network variation map

The network variation map is a computationally drawn diagram of network variations containing aligned sets of related networks involved in the same pathway. The map may also be created by collecting all types of variant networks involved in the same disease. As shown in Figure 2, the network (*N* number) links in the new pathway map viewer is grouped by the network variation map (nt number), directly linking to known variations that are not represented in the KEGG pathway map. Figure 4 is an example of the network variation map, nt06131 for Apoptosis (viruses and bacte-

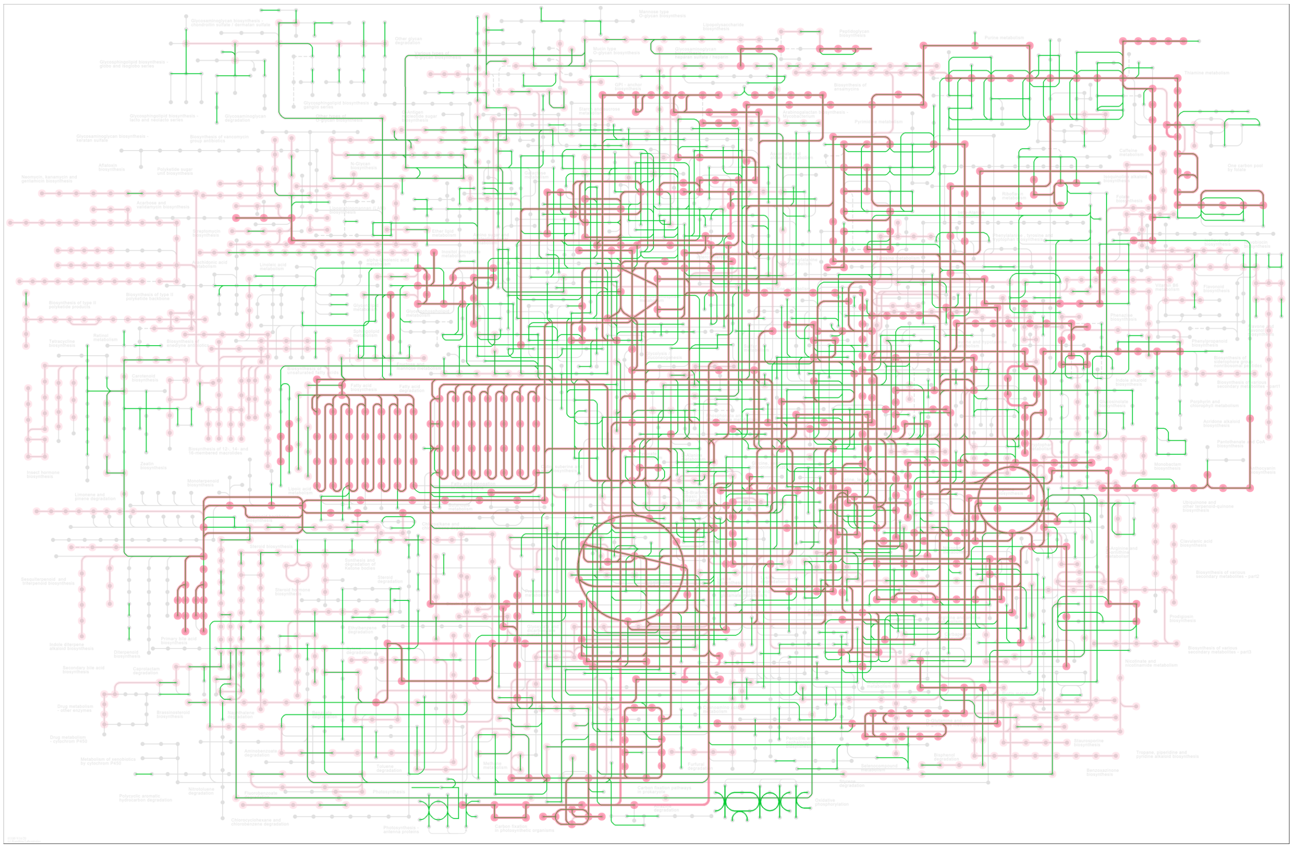


Figure 3. The global map of metabolic pathways can now be viewed in two modes: normal link mode and the module link mode, the latter treating the map as consisting of modules rather than individual genes or KOs. Here the global map of a Tara Oceans sample (T30798_01100) is shown in the module link mode with the coloring of pink for the background of all modules, green for mapped genes, and brown for complete modules identified in the sample.

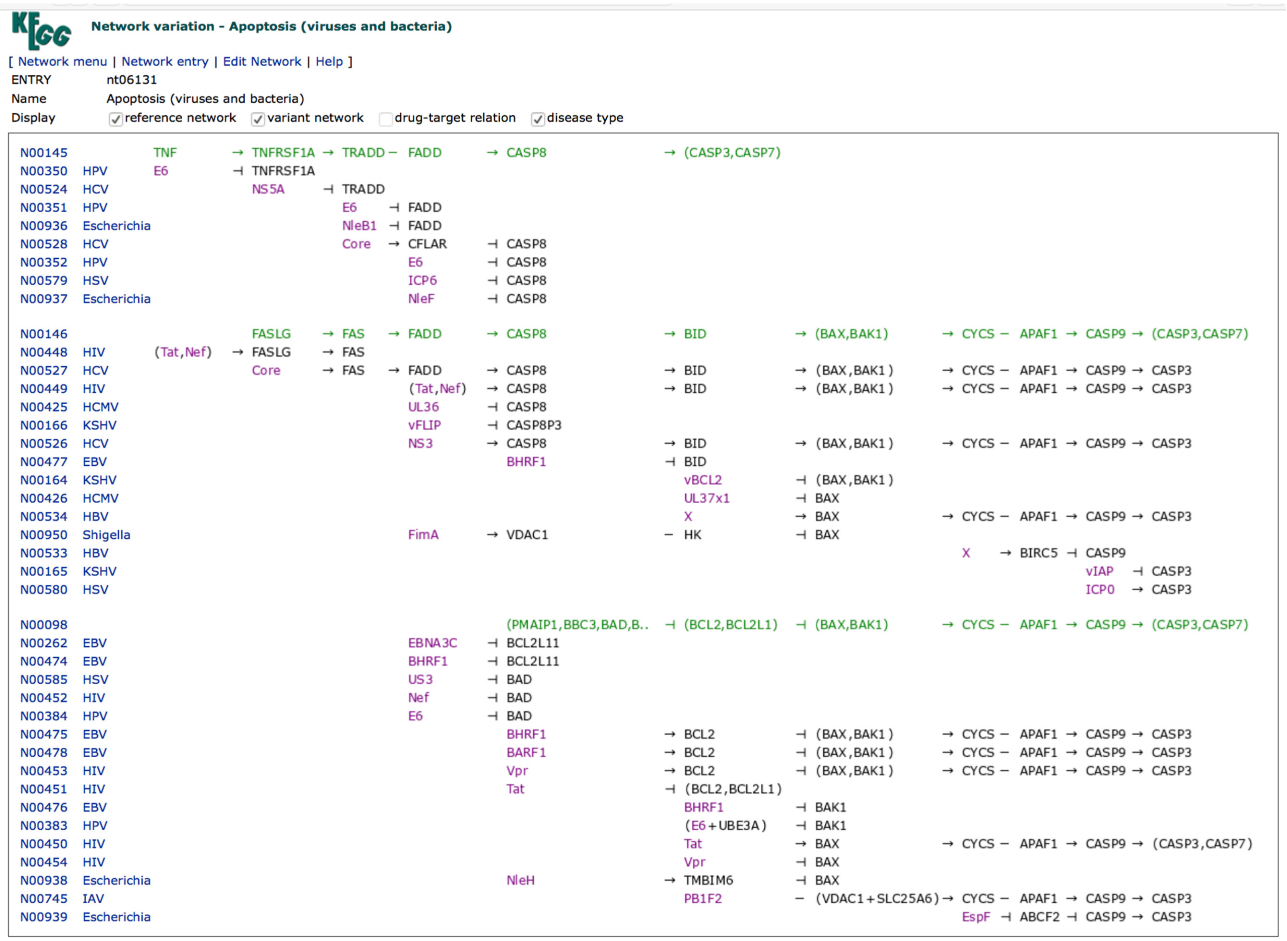
ria). As shown here, the variation map generally contains blocks of aligned networks, each block consisting of a reference network in green and variant networks with color coding of gene variants in red, pathogen proteins in purple and environmental factors in blue. Variant networks are linked to associated diseases, viral and bacterial infections in Figure 4, enabling comparative analysis of network perturbations.

Viruses are known to either inhibit or activate apoptosis pathways depending on the virus type, which are shown in the variation map nt06131, but can be seen more clearly in the corresponding pathway maps. Figure 5 shows portions of the two pathway maps: hsa05167 for KSHV (Kaposi sarcoma-associated herpesvirus) infection and hsa05170 for HIV-1 (Human immunodeficiency virus 1) infection. The highlighted segments of apoptosis pathways in each map correspond to the variant networks included in nt06131. Anti-apoptosis is one of the hallmarks of cancer (5), and oncogenic viruses, such as KSHV, inhibit apoptosis pathways. In contrast, HIV evades the host immune system by activating apoptosis of CD4+ T helper cells.

The KEGG NETWORK database currently contains disease-associated variant networks for cancers, neurodegenerative diseases, endocrine and metabolic diseases including inborn errors of metabolism, viral infections and some bacterial infections. The most recent addition consists of six neurodegenerative diseases, Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, Huntington disease, spinocerebellar ataxia and prion disease, for which variant networks have been defined from improved pathway maps. Common features of neurodegeneration (6) are found to be linked to molecular networks, including accumulation of abnormal protein aggregates, impairment of ubiquitin-proteasome system, endoplasmic reticulum stress, autophagy impairment, mitochondrial dysfunction and axonal transport defect. The network variation map nt06410 for calcium signaling is the most characteristic signaling pathway involved in many of these common features.

KO annotation and taxonomy

The KEGG Orthology groups or KOs are defined as functional orthologs for the nodes of KEGG pathway maps and BRITE hierarchies. In principle, KOs are created as sequence similarity groups in order to make KO assignment possible from sequence data. As of September 2020, there are about 24 000 KOs with 82% having links to experimentally characterized sequence data. Unfortunately, however, there are still legacy KOs that started as EC number groups and contain diverse sets of sequence data. Legacy KOs are gradually being divided into smaller KOs by considering taxonomic groups.



Network variation - Apoptosis (viruses and bacteria)

[Network menu | Network entry | Edit Network | Help]

ENTRY nt06131

Name Apoptosis (viruses and bacteria)

Display ☑ reference network ☑ variant network ☐ drug-target relation ☑ disease type

```
N00145                TNF       → TNFRSF1A → TRADD  − FADD       → CASP8                → (CASP3,CASP7)
N00350   HPV          E6        ⊣ TNFRSF1A
N00524   HCV                      NS5A     ⊣ TRADD
N00351   HPV                                 E6     ⊣ FADD
N00936   Escherichia                         NleB1  ⊣ FADD
N00528   HCV                                 Core   → CFLAR      ⊣ CASP8
N00352   HPV                                          E6         ⊣ CASP8
N00579   HSV                                          ICP6       ⊣ CASP8
N00937   Escherichia                                  NleF       ⊣ CASP8

N00146                            FASLG    → FAS    → FADD       → CASP8                → BID           → (BAX,BAK1)     → CYCS − APAF1 → CASP9 → (CASP3,CASP7)
N00448   HIV          (Tat,Nef) → FASLG    → FAS
N00527   HCV                      Core     → FAS    → FADD       → CASP8                → BID           → (BAX,BAK1)     → CYCS − APAF1 → CASP9 → CASP3
N00449   HIV                                          (Tat,Nef)  → CASP8                → BID           → (BAX,BAK1)     → CYCS − APAF1 → CASP9 → CASP3
N00425   HCMV                                         UL36       ⊣ CASP8
N00166   KSHV                                         vFLIP      ⊣ CASP8P3
N00526   HCV                                          NS3        → CASP8                → BID           → (BAX,BAK1)     → CYCS − APAF1 → CASP9 → CASP3
N00477   EBV                                                       BHRF1                ⊣ BID
N00164   KSHV                                                                             vBCL2         ⊣ (BAX,BAK1)
N00426   HCMV                                                                             UL37x1        ⊣ BAX
N00534   HBV                                                                              X             → BAX            → CYCS − APAF1 → CASP9 → CASP3
N00950   Shigella                                     FimA       → VDAC1                − HK            ⊣ BAX
N00533   HBV                                                                                                               X    → BIRC5 ⊣ CASP9
N00165   KSHV                                                                                                                            vIAP  ⊣ CASP3
N00580   HSV                                                                                                                             ICP0  → CASP3

N00098                                                             (PMAIP1,BBC3,BAD,B.. ⊣ (BCL2,BCL2L1) ⊣ (BAX,BAK1)     → CYCS − APAF1 → CASP9 → (CASP3,CASP7)
N00262   EBV                                          EBNA3C     ⊣ BCL2L11
N00474   EBV                                          BHRF1      ⊣ BCL2L11
N00585   HSV                                          US3        ⊣ BAD
N00452   HIV                                          Nef        ⊣ BAD
N00384   HPV                                          E6         ⊣ BAD
N00475   EBV                                                       BHRF1                → BCL2          ⊣ (BAX,BAK1)     → CYCS − APAF1 → CASP9 → CASP3
N00478   EBV                                                       BARF1                → BCL2          ⊣ (BAX,BAK1)     → CYCS − APAF1 → CASP9 → CASP3
N00453   HIV                                                       Vpr                  → BCL2          ⊣ (BAX,BAK1)     → CYCS − APAF1 → CASP9 → CASP3
N00451   HIV                                                       Tat                  ⊣ (BCL2,BCL2L1)
N00476   EBV                                                                              BHRF1         ⊣ BAK1
N00383   HPV                                                                              (E6+UBE3A)    ⊣ BAK1
N00450   HIV                                                                              Tat           → BAX            → CYCS − APAF1 → CASP9 → (CASP3,CASP7)
N00454   HIV                                                                              Vpr           ⊣ BAX
N00938   Escherichia                                               NleH                 → TMBIM6        ⊣ BAX
N00745   IAV                                                                              PB1F2         − (VDAC1+SLC25A6)→ CYCS − APAF1 → CASP9 → CASP3
N00939   Escherichia                                                                                                       EspF ⊣ ABCF2 ⊣ CASP9 → CASP3
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Figure 4. The network variation map nt06131 for Apoptosis (viruses and bacteria) showing aligned sets of reference networks in green and variant networks with viral or bacterial proteins in purple. Variant networks are linked to disease types, mostly viral infections but including five bacterial infections.

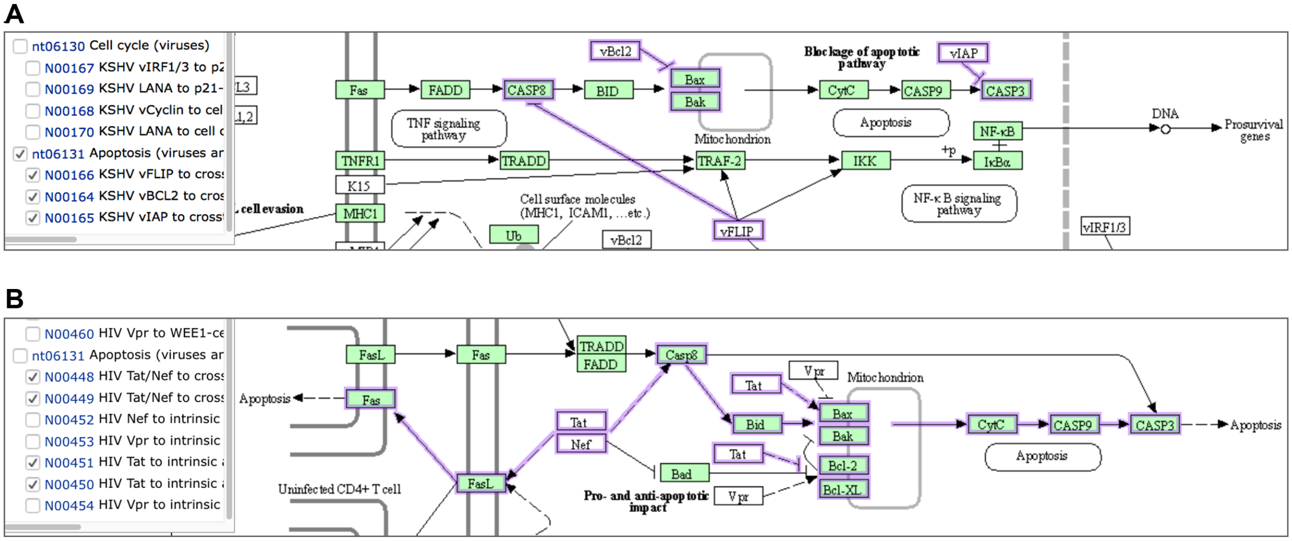
A
☐ nt06130 Cell cycle (viruses)
☐ N00167 KSHV vIRF1/3 to p2
☐ N00169 KSHV LANA to p21-
☐ N00168 KSHV vCyclin to cel
☐ N00170 KSHV LANA to cell c
☑ nt06131 Apoptosis (viruses ar
☑ N00166 KSHV vFLIP to cros
☑ N00164 KSHV vBCL2 to cros
☑ N00165 KSHV vIAP to cross
L3
1,2
cell evasion
Fas
FADD
CASP8
BID
vBcl2
Bax
Bak
Mitochondrion
Blockage of apoptotic pathway
vIAP
CytC
CASP9
CASP3
Apoptosis
TNF signaling pathway
TNFR1
TRADD
TRAF-2
IKK
NF-κB
IκBα
+p
DNA
Prosurvival genes
K15
MHC1
Cell surface molecules (MHC1, ICAM1, ...etc.)
Ub
vBcl2
vFLIP
NF-κB signaling pathway
vIRF1/3
B
☐ N00460 HIV Vpr to WEE1-ce
☐ nt06131 Apoptosis (viruses ar
☑ N00448 HIV Tat/Nef to cross
☑ N00449 HIV Tat/Nef to cross
☐ N00452 HIV Nef to intrinsic
☐ N00453 HIV Vpr to intrinsic
☑ N00451 HIV Tat to intrinsic
☑ N00450 HIV Tat to intrinsic
☐ N00454 HIV Vpr to intrinsic
FasL
Fas
TRADD
FADD
Casp8
Apoptosis
Fas
Tat
Nef
Vpr
Mitochondrion
Tat
Bid
Bax
Bak
Tat
Bcl-2
Bcl-XL
Bad
Vpr
CytC
CASP9
CASP3
Apoptosis
Apoptosis
Uninfected CD4+ T cell
FasL
Pro- and anti-apoptotic impact

Figure 5. Selected networks in the variation map nt06131 are shown on the pathway maps: (**A**) inhibition of apoptosis by KSHV in the pathway map of hsa05167 for Kaposi sarcoma-associated herpesvirus infection and (**B**) activation of apoptosis by HIV in the pathway map of hsa05170 for Human immunodeficiency virus 1 infection.

Riboviria	
Pararnavirae	
Artverviricota	
Revtraviricetes	
Blubervirales	(VII dsDNA-RT)
Ortervirales	
Caulimoviridae	(VII dsDNA-RT)
Metaviridae	(VI ssRNA-RT)
Retroviridae	(VI ssRNA-RT)
Orthornavirae	
Duplornaviricota	(III dsRNA)
Pisuviricota	
Duplopiviricetes	(III dsRNA)
Pisoniviricetes	(IV +ssRNA)
Stelpaviricetes	(IV +ssRNA)
Kitrinoviricota	(IV +ssRNA)
Lenarviricota	(IV +ssRNA)
Negarnaviricota	(V -ssRNA)

Duplodnaviria	(I dsDNA)
Varidnaviria	(I dsDNA)
Monodnaviria	
Shotokuvirae	
Cossaviricota	
Papovaviricetes	(I dsDNA)
Mouviricetes	(II ssDNA)
Quintoviricetes	(II ssDNA)
Cressdnaviricota	(II ssDNA)
Loebvirae	(II ssDNA)
Sangervirae	(II ssDNA)
Trapavirae	(II ssDNA)

Figure 6. The correspondence between the seven groups of Baltimore classification (colored) and the hierarchy of ICTV virus classification consisting of realm (-viria), kingdom (-virae), phylum (-viricota), class (-viricetes) and family (-viridae).

The KEGG taxonomy data for cellular organisms and viruses are taken from the NCBI taxonomy database (7) and displayed with a predefined framework of the classification system. For cellular organisms, the ordering among the same taxonomic rank is not alphabetical, but rather manually defined. This is why *Homo sapiens* always appears on top in the KEGG taxonomy. For viruses, the traditional Baltimore classification (8) is used at the top level and integrated into the ICTV (International Committee on Taxonomy of Viruses) classification system (9), according to the correspondence shown in Figure 6.

For the internal annotation of the KEGG GENES database, a new tool named KoAnn (KO Annotation) has been developed for assigning KOs to individual genes. The KoAnn tool uses the SSDB database and the GFIT tables in a similar way as the previously developed KOALA tool (10). The SSDB database is computationally generated from the GENES database and contains sequence similarity scores and best hit relations for all gene pairs in pairwise genome comparisons. The GFIT table is a summary table for each gene of each organism listing top scoring genes in other organisms with attributes including similarity score, identity, best hit flag, sequence length and overlap of alignment. Because KoAnn makes safer predictions using a different weighting scheme overcoming the problems of KOALA, the KO assignment is now more stable and reliable.

As of September 2020, KOs are assigned to 52% of the over 31 million genes (mostly proteins but including RNAs) for cellular organisms, but only 22% of the 460 thousand genes for viruses. Sequence variations of viral proteins appear to be very large, and it will be impossible to decompose viral proteins into KOs. Our approach is to define specific groups of sequences when the need arises for representation of KEGG pathway maps, BRITE hierarchies and other functional features. The grouping is often done by extracting a smaller group from a larger group, such as shown below for coronavirus spike glycoproteins.

K19254 S; Coronaviridae (excluding betacoronavirus) spike glycoprotein

K24325 S; betacoronavirus (excluding SARS and MERS) spike glycoprotein

K24152 S; SARS coronavirus spike glycoprotein

K24324 S; MERS coronavirus spike glycoprotein

K24152 currently contains spike glycoproteins from SARS-CoV, SARS-CoV-2 (COVID-19 virus), and a bat coronavirus.

Drug information

The health information category of KEGG (Figure 1) contains drug labels for all prescription drugs and OTC drugs in Japan and in the USA. The Japanese drug labels are obtained from JAPIC (Japan Pharmaceutical Information Center) every month and processed (i) to assign KEGG DRUG D numbers to drug products according to the active ingredient, (ii) to assign D/C/E numbers to pharmaceutical additives of each drug product, (iii) to extract and standardize drug-drug interactions associated with contraindication and precaution using KEGG identifiers and ATC codes, (iv) to extract and standardize drug metabolism data using KEGG identifiers and (v) to link indications to KEGG DISEASE H numbers. Similar processing is performed on FDA drug labels every month excluding additives and drug-drug interactions. Furthermore, KEGG DRUG incorporates the most up-to-date drug information from the USA, Japan and Europe, keeping track of new drug approvals by FDA, PMDA and EMA, and new drug names incorporated in USAN, JAN and INN.

As a result of these efforts, KEGG has now become one of the most utilized drug information resource for Japanese society at large, being heavily accessed via web searches of drug names. Although the Japanese-language contents may not be of use to non-Japanese users, the processing of the entire set of drug labels has made KEGG annotations more accurate and comprehensive. The DRUG database contains, among others, manually curated data for drug targets with associated pathways, drug metabolizing enzymes and transporters with their interactions, and efficacy and disease information. Furthermore, gene variants as drug targets or markers are incorporated in the DRUG and NETWORK databases.

Virus-cell interaction

Thus far, viruses have been treated in KEGG as perturbants causing human diseases. There are eleven pathway maps for viral infections and their corresponding networks and network variation maps have been developed. Comparisons of viral proteins with bacterial effector proteins have also been made as perturbants in the network variation maps. However, knowledge of viral proteins represented in KEGG is still very much limited. In order to increase the number of experimentally characterized viral proteins and to define functional orthologs (KOs), we started accumulating different types of virus-cell interaction data, such as the interactions of viral entry proteins and cellular receptors, irrespective of whether signaling pathways inside the cell are known or not. We hope an increased number of viral KOs with known functions will enable viral genome based predictions of viral perturbations and possibly lead to practical applications. Eventually, however, in order to better understand viruses, it may be necessary to treat cellular organisms and viruses as a coevolving ecosystem rather than as individual system-perturbation relationships.

DATA AVAILABILITY

KEGG is a self-sustaining database. Without any substantial public funding, it is based mainly on the ‘community funding’ model, whereby the KEGG user community contributes financially for the development and maintenance of the database. KEGG is updated daily and made available at the KEGG website (https://www.kegg.jp/). The content is mirrored to the GenomeNet website (https://www.genome.jp/kegg/) one day later. A fixed version is released every three months with the release number.

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Conflict of interest statement. None declared.

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