Undergraduate Educator Network Webinar Series

Sponsored by Undergraduate Education Subcommittee SOT Education Committee

June 4, 2015 12:00 Noon ET

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Welcome

Kristine Willett, PhD
Co-Chair, Undergraduate Subcommittee
UEN Webinar Moderator
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Chair, Undergraduate Subcommittee
Chair, 2014-2015 Webinar Series
US Coast Guard Academy

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Using Open Source Biological Pathway Databases for Education and Discovery

Marc E. Gillespie, PhD
St. John’s University
Webinar Objectives

1. Analyze expression datasets and other data rich experimental results.
   - Faculty and Students can use topic specific datasets to highlight molecular function and functional interconnections.
   - Describe the methods that are used for biological pathway analysis.
2. Multiple methods are available. What are they, how are they used?
   - How might some of these methods be integrated into a class, or independent assignment activity to introduce or reinforce classroom topics?
   - Identify pathways that are over-represented within experimental data sets.
Webinar Objectives

3. What is pathway over-representation? What are the pValues assigned to these matches telling me?
   • What can I learn from this analysis?

4. Analyze expression datasets and other data rich experimental results.
   • Faculty and Students can use topic specific datasets to highlight molecular function and functional interconnections.
   • Describe ID mapping, pathway assignment and over-representation analysis and include these analysis as modules within a classroom setting.
Webinar Objectives, cont.

5. Best practices for summarizing pathway data analysis for students and faculty.
   • Common pitfalls
Webinar Overview

• Introduction to Pathway Databases
• Introduction to Reactome
• Worked examples for Reactome Use
Systems Biology

An entire set of approaches that all share the study of complex biological systems. By studying the components and process of these systems new patterns and process can be identified.

These new patterns are often called emergent properties.
You have to be someone with tenacity and patience. And love for science.

Dr. Gerhard Michal
Editor of the Roche Biochemical Pathways

Version 1 - 1965
Biological Pathway Diagrams

Goals:
Appreciation for individual steps of a process in the context of the whole process.

Bonus:
Appreciation for each process in the context of the entire organism.
Rationale – Journal information


"Caspase-8 is the key initiator caspase in the death-receptor pathway. Upon ligand binding, death receptors such as CD95 (Apo-1/Fas) aggregate and form membrane-bound signalling complexes (Box 3). These complexes then recruit, through adapter proteins, several molecules of procaspase-8, resulting in a high local concentration of zymogen. The induced proximity model posits that under these crowded conditions, the low intrinsic protease activity of procaspase-8 (ref. 20) is sufficient to allow the various proenzyme molecules to mutually cleave and activate each other (Box 2). A similar mechanism of action has been proposed to mediate the activation of several other caspases, including caspase-2 and the nematode caspase CED-3 (ref. 21)."

How can this be represented as a pathway?
Rationale - Figures

Open Source Pathway Databases

- A free, online, open-source curated database of pathways and reactions in human biology
- Authored by expert biologists, maintained by editorial staff & curators.
- Mapped to cellular compartment (but not tissue or developmental stage)
- Extensively cross-referenced
- Used to infer orthologous events in non-human species
- Tools for data analysis
Reactome data model: all of biology represented as reactions that transform input entities into output ones.

- Input 1: protein (UniProt), DNA/RNA (Ensembl), μmolecule (ChEBI) or complex (GO/PRO)
- Input 2: location (GO cell component)
- Regulation
- CatalystActivity (GO molecular function)
- Abnormality? (DO or EFO)
- Pathway (GO biological process)

Output 1: Reaction

Output 2: Reaction
From the entire human reaction network ...
...zoom into Apoptosis within Programmed Cell Death ...
... and to a molecule-level view of the Apoptotic Execution Phase.
... as displayed on our website
“structure” details from PDB for a protein
Diseases in Reactome have three causes.
- A mutated gene encodes an inactive product.
- A mutated gene encodes a product with a novel function.
- Infection introduces genes or gene products with novel functions.

Disease processes are variants of normal ones and fall into a hierarchy that parallels the normal one. Infections are a separate branch. Disease phenotypes are annotated with cross-references to DO and EFO.
Questions So Far…

Send questions and comments to “All Panelists” via Q&A panel.

Select the “Raise Hand” icon below the participant list if you wish to be unmuted.
Search results for **apoptosis**

**Species**
- Homo sapiens (335)
- Entries without species (9)
- Sus scrofa (45)
- Danio rerio (41)
- Mus musculus (40)
- Xenopus tropicalis (37)

**Types**
- Reaction (190)
- Pathway (84)
- Protein (31)
- Complex (28)
- Regulation (6)
- Set (3)

**Pathway** (3 results from a total of 84)
- Apoptosis (Homo sapiens)
  Apoptosis is a distinct form of cell death that is functionally and morphologically different from necrosis. Nuclear
- Regulation of Apoptosis (Homo sapiens)
  A regulated balance between cell survival and apoptosis is essential for normal development and homeostasis of
- Influenza Virus Induced Apoptosis (Homo sapiens)
  Influenza A virus induces apoptosis in a variety of ways including activation of host TGF-beta by expression of viral

**Reaction** (3 results from a total of 190)
- 14-3-3 epsilon attenuates NAD(+)-related apoptosis (Homo sapiens)
  NAD(+)-dependent reactions form a complex with the 14-3-3 epsilon isoform. The last one interacts with caspase 3 through its C terminal
- NOD1 induced apoptosis is mediated by RIP2 and CARD8 (Homo sapiens)
  NOD1 was found to coimmunoprecipitate with several proapoptotic containing long prodomain with CARDs or
- Influenza A virus induces apoptosis in a variety of ways including binding of viral PB1-F2 to host mitochondrial

**Compartment**
1. Analyze Expression Datasets

The Big Experiment

List of Differentially Expressed Molecules

Pathways and beyond.....
2. Overrepresentation analysis

Asking the question: Is there a surprising result in my data set? With the data set being a list of genes and the surprise being that they are clustered in some biological process.

Fisher’s exact test (hypergeometric test)

Example: Bag O’ Marbles

P-value – The probability of identifying the genes in the enriched pathway by chance.
Influencers: size of the gene list and background gene list.
3. Analysis of user-supplied expression data
4. Let’s Practice
Questions So Far....

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5. Classroom Integration

What do these genes have in common? What process are they involved in? How do they work together?

• MyD88
• TRAM
• TRIF
• TIRAP
• MyD88
• Mal
5 – Classroom Integration

Using Pathway Databases To Support And Extend Student Understanding Of Scientific Literature
Example: Benzene

Global Gene Expression Profiling of a Population Exposed to a Range of Benzene Levels

Cliona M. McHale,1 Luoping Zhang,1 Qing Lan,2 Roel Vermeulen,3 Guilan Li,4 Alan E. Hubbard,1 Kristin E. Porter,1 Reuben Thomas,5 Christopher J. Portier,5 Min Shen,2 Stephen M. Rappaport,1 Songnian Yin,6 Martyn T. Smith,1 and Nathaniel Rothman2
Credits

OICR / CSHL
Lincoln Stein
Marc Gillespie
Robin Haw
Bruce May
Marija Orlic-Milacic
Karen Rothfels
Sheldon McKay
Joel Weiser
Guanming Wu

EBI
Henning Hermjakob
Kostas Billis
Antonio Fabregat-Mundo
Phani Garapati
Bijay Jassal
Steve Jupe
Max Koch

NYU
Peter D’Eustachio
Lisa Matthews
Veronica Shamovsky

NHGRI Grant # U41 HG003751

EU 6th Framework Programme grant
LSHG-CT-2005-518254 "ENFIN"
Questions and Comments

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UEN Webinar Series

Past Recordings and slides:

- Having It All: Teaching, Research, and Service at a Small Liberal Arts College: A Toxicologist's Perspective
- Education and Enrichment Activities for Educators
- The Use of Technology to Teach Toxicology and Related Disciplines
- Evidence-Based Instructional Practices in Undergraduate Science Courses
- Academic Service Learning (AS-L) in an Undergraduate Pharmacology Course
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Thank you for participating today!

Please provide feedback via the link sent by email

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