Systems Pharmacology Approach for the Prediction of Adverse Drug Reactions

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ABSTRACT

In drug development ensuring patient safety is crucial, and new ways to predict adverse drug reactions are needed. An adverse drug reaction is a harmful and unintended reaction to a drug that may be considered as 'on-target' or 'off-target.' A systems pharmacology approach to collating information about proteins in a pathway beyond a known drug target, along with clinical information about adverse effects of drugs known to interact with different proteins in the same pathway, could potentially predict a new drug's adverse reactions. The article "Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010," (Downing et al. 2017) describes novel therapeutics with significant safety findings identified after drugs were approved, including adalimumab, golimumab, sunitinib, and pregabalin. These drugs all act within the MAPK pathway, which has sub-pathways linked by the MEK1 gene. This gene was therefore selected as a proof-of-concept evaluation to test the systems pharmacology pathway approach. Using R, a statistical analysis programming language, and Metabase, an R interface to Metacore, a manually-curated database of molecular interactions, an algorithm was developed to find genes within a parameterized distance of MEK1 and drugs that target those genes. Additionally FAERS, the FDA's adverse event reporting system will provide adverse reactions of drugs of interest. Using visual-analytic descriptive techniques, the adverse effects mapped to the MAPK pathway by will be compared with the adverse effects of the four drugs named above to evaluate this systems pharmacology approach to help predict what adverse reactions may be related to a new drug.

OBJECTIVES

- Design, develop and test a pharmacoinformatics approach integrating information from several scientific databases, with input from disciplines such as pharmacology and biology to find genes within a parameterized distance of MEK1 and identify drugs that target those and their adverse events.
  - R, statistical programming language, was used to mine data from Metacore, an R interface to Metabase, a database of molecular interactions and drugs. This data included genes, their locations relative to one another, the mechanism of reactions between genes, the effect they have on their target organ, and drugs.
  - FAERS, the FDA's adverse event reporting system, was used to identify known adverse events of drugs affecting the pathway of interest.

BACKGROUND

- The article "*Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*" was used to identify approved drugs with safety events that shared a common pathway.
  - Out of 48 drugs analyzed, the four below drugs target the MAPK pathway:

Drug Name	Molecular Target	Adverse Events (count of reports)
Adalimumab	Tumor necrosis factor	Arthralgia (4781) Pyrexia (3765) Nausea (3119) Crohn's Disease (2800)
Golimumab	Tumor necrosis factor	Pneumonia (277) Arthralgia (92) Headache (89) Malaise (60)
Sunitinib	Platelet-derived growth factor receptor beta	Thrombocytopenia (472) Stomatitis (373) White blood cell count decreased (252) Hemoglobin decreased (193)
Pregabalin	Voltage-dependent calcium channel alpha-2/delta-1	Nausea (2177) Malaise (2062) Fatigue (1947) Dyspnoea (1600)

- The MAPK Pathway is a chain of proteins that communicate a signal from the cell membrane to the DNA in the nucleus of the cell (Figure 1).
  - Two sub-pathways of the MAPK Signaling Pathway, the **Classical MAP kinase pathway** and the **JNK and p38 MAP kinase pathway** connect via the MEK1 gene.
  - The MEK1 Gene was selected to test the systems pharmacology pathway approach.

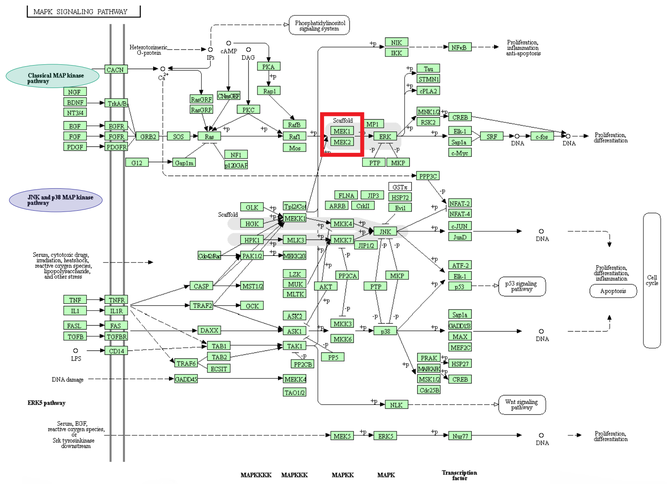

Figure 1. KEGG Representation of the MAPK Pathway.

METHODS

- To identify upstream or downstream proteins of MEK in various pathways, the MEK gene was identified as either the start (head) or end (tail) of a sequence of proteins in well-described (high trust) canonical signaling pathways, defined by Metabase as 'noodles.'
- All genes in identified noodle pathways were listed, and the drugs that target those genes and their respective adverse events were identified.

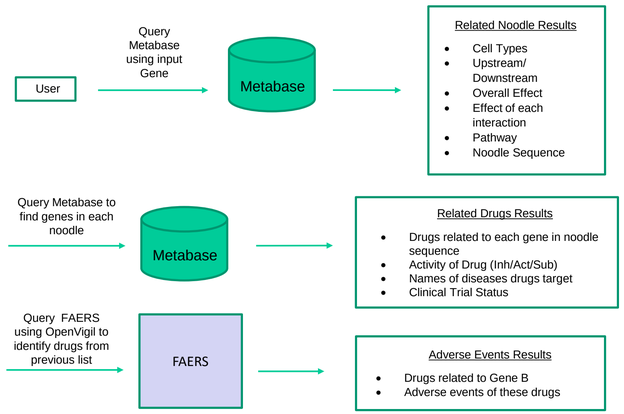

Figure 2. Flowchart of the pharmacoinformatics Approach.

RESULTS

Related Noodles

- Using R, six distinct noodle pathways were identified in Metabase, each having MEK1 as either the **Head** or **Tail** of the noodle.

Gene A	Gene B	Noodle	Pathway Name
MEK1	Tubulin beta 2B	MEK1--MSX1--Tubulin beta 2B	BMP signaling in embryonic stem cell neural differentiation
MEK1	Neurogenin 2	MEK1--MSX1--Neurogenin 2	BMP signaling in embryonic stem cell neural differentiation
MEK1	NCAM1	MEK1--MSX1--NCAM1	BMP signaling in embryonic stem cell neural differentiation
IL-6	MEK1	IL-6--IL-6 receptor--MEK1	IL-6 signaling in breast cancer cells
GnRH1	MEK1	GnRH1--GnRH receptor--MEK1	Gonadotropin-releasing hormone (GnRH) signaling
Urease B (H. pylori)	MEK1	Urease B (H. pylori)--CD74--MEK1	Effect of H. pylori infection on inflammation in gastric epithelial cells

- Three distinct noodles were found related to the BMP signaling pathway (Figure 3), and this pathway representation in Metabase is shown as an example below (Figure 4).

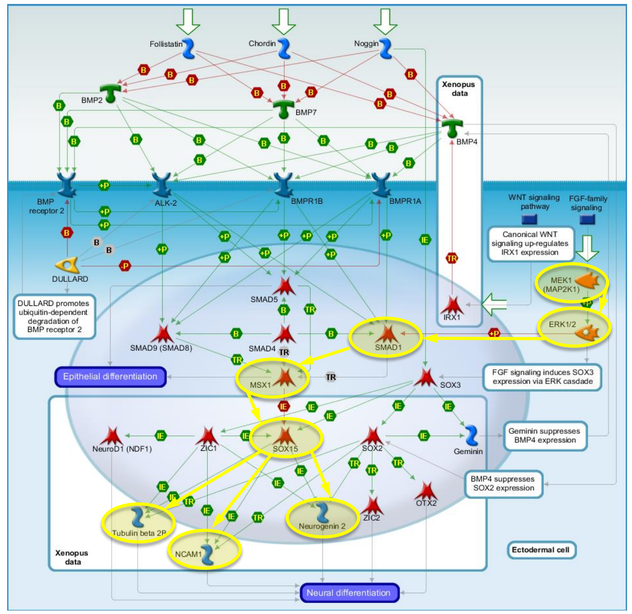

Figure 3. Metabase BMP Signaling Pathway Depicting the three Distinct Noodles in yellow.

Related Drugs

- An R script was written to select distinctive genes in the BMP signaling pathway, and any FDA approved drugs targeting these genes from Metabase:
  - Nine distinct genes SOX15, TUBB2B, MAP2K1, MAPK1, MAPK3, MSX1, SMAD1, NEUROG2, and NCAM1 were identified.
  - Six FDA approved drugs were found to target these nine genes.

Drug Name	Target	Disease Name	Action
Eribulin	Tubulin beta-1 chain (in microtubules)	Breast neoplasms	Inhibitor
Estramustine	Tubulin beta-1 chain (in microtubules)	Prostatic neoplasms	Inhibitor
Ixabepilone	Tubulin beta-3 chain (in microtubules)	Breast neoplasms	Inhibitor
Paclitaxel	Tubulin beta-1 chain (in microtubules)	Breast neoplasms	Inhibitor
Vindesine	Tubulin beta-1 chain (in microtubules)	Lung neoplasms	Inhibitor
Vinorelbine	Tubulin beta chain (in microtubules)	Carcinoma, Non-Small-Cell Lung	Inhibitor

Adverse Events

- Using OpenVigil to access FAERs, the FDA's Adverse Event Reporting System, the adverse events for the drugs that targeted the genes involved in the BMP Signaling Pathway.
- 14 adverse events were detected for drugs targeting the MAPK and BMP pathways, 11 were found that affected both pathways (Figure 4).

Drug Name	Adverse Events (count of reports)
Eribulin	Neutropenia (56) Pyrexia (29) Pneumonia (27) Thrombocytopenia (12)
Estramustine	Dyspnoea (25) Thrombocytopenia (14) Pulmonary embolism (14) Malaise(10)
Ixabepilone	Stomatitis (51) Thrombocytopenia (37) Arthralgia (37) White blood cell count decreased (35)
Paclitaxel	Dyspnoea (1461) Pyrexia (1075) Pneumonia (591) White blood cell count decreased (589)
Vindesine	Thrombocytopenia (15) Pyrexia (14) Pneumonia (12) Hemoglobin decreased (9)
Vinorelbine	Pyrexia (258) Nausea (159) Pneumonia (137) Fatigue (135)

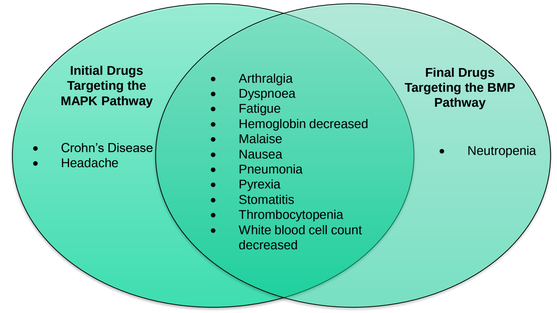

Figure 4. Comparison of Adverse Events of Drugs Targeting Pathways.

CONCLUSION

- Multiple adverse events were identified in common for drugs targeting upstream and downstream proteins in the MAPK and BMP pathways; differentiating pathways by tissue type may further help to predict the adverse events of a new drug target.
- This new integrated informatics approach that uses Metabase, FAERS, KEGG, and other databases has the potential to identify adverse events.

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