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Applying IPA for Your Biomarker Research

IPA® is software that combines powerful analysis tools with a rich biological knowledge base that helps you extract biological meaning from your data. If you are studying gene expression using microarray, RT-PCR, next-generation sequencing, biomarkers, microRNAs, or other high-throughput experimental approaches, IPA can help you narrow in on the most important molecules in your dataset and discover how they affect biological functions and diseases. You can easily see your results projected onto well-known pathways. This helps orient you to your dataset and makes an interactive framework ideal for navigating complex biology.

For biomarker research, the challenge is identifying, prioritizing, and validating good biomarkers. IPA-Biomarker® is functionality in IPA that enables prioritization of experimentally validated and predicted targets and leverages IPA's rich biomarker content. Learn more about IPA's biomarker capabilities and content at <http://www.ingenuity.com/products/ipa-biomarker.html>.

Examples of IPA Referenced in Recent Publications on Biomarkers

Through April 2011, IPA has been referenced in over 4,000 publications, with IPA and biomarkers referenced in about 900 publications. Below are four examples where IPA was used by scientists for their research. You can search for additional publications that cite biomarkers and IPA at <http://www.ingenuity.com/library/search-pub.html>.

1. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis

<http://www.nature.com/nature/journal/v466/n7309/full/nature09247.html>

Nature, August 19, 2010. Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T, Wilkinson KA, Banchereau R, Skinner J, Wilkinson RJ, Quinn C, Blankenship D, Dhawan R, Cush JJ, Mejias A, Ramilo O, Kon OM, Pascual V, Banchereau J, Chaussabel D, O'Garra A.

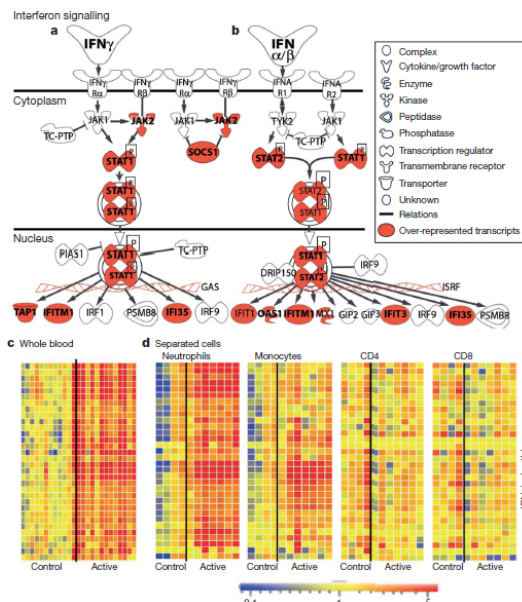


Figure 1: Interferon-inducible gene expression in active TB. Canonical pathway of **Ingenuity Pathways Analysis (IPA)** for interferon signaling; symbol indicates gene function (legend on right).

Transcripts over-represented in test set patients with active TB shaded red. a, Type II IFN-c. b, Type I IFN-ab signaling. Transcript abundance of representative IFN-inducible genes inactive TB from (c) whole blood and (d) separated blood leucocyte population. Transcript abundance/expression is normalized to the median of the healthy controls.

Keywords

Tuberculosis, Inflammation, Infectious diseases, Transcriptional Biomarkers

Experimental Platform

Microarray

Institution Affiliations

Division of Immunoregulation, MRC National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK

Literature Citations

“Additional functional analysis of differentially expressed genes was performed using **Ingenuity Pathways Analysis (IPA)** (Ingenuity Systems, www.ingenuity.com). Canonical pathways analysis identified the pathways from the Ingenuity pathways analysis that were most significantly represented in the data set. The significance of the association between the data set and the canonical pathway was measured using Fisher’s exact test to calculate a P value representing the probability that the association between the transcripts in the data set and the canonical pathway was explained by chance alone, with a Benjamini–Hochberg correction for multiple testing applied. The program can also be used to map the canonical network and overlay it with expression data from the data set.”

2. Bypass Mechanisms of the Androgen Receptor Pathway in Therapy-Resistant Prostate Cancer Cell Models

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0013500>

PLoS ONE, October 2010, Rute B. Marques, Natasja F. Dits, Sigrun Erkens-Schulze, Wytse M. van Weerden, Guido Jenster

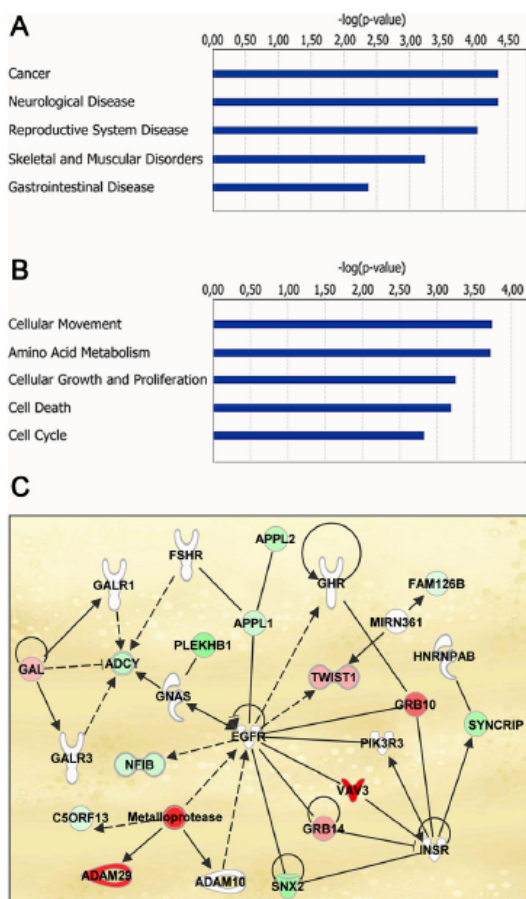


Figure 2: Biological processes deregulated in the hormonerefractory sublines. Top 5 biological functions enriched in the therapy-resistant sublines: (A) diseases and disorders, (B) molecular and cellular functions. (C) Example of Network analysis for PC346DCC showing deregulation of hormone and growth-factor receptor signaling: up-regulated genes are represented in red and repressed genes in green. Analysis was performed using **Ingenuity Pathway Analysis (IPA) software** (www.ingenuity.com). doi:10.1371/journal.pone.0013500.g003

Keywords

Prostate Cancer, Biomarkers, Androgen

Experimental Platform

Microarray, RT-PCR

Institution Affiliations

Department of Urology, Josephine Nefkens Institute, Erasmus Medical Center, Rotterdam, The Netherlands

Literature Citations

"The selected 487-gene signature was classified according to Gene Ontology (GO) Biological Processes using the Database for Annotation, Visualization and Integrated Discovery (DAVID)[26,27]. Annotation clustering analysis showed enrichment in categories involved in organ development, reproductive system differentiation, cellular growth, differentiation and apoptosis (Table 4). **Ingenuity Pathway Analysis (IPA)** was used to identify enrichment in "diseases and disorders", "molecular and cellular functions", and to search for intrinsic pathways/networks within the selected gene sets (www.ingenuity.com). Cancer and reproductive system disease were ranked in the top 3 of "diseases and disorders", which logically confirmed the enrichment of genes associated with PCa, such as hepsin, clusterin, vitamin D receptor, trefoil factor 3, tumor protein D52, the AR itself and several of its target genes (Fig. 3A and 3B, respectively). Furthermore, we used Network analysis to screen the 276-gene signature of PC346DCC for potential alternative growth pathways that could be involved in bypassing the AR signaling. Interestingly, signaling via growth-hormone receptor (GHR), insulin receptor (INSR) and epidermal growth factor receptor was among the top 10 Networks (score = 20) showing deregulation in PC346DCC (Fig. 3C)."

3. Discovery of pathway biomarkers from coupled proteomics and systems biology methods

<http://www.biomedcentral.com/content/pdf/1471-2164-11-S2-S12.pdf>

BMC Genomics, 2010. Fan Zhang, Jake Y Chen

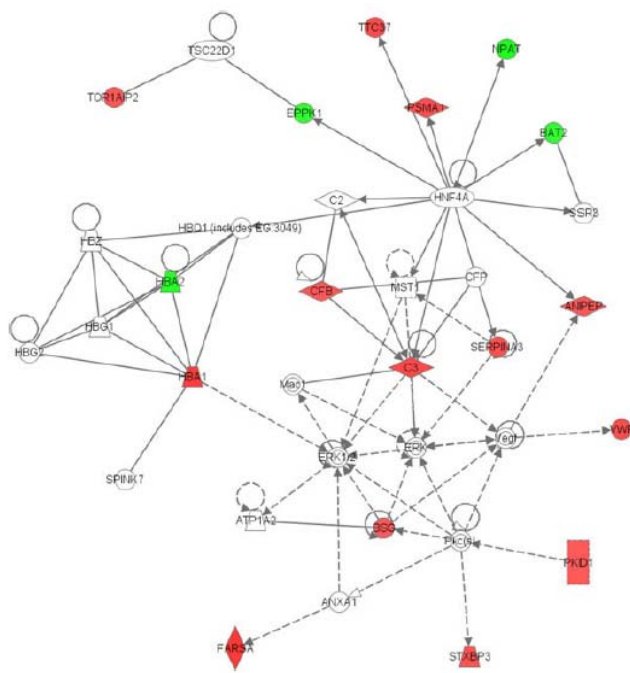


Figure 3: The 25 Proteins Are Involved in an Endocrine System Disorders Network. Red stands for over-expressed and green for under expressed. A comparison of the set of 254 proteins with published findings from proteomic analysis of human breast cancer cell lines yielded 25 differentially expressed proteins in common. Top networks were identified by using **Ingenuity Pathway Analysis (IPA)**.

Keywords

Breast Cancer, Protein Biomarkers

Experimental Platform

LC/MS

Institution Affiliations

Indiana University School of Informatics, Indianapolis, IN 46202. Dept. Computer and Information Science, Purdue School of Science, Indianapolis, IN 46202. Indiana Center for Systems Biology and Personalized Medicine, Indianapolis, IN 46202.

Literature Citations

"Then, top networks and pathways were identified with **Ingenuity Pathways Analysis (IPA)**, KEGG and HPD pathway databases. And Level 2 and 5 of biological process in gene ontology were mainly studied. And then, two testing cancer dataset were used to validate the result. Last, assay development and clinical trials for panel biomarkers are planned for the future.... **Ingenuity Pathway Analysis (IPA)** was used for building network."

4. Prognostic Biomarkers for Esophageal Adenocarcinoma Identified by analysis of Tumor Transcriptome

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0015074>

PLoS ONE, November 2010. Soo Mi Kim, Yun-Yong Park, Eun Sung Park, Jae Yong Cho, Julie G. Izzo, Di Zhang, Sang-Bae Kim, Jeffrey H. Lee, Manoop S. Bhutani, Stephen G. Swisher, Xifeng Wu, Kevin R. Coombes, Dipen Maru, Kenneth K. Wang, Navtej S. Buttar, Jaffer A. Ajani, Ju-Seog Lee

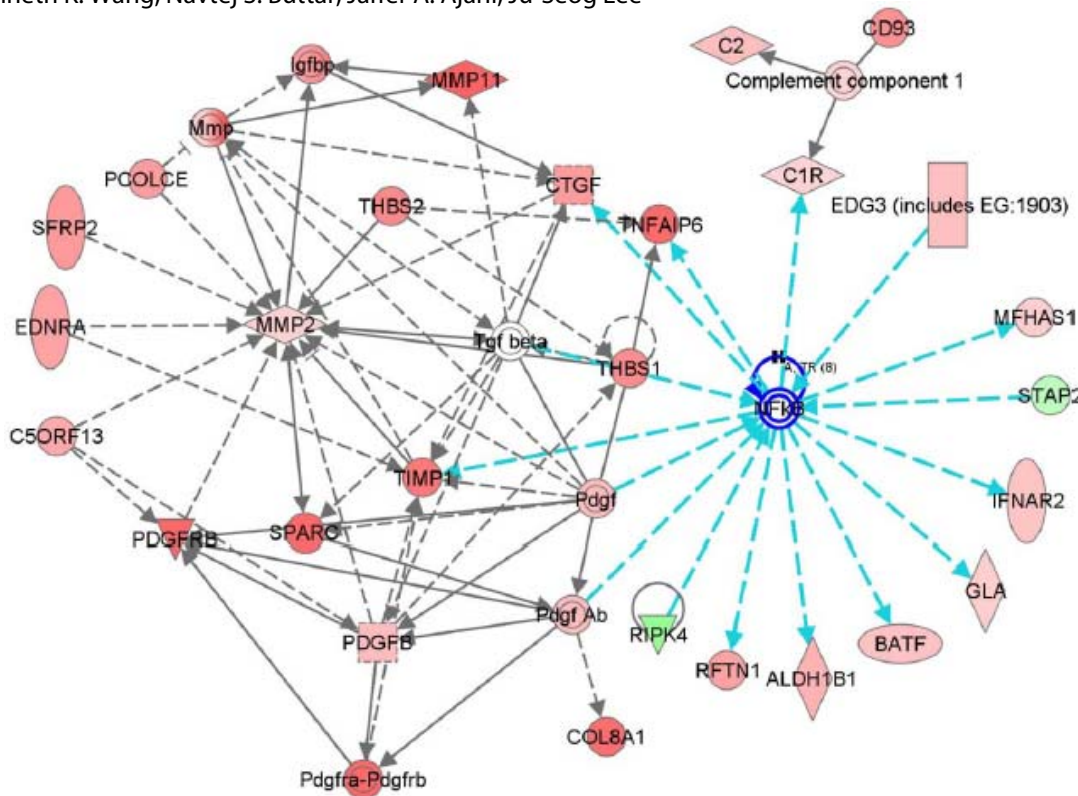


Figure 4: Gene networks from **Ingenuity Pathway Analysis (IPA)**. Global networks of inter-connection among genes and expression patterns of genes in network #1 in Appendix Table 1. Red and green colors in each shape indicate up- or down-regulation of expression in cluster B when compared with cluster A and C. Genes in gray color are not in the list but associated

with the regulated genes. Each line and arrow represents functional and physical interaction and direction of regulation demonstrated in the literature. Genes inter-connected with NF- κ B are highlighted in blue lines.

Keywords

Biomarkers, Esophageal, Tumor, Adenocarcinoma

Experimental Platform

Gene Expression Profiling, DNA microarray technology, RT-PCR

Institution Affiliations

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Literature Citations

"The expression level of each gene was transformed into a log 2 base before further analysis. Gene network analysis was carried out using **Ingenuity Pathways Analysis (IPA) software** (Ingenuity Systems Inc., CA, USA).... Having found a gene expression pattern well reflecting prognosis of EAC patients, we next tried to uncover gene networks that might be enriched in these genes. Gene network analysis using **Ingenuity Pathway Analysis (IPA)** (Ingenuity Systems, CA, USA) was applied to the genes and their expression patterns. This analysis revealed a series of putative networks, of which the 20 with the highest scores are listed in Table S1. For example, functional connectivity of the top network (network#1) revealed a strong overrepresentation of NF- κ B (Figure 3). Although the expression of NF κ B was not altered, the expression levels of many downstream target genes of NF- κ B were up-modulated in patients in cluster B, strongly indicating that transcriptional activity of NF- κ B is high in cluster B and might be responsible for the poorer prognosis of these patients."

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