

Ingenuity[®] Science Spotlight:

Articles featured in the Ingenuity Science Spotlight represent some of the best and most diverse examples of how IPA[®] has contributed to research across multiple platforms, research areas, and research goals.



A network-based analysis of systemic inflammation in humans.

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<http://www.ncbi.nlm.nih.gov/pubmed/16136080?dopt=Abstract>

Members of the collaborative research program called Inflammation and Host Response to Injury are seeking to identify the biological processes that underlie systemic inflammation, the uncontrolled, body-wide inflammation associated with severe trauma and burns. In a novel study approach, healthy human volunteers were injected with endotoxin, triggering the innate immune response that leads to acute inflammation. This inflammatory response is self-limiting and resolves within 24 hours. The team evaluated gene expression in whole blood leukocytes taken from subjects before endotoxin exposure and at several time points afterwards. They found that endotoxin induced changes in the expression of 3,714 genes.

To more clearly understand the temporal nature of the gene expression changes, the team created a model inflammatory cell that included 292 genes that participate in innate immunity and inflammation, and their direct molecular pathway interactions as detailed in the Ingenuity Knowledge Base. The time course expression data revealed how these genes are modulated during the immuno-inflammatory response to endotoxin challenge and its resolution. Among their findings:

- Expression of many proinflammatory cytokines and chemokines (for example, *TNFSF2 (TNF)*, *IL1A*, *IL1B*, and *CSC1 (GROa)*) reach peak levels at 2-4 hr after exposure to endotoxin.
- Expression of numerous transcription factors that activate and curb the innate immune response is increased at 4-6 hr after exposure to endotoxin.
- Increases in the mRNA of secreted and membrane-associated proteins (*IL1RAP*, *IL1R2*, *IL10*, and *TNFRSF1A*) occurs 4-6 hrs after exposure to endotoxin.

Using IPA, the team constructed a gene network of the global biological processes involved in the response to endotoxin challenge. Within this computationally generated global network, they identified nine sub-networks or *functional modules* involved in mitochondrial energy production, protein synthesis, protein degradation, the COP9 signalosome, and the proteasome. Their work documents how endotoxin affects these highly interconnected network modules. Notably, modules involved in mitochondrial energy

production, protein synthesis, and protein degradation were suppressed, implicating their involvement in innate immune system tolerance

Supplemental information to the paper includes more details about the network analysis methodology and demonstrates how to use IPA to elucidate coordinated pathway function from microarray time-series datasets.