# Machine learning sheds light on the biology of toxin exposure

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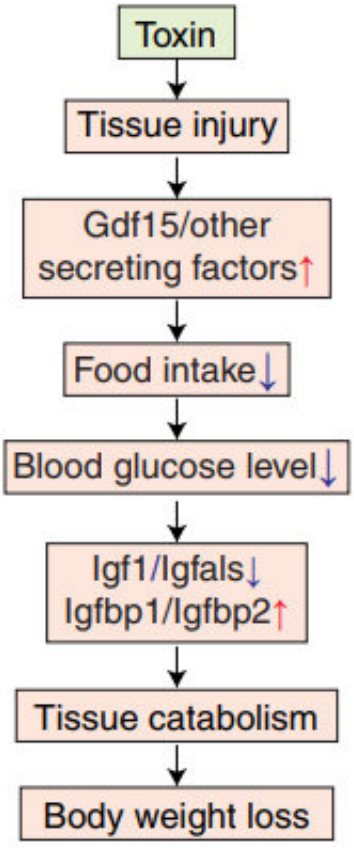


A new proposed mechanism of toxin-induced body weight loss. Shimada and Mitchison, 2019.

Exposure to potentially harmful chemicals is a reality of life. Our

ancestors, faced with naturally occurring toxins, evolved mechanisms to detoxify and expel damaging substances. In the modern world, our bodies regularly process chemicals, from medicines and food additives to agricultural and industrial chemicals, to protect our tissues from harm.

As the organs responsible for metabolizing and excreting toxic chemicals, the liver and kidneys bear the brunt of this exposure and are at the highest risk for toxin-induced damage. Understanding how these organs respond to, or are damaged by, toxins is of particular importance in pharmaceutical development and public health research.

Now, Harvard Medical School investigators have developed a machine learning approach using high-quality, large-scale animal model data that sheds new light on the biology of the liver and kidneys after toxin exposure.

The findings, recently published in *Molecular Systems Biology*, reveal new mechanisms of toxin vulnerability and tolerance that may be broadly relevant to studies of human disease, the authors said.

Their analysis—based on a publicly available data set of the effects of 160 different chemicals on physiology, histopathology and gene expression in rats—revealed nine distinct patterns of response to chemical exposure that the authors termed "disease states."

These states shed light on the dynamics of toxin-induced liver and kidney injury, including defense mechanisms and novel biomarkers, and provide insights into molecular signals that cause toxin-induced appetite suppression and weight loss.

"We used machine learning to ask a simple question: What can we learn from this rich data set about what happens to the liver and kidneys after exposure to different chemicals?" said lead study author Kenichi

Shimada, HMS research fellow in therapeutic science in the Laboratory of Systems Pharmacology.

Shimada and co-author Tim Mitchison, the Hasib Sabbagh Professor of Systems Biology in the Blavatnik Institute at HMS, focused on the Open TG-GATEs database, the result of a 10-year effort by a Japanese public-private consortium to assess 170 different compounds with the aim of improving and enhancing drug safety. These compounds represent a wide range of chemicals and medications, including common ones such as ibuprofen and acetaminophen, known for their toxic effects on the liver and kidneys at high doses.

Each compound was administered at multiple dosages and time points to rats, as well as to rat and human liver cells grown in culture. For each of these treatment conditions, a variety of measures were collected, including blood chemistry, physiological measures such as body and tissue weight, histology and gene expression data.

To identify commonalities and patterns in how the liver and kidneys respond to different drugs, Shimada and Mitchison developed an unsupervised machine-learning approach in which a computational algorithm—without relying on predefined questions, labels or categorizations in order to avoid researcher-introduced bias—analyzed data on 160 compounds administered in rats, representing more than 3,500 treatment conditions.

## Injury patterns

Their initial analyses relied on blood chemistry and body and tissue weight data, which reflect the standard clinical tests used to diagnose human patients.

These analyses revealed nine different patterns of response to chemical

exposure that the researchers termed disease states. Additional computational analyses of gene expression and histopathology data—microscope-based examinations of tissue performed by pathologists that are also used in routine clinical assessment of toxicity—shed light on the distinct characteristics of each disease state.

The states fell into two broad categories. One set reflected tissue injury. For example, exposure to nonsteroidal anti-inflammatory drugs such as ibuprofen induced a late-onset response in the liver associated with bleeding, a well-documented side effect of these drugs. The team saw a pattern of response marked by increased gene expression linked with inflammation and blood coagulation, decreased levels of red blood cells and hemoglobin, and elevated markers for red blood cell production.

Other injurious disease states corresponded with response patterns that indicated acute liver injury, bile duct impairment, liver cell damage and kidney damage.

The other group of disease states reflected neutral, unknown or even potentially beneficial responses. For example, synthetic hormones triggered a defensive response pattern marked by enhanced tolerance to toxins. The activity of genes involved in toxin metabolism increased, and so did biomarkers that indicated increased resistance to ferroptosis—a recently recognized form of regulated cell death triggered by the accumulation of metabolic byproducts.

## Tolerance transition

Unexpectedly, the team found that some injurious states transitioned to this defensive response over time. Increased toxin tolerance was strongly associated with increased resistance to ferroptosis in the liver, but not to other forms of cell death. A better understanding of this process may help uncover ways to target ferroptosis and improve the liver's ability to

tolerate drugs.

"Often, patients have to stop taking medication because of adverse side effects and wait for their bodies to recover before they can begin again," Shimada said. "This gives us a starting point to study tolerance in a controlled format, and perhaps find ways to improve dosing schedules or even pretreat patients so that they are better able to cope with toxicity and suffer less tissue injury."

Shimada and Mitchison also shed light on why weight loss is such a common feature of toxin exposure by analyzing genetic and molecular biomarkers alongside changes in body weight.

They found that the expression activity of insulin-like growth factor-1 (Igf1) and three other associated genes were strongly up- or down-regulated. In the data set, rate of food consumption was most strongly linked with body weight over time, as expected, which could be partially explained by the role these genes play in blood sugar levels. These signals appear to collectively mediate organ-to-body communication as part of the toxin response, the authors said.

The team also identified a gene, Gdf15, that was linked to appetite suppression. The protein encoded by this gene is known to regulate feeding by acting on receptors in the brain stem. Increased Gdf15 gene expression activity, particularly in the kidneys, was a consistent response to tissue injury. The pathway may represent a novel mechanism for appetite suppression and toxin-induced weight loss, but further studies are needed to clarify its role, the authors said.

Because the data set is based on animal models, the findings are not immediately applicable in humans, Shimada said. In addition, the computational analyses revealed statistical clusters of toxin-induced changes in the kidneys and liver but are not inclusive of other organ

systems and likely miss responses unique to one drug or do not share similarities with other responses.

The methodology and findings, however, provide important new insights into biomarkers and mechanisms underlying toxin response and offer a framework for future research, such as more refined toxicology studies in humans, the authors said.

"Data-driven diagnosis of disease is an eventual goal for researchers, and it is absolutely achievable with access to high quality data as in our paper," Shimada said. "I think the biological features we discovered, and in particular the tolerance mechanisms, can, with further study, inform treatment strategies and perhaps even the design of better medicines."

**More information:** Kenichi Shimada et al, Unsupervised identification of disease states from high-dimensional physiological and histopathological profiles, *Molecular Systems Biology* (2019). DOI: 10.15252/msb.20188636

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