Unravelling NASH and insulin resistance: Insights from the department of human health and nutritional sciences

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Emily Warrender July 9, 2025

Open Access Government sits down with a researcher from the Department of Human Health and Nutritional Sciences to discuss their groundbreaking work on nonalcoholic steatohepatitis (NASH) and insulin resistance. Their research delves into the molecular underpinnings of these increasingly prevalent conditions, offering new avenues for understanding, prevention, and treatment

Given your research focuses on nonalcoholic steatohepatitis (NASH) and insulin resistance, what do you believe are the most critical public health implications of these conditions today?

NASH and insulin resistance are increasing public health problems with widespread social and economic consequences. Public health efforts must shift toward early detection, improved education, and targeted interventions that address the metabolic origins of the disease.

By addressing obesity and promoting lifestyle changes, healthcare systems can help mitigate the growing impact of these interrelated chronic conditions.

How do you envision your research findings translating into practical strategies for improving human health and nutrition at a population level? Are there any immediate applications you foresee?

Our studies expand the fundamental knowledge of liver health by integrating the regulation of lipid metabolism, epigenetics, and therapeutic interventions into a unified framework for better understanding and treating non-alcoholic steatohepatitis (NASH).

They reinforce the importance of membrane phospholipid homeostasis in preventing fat accumulation and the development of insulin resistance and introduce epigenetic modulations as a promising avenue for reversing disease progression.

Examining: Pcyt2 deficiency causes age-dependent development of nonalcoholic steatohepatitis and insulin resistance, that could be attenuated with phosphoethanolamine.

Your work identifies Pcyt2 deficiency as a causative factor in NASH and insulin resistance. Could you elaborate on the significance of this specific molecular pathway in the context of metabolic disease development?

The study elucidates the pivotal role of the Kennedy pathway for phosphatidylethanolamine (PE) synthesis in maintaining metabolic homeostasis. In this pathway, the enzyme Pcyt2 catalyzes the rate-limiting step, and in conditions of Pcyt2 deficiency, as shown in the heterozygous mouse model (Pcyt2+/-), the reduced flux through this pathway sets off a cascade of metabolic dysfunctions that affect gene expression and signal transduction, contributing to altered glucose and lipid metabolism. Importantly, even before overt liver disease is detectable, young mice with Pcyt2 deficiency exhibit altered expression of the key metabolic regulators. As they age, mice develop NASH characterized by insulin resistance, liver fibrosis, and inflammation. The supplementation with phosphonoethanolamine (PEA), an artificial substrate for Pcyt2, can reverse the metabolic derangements caused by its deficiency.

This suggests that in scenarios where the Kennedy pathway is compromised, restoring or bypassing its rate-limiting step could ameliorate liver steatosis, inflammation, and insulin resistance. Immediate applications could involve developing pharmacological agents or nutritional supplements that enhance or mimic Pcyt2 activity, which might be especially beneficial in high-risk populations predisposed to NASH and related metabolic disorders.

Your study highlights the age-dependent development of these conditions. What implications does this age dependency have for preventative or therapeutic strategies, particularly for an ageing population?

The study showed that early defence mechanisms may buffer against the full-blown development of NASH. As the body ages, the cumulative impact of altered membrane dynamics, reduced energy metabolism, and increased oxidative stress overturns the balance, leading to liver pathology and systemic metabolic dysfunction. The gradual, age-dependent disease progression indicates a critical window for early intervention before compensatory mechanisms begin to fail. Screening for the subtle metabolic changes or biomarker shifts in individuals at risk could enable preventative measures before irreversible damage occurs.

Therapeutic regimens tailored for older individuals might require a combination approach that not only incorporates nutrition modulation but also addresses inflammation and oxidative stress. Stratifying individuals based on their metabolic profile and age could help in fine-tuning intervention strategies. For instance, older patients demonstrating early biochemical signs of membrane dysfunction might be prioritized for targeted therapies, whereas younger at-risk individuals might focus primarily on preventive lifestyle changes.

Beyond the molecular findings, how might the insights from this paper influence our understanding of dietary recommendations or nutritional interventions for individuals at risk of NASH?

The impairments in the Kennedy pathway for phospholipid PE synthesis result in a dramatic imbalance in membrane composition and play a significant role in NASH development. Individuals at risk of NASH, especially those whose metabolic profiles

indicate impaired phospholipid profiles, might benefit from diets that optimize not only macronutrients but also specific bioactive compounds that ensure proper phospholipid metabolism. The demonstration that supplementation with PEA can mitigate the progression of NASH in an animal model paves the way for considering similar strategies in humans. However, further research is necessary to confirm the safety and efficacy of PEA in clinical settings.

Examining: Epigenome-wide methylation analysis shows phosphonoethylamine alleviates aberrant DNA methylation in NASH caused by Pcyt2 deficiency.

This publication delves into epigenome-wide methylation changes. How does the concept of epigenetics, and specifically DNA methylation, offer a new lens through which to understand the progression and potential treatment of NASH?

In the context of NASH, the discovery of widespread shifts in methylation patterns suggests that the progression of liver pathology is not solely driven by permanent genetic mutations but also by reversible epigenetic changes. Unlike genetic alterations, these modifications can potentially be corrected or even re-programmed with appropriate interventions.

Pcyt2 deficiency is associated with widespread aberrant epigenetic reprogramming in genes crucial for energy metabolism and cellular homeostasis. As such, epigenetic changes compound the metabolic dysfunction by further altering gene expression, potentially leading to inflammation, fibrosis, and insulin resistance seen in NASH.

Treatment with PEA dramatically attenuates abnormal DNA methylation, suggesting that targeted nutritional or pharmacological interventions can not only ameliorate metabolic disturbances but also reverse detrimental epigenetic modifications. In practical terms, developing treatments that modulate DNA methylation could improve gene expression patterns associated with lipid metabolism and inflammation, thereby halting or even reversing the progression of liver disease.

The finding that phosphonoethylamine alleviates aberrant DNA methylation is significant. Could you explain the practical implications of targeting epigenetic modifications for the treatment of NASH?

The proof-of-concept that PEA can mitigate abnormal DNA methylation opens an avenue for the development of new drugs targeting epigenetic modifiers. Future agents could be designed to either mimic the action of PEA or directly inhibit aberrant methylation processes, offering another therapeutic tactic to manage or reverse NASH. This not only broadens the therapeutic arsenal but also allows for continuous innovation in the field of metabolic disease treatments.

The field of epigenetic modifications offers a promising and multifaceted strategy for treating NASH. It provides the possibility to reverse pathological gene expression, create early diagnostic tools, and implement personalized therapies, all of which could

dramatically impact patient outcomes. This approach signifies a shift from merely managing symptoms towards addressing the root molecular disturbances that drive liver disease.

How might the insights from your epigenome-wide methylation analysis contribute to the development of personalized nutrition or precision medicine approaches for individuals with NASH?

Aberrant DNA methylation is an early indicator of NASH progression.

By mapping these changes, especially in genes regulating insulin signaling, inflammation, and lipid metabolism, researchers can identify which individuals are at heightened risk even before clinical symptoms become apparent. This opens the possibility of developing blood-based epigenetic biomarkers that enable clinicians to monitor disease progression and therapeutic efficacy in real-time, tailoring interventions to each patient's molecular profile.

Dietary interventions could be designed not only to focus on nutrient balance but also to provide the right substrates to correct or prevent deleterious changes affecting liver metabolism. This precision approach could, for instance, target those with a predisposition to altered methylation in pathways critical for insulin signaling and energy metabolism, thereby mitigating the risk of full-blown NASH. Treating epigenetic modifications as dynamic biomarkers and therapeutic targets not only enriches our understanding of NASH pathophysiology but also offers a blueprint for precision medicine.

The potential to adjust dietary interventions based on an individual's unique methylation profile represents a significant leap forward in personalized healthcare for metabolic diseases.

How do you see the research in the two publications contributing to the broader scientific dialogue surrounding liver health and metabolic disorders?

These two publications contribute to the broader knowledge surrounding liver health and metabolic disorders. The studies integrate lipid metabolism, epigenetics, and therapeutic interventions into a unified framework for understanding and treating NASH. They reinforce the importance of phospholipid homeostasis and epigenetic modulations as a promising avenue for reversing disease progression. These insights could reshape clinical approaches, leading to more effective, personalized treatments for metabolic liver disorders. Key contributions include:

1. the establishment of Pcyt2 deficiency as a novel mechanism in age- dependent metabolic dysfunction, which links impaired membrane phospholipid metabolism to the progression of NASH, reinforcing the idea that lipid composition plays a fundamental role in liver disease beyond simple fat accumulation.

2. evidence that PEA supplementation can reverse metabolic and inflammatory damage caused by Pcyt2 deficiency and that targeting phospholipid biosynthesis could be a viable therapeutic strategy for NASH.
3. advancing the epigenetic perspective in metabolic disorders by revealing that aberrant DNA methylation plays a significant role in NASH pathogenesis.
4. demonstrating the reversibility of DNA methylation by PEA showing that epigenetic interventions, whether through diet, supplements, or pharmacological agents, could be used to restore normal gene function and prevent disease progression.

Final messages and the power of the liver

If I had to distill the key message from these research publications into something accessible to the public, it would be this:

Your Liver's Hidden Protector: How Molecular Balance Could Be the Key to Better Health.

Did you know that liver disease isn't just about sugar and fat? Recent research reveals a surprising connection between your liver's health and crucial molecular processes of phospholipid metabolism and epigenetic regulation. Scientists have uncovered that when this balance is disrupted, it can lead to nonalcoholic steatohepatitis (NASH), a serious liver condition linked to insulin resistance and metabolic disorders. But here's the most exciting finding: this damage might not be permanent. A new discovery reveals that PEA supplementation can reverse harmful changes in DNA methylation, thereby restoring normal liver function at the cellular level.

Primary Contributor

Marica Bakovic
University of Guelph