Cause of insulin-resistance underlying Type 2 diabetes revealed?

Protein not previously thought to be linked to diabetes may be the underlying cause.

Type 2 diabetes, a disease that affects approximately 285 million people globally, is characterized by resistance to insulin that prevents the body's cells from taking up sugar. A research team, led by Alexey Pshezhetsky of the Sainte-Justine University Hospital Research Center, University of Montreal (QC, Canada) have recently discovered that lack of neuraminidase 1 (Neu1) may by the underlying cause of insulin resistance.

The Canadian research team found that activity level of the insulin receptor at the cell surface is significantly dampened through interactions with a sugar molecule, known as sialic acid. To remain receptive to insulin it is imperative that cells clear this sugar from their surface. The removal process is enacted by Neu1.

Work with Neu1, which Pshezhetsky has been involved in for years, began with the investigation of its catabolic activity in the lysosomes and its association with lysosomal storage disease. It was only when the research team discovered that Neu1 is also found on the cell surface that they began to suspect a potential involvement in glucose metabolism regulation. Their suspicions, that cells lacking Neu1 have more sialic acid at their surface and are consequently more resistant to insulin, were indeed verified in this study. In addition, they found that genetically modified mice with 10% of the normal Neu1 activity develop insulin resistance and hyperglycemia twice as fast as normal upon exposure to a high-fat diet. This study therefore reveals a novel role of Neu1 in the insulin

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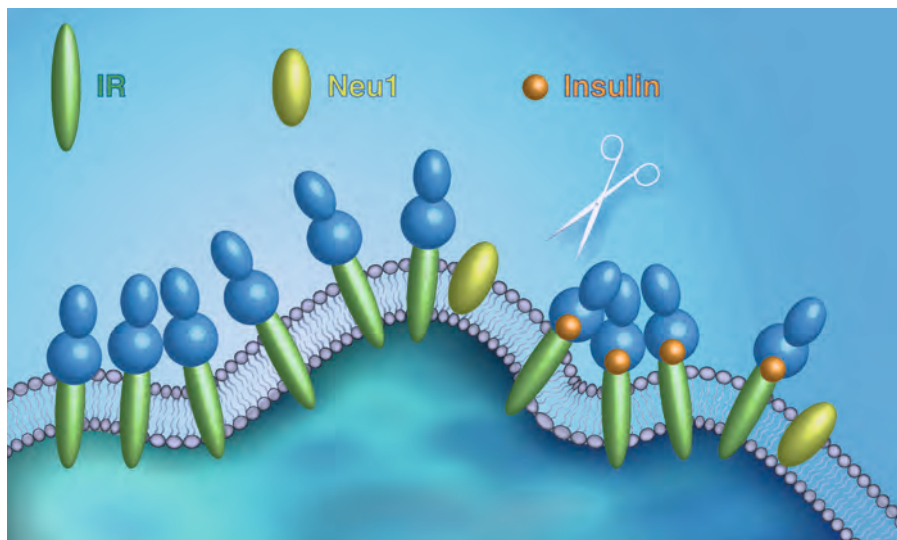
Proposed feedback mechanism for activation of the insulin receptors by Neu1. Image courtesy of A Pshezhetsky.

signaling pathway. Given that there are many molecular players involved in this pathway, Pshezhetsky strongly believes that there could be other molecules that may be related to insulin resistance, and that rare and ultra-rare variants in these many proteins could explain the missing heritability of the disease.

This breakthrough has given researchers new insights into potential treatment opportunities for the restoration of normal insulin activity; 'activating the insulin receptor by manipulating the level of neuraminidase might give doctors and opportunity to treat diabetes Type 2,' says Pshezhetsky. Additionally, now that Neu1 has been put

on the map, so to speak, there may be incentive to measure its level across human populations in order to define groups who are at additional risk of having diabetes.

– Written by Katie Lockwood

IN THE CLINIC

World's most extensive cancer pharmacology database generated

Researchers at the National Cancer Institute (NCI) have conducted whole-exome sequencing of the NCI60 human tumor cell lines, creating the world's largest dataset of cancer-specific genetic variations. The database has been made publicly available for the benefit of the research community.

The NCI60 cancer cell lines are the most ubiquitously studied cells in cancer research and are representative of cancer tissue from the breast, ovary, prostate, colon, lung, kidney, brain, blood and skin. The cells have been subjected to thousands of screenings and testing compounds for anti-cancer potential, as well as being extensively characterized by genome-wide expression and methylation studies. Indeed, Richard Simon, a lead author on this research believes that these cell lines now serve as a 'lingua franca' for relating compound sensitivity to genomic and proteomic variation.

The team's goal to identify point mutations, and short insertions and deletions in all coding regions in the NCI60 panel was reached through the employment of next-generation sequencing technology and computational pipelines, generating an impressive database with a total of 6 billion

data points connecting drugs with genomic variants.

The researchers categorized the variants into type I and type II depending on whether they were variants found in the normal population or were cancer specific. Statistical models, such as the Super Learner algorithm were subsequently used to predict the sensitivity of cells harboring type II variants to various compounds, including 103 US FDA-approved anticancer drugs and 207 investigational drugs.

> "...preliminary studies indicate how the database can be used to generate and test novel hypotheses regarding genetic variation and drug response. Thus, the database will be an invaluable resource for allowing drugs to pass much faster through the development pipeline."

Analyses were performed in order to relate genetic variants to compound sensitivity. Data validation was performed using proof-of-principle pharmacogenomic correlations (e.g., between variants in genes such as *TP53*, *BRAF*, *ERBB*s and *ATAD5* and anticancer compounds such as nutlin, vemurafenib, erlotinib and bleomycin). These preliminary studies indicate how the database can be used to generate and

test novel hypotheses regarding genetic variation and drug response. Thus, the database will be an invaluable resource for allowing drugs to pass much faster through the development pipeline. This is crucial in the field of oncology where the recent and ongoing personalization of treatment has seen a rise in the number of drugs which are targeted toward an individual's tumor's genomic alteration.

With the database being available to all researchers via two portals; the CellMiner and the Ingenuity systems database, Simon told *Clinical Practice* that he hopes that "these data will be of value to the many public and privately funded groups trying to develop improved treatments for patients with cancer." If these hopes materialize then we can expect an explosive growth in personalized cancer treatment, taking it closer to the needs of the individual.

– Written by Katie Lockwood

Roche halts aleglitazar drug trial following midtrial safety review

A drugs trial for Type 2 diabetes medication has been stopped following a review highlighting safety issues.

Roche (Basel, Switzerland) has recently stopped the Phase III AleCardio trial of aleglitazar following concerns expressed by an independent clinical board due to "safety signals and lack of efficacy". All other trials by Roche involving aleglitazar have consequently also been halted.

The drug was part of a class of treatment that was hoped to benefit individuals with a genetic susceptibility to Type 2 diabetes that may be at risk of cardiovascular disease.

A spokesman for Roche, speaking to The New York Times, explained that the associated safety problems extended to increased risk of bone fractures, kidney problems and heart failure in study participants.

There are other diabetes drugs that work in a similar manner to aleglitazar currently on the market, including GlaxoSmithKline's (Brentford, UK) Avandia®, which has recently been in the news again regarding its restricted usage. Use of Avandia was heavily restricted in 2010 following concerns of increased heart attack risk, but recently an advisory panel to the US FDA has controversially suggested that this is not the case and the restrictions should be loosened.

Roche's chief medical officer, Hal Barron, explained that those patients involved in the Phase III AleCardio trial will not be left without treatment: "The safety of patients is our first priority. Roche is working with investigators to support the management of patients and their transition from aleglitazar treatment to other blood sugar control therapies." In addition, the company stated "we are disappointed by this outcome as we hoped that aleglitazar would provide significant benefit for patients with Type 2 diabetes who are at risk of cardiovascular disease."

Further analysis of the results of this trial will be carried out, so that a full understanding of the findings can be established and will be made available at a future medical meeting.

– Written by Hannah McDonald

> **"**The drug was part of a class of treatment that was hoped to benefit individuals with a genetic susceptibility to Type 2 diabetes that may be at risk of cardiovascular disease.**"**

Kidney injury may be prevented by simple ultrasound treatment

Acute kidney injury, a rapid loss of kidney function, is a potentially serious condition in hospitalized patients, commonly arising after major surgery. A recent study published in the *Journal of the American Society of Nephrology* carried out by Mark Okusa (University of Virginia, USA) and colleagues suggests that this condition may be treated with ultrasound, providing a relatively simple and noninvasive solution to what is becoming an increasingly prevalent condition. This solution will come as a great relief to many patients suffering with the condition as besides supportive care the current established treatment options are somewhat lacking.

The research team delivered ultrasound to anesthetized mice 24 h prior to blood disruption to the kidneys. When blood flow was restored, the preservation of kidney health in these mice was significantly better than in the control group, which exhibited significant kidney injury. A likely explanation for the protective effect of ultrasound was revealed in further analyses suggesting that the treatment stimulated an anti-inflammatory response originating from the spleen. The authors also speculate that this protective effect could potentially be effective for prevention of injury in other organs, such as the lungs. Indeed, if proven to be effective in other organs we may see this treatment option gain widespread influence, as its simplicity makes it an appealing choice for clinicians.

– Written by Katie Lockwood

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