

SEPTEMBER 2022

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# In This Issue of *Diabetes*

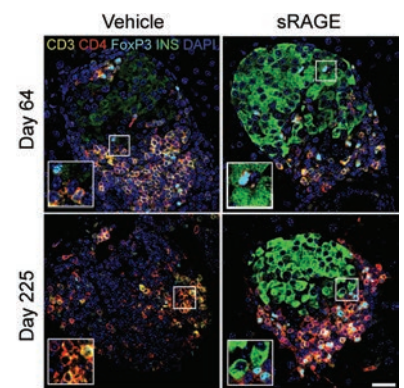
By Max Bingham, PhD

## sRAGE Prevents Type 1 Diabetes in Mice

Recombinant human soluble advanced glycosylation end product receptor (sRAGE), a biologic, appears to prevent type 1 diabetes in mice by increasing or expanding regulatory T cells. Crucially, the study by Leung et al. (p. 1994) also shows that the apparent efficacy was reproducible in at least two research centers in parallel and in human T-cell assays. Based on the results, the authors suggest that the approach represents a “promising new therapy” for preventing type 1 diabetes and warrants further development. The approach focuses on advanced glycation end products (AGEs) and the corresponding receptor, termed RAGE, that has previously been implicated in the development of type 1 diabetes. sRAGE, meanwhile, is a naturally occurring antagonist that competes for RAGE ligands. According to the authors, reduced levels of sRAGE can coincide with the seroconversion associated with type 1 diabetes development. They found that short-term (2-week) administration of the antagonist in mice prone to getting type 1 diabetes resulted in a threefold decrease in incidence of diabetes after 225 days. Notably, blood glucose levels were also significantly lower over the duration of the experiments. Further experiments looked at why sRAGE was able to reduce diabetes incidence. In short, the findings center on one process, regulatory T-cell expansion. The authors found that sRAGE treatment expanded regulatory T cells in islets and local lymphoid tissues, resulting in increased insulin content and secretion. sRAGE also improved regulatory T-cell function and numbers in human T-cell experiments, while the RAGE ligands, AGEs, were shown to impair regulatory T-cell function. Commenting further, author Josephine Forbes said: “This is part of a wider international program by our team to produce a safe and effective therapy for type 1 diabetes prevention that could be adjunct to other agents in current clinical trials. We are investigating this pathway from all angles to find the most effective and safe way to target RAGE in individuals at risk for type 1 diabetes development.”

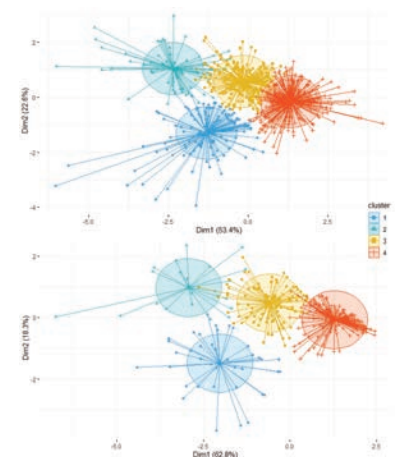
## Fat Accumulation Patterns May Determine Type 2 Diabetes Risk

Four different groups of individuals may exist who have differing patterns of fat distribution, which in turn translates into variations in risk for incident type 2 diabetes. According to Yamazaki et al. (p. 1937), the findings suggest that fat distribution patterns are more important than general adiposity in predicting risk. The case-cohort–designed study, based in Japan, used a k-means clustering approach to identify groups of individuals according to fat distribution patterns and their relationship with diabetes risk. The authors also used a cross-sectional study, based in Germany, to validate their findings. In both cases, fat accumulation patterns were estimated in liver, pancreas, skeletal muscle, and visceral bed with various body scanning approaches. They found that four clusters of individuals existed: a hepatic steatosis group, a pancreatic steatosis group, a trunk myosteatorsis group, and finally a steatopenia group (i.e., lowest level of fat in general). Using this last group as a reference, the adjusted hazard ratios (95% CI) for incident type 2 diabetes were 4.02 (2.27–7.12) for the hepatic steatosis group, 3.38 (1.65–6.91) for the pancreatic steatosis group, and 1.95 (1.07–3.54) for the trunk myosteatorsis group. Similar patterns were identified in the German study. Looking further at parameters of glycemia, the authors found insulin sensitivity and insulin secretion levels varied across the groups, potentially explaining the variations in type 2 diabetes risk. They highlight that their data are largely consistent with previous studies that have looked at individual fat compartments but that further research will be needed to explore detailed mechanisms involved in the interactions between fat compartments in different locations. Commenting further, author Hajime Yamazaki said: “These findings underscore the metabolic relevance of fat distribution across the human body. Our study shows the importance of investigating all fat compartments in concert rather than focusing on a single fat compartment. This could facilitate experimental research to elucidate the underlying biological interplay among fat compartments.”



Representative photomicrographs of multiplexed immunofluorescence staining. Scale bar, 40  $\mu$ m.

Leung et al. Soluble RAGE prevents type 1 diabetes expanding functional regulatory T cells. *Diabetes* 2022;71:1994–2008



Four clusters of fat accumulation variously associated with diabetes risks. Top, Japan cohort; bottom, Germany cohort.

Yamazaki et al. Fat distribution patterns and future type 2 diabetes. *Diabetes* 2022;71:1937–1945

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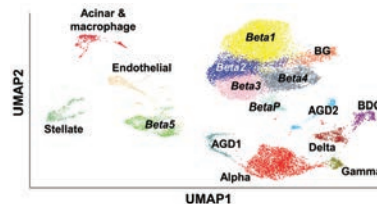
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### Heterogeneity in $\beta$ -Cell Responses to Diabetogenic Diet in Mice

The genetic response of islet  $\beta$ -cell populations to a diabetogenic diet may determine their dysfunction and eventual loss and ultimately the development of diabetes, according to Gottmann et al. (p. 1962). Specifically, the authors describe how  $\beta$ -cells from a mouse model resistant to diabetes progress stepwise to a form that is protective when faced with a diabetogenic diet. Meanwhile,  $\beta$ -cells from a diabetes-prone mouse model never make it; instead, these cells end up with an expression profile that is indicative of stress and potentially a prelude to later loss of function. The findings come from a comparison of two different mouse models of obesity: one resistant to developing diabetes (OB mice) and one prone to it (NZO mice). The authors then used single-cell RNA sequencing and various bioinformatics approaches to examine the effects of a short (2-day) diabetogenic dietary challenge. They found that on a control diet, both mouse strains exhibited six clusters of  $\beta$ -cells that were fairly similar in abundance. Following the diabetogenic diet, islets from diabetes-resistant OB mice had  $\beta$ -cells that had a reduced or “protected” cell identity. This included downregulation of a series of cellular features and a phenotype suggestive of decreased stress response and apoptosis. In contrast,  $\beta$ -cells from the diabetes-prone NZO mice showed signs of metabolic pressures and stress, which the authors suggest is indicative of later  $\beta$ -cell loss. While the two strains started with similar profiles of  $\beta$ -cells, cells of the NZO mice essentially did not respond as fully as those of the OB mice and never developed as far as the protected cell identity of the OB mice. Commenting further, author Annette Schürmann said: “Our study provides novel insights explaining why obesity does not always lead to type 2 diabetes. The capacity of mice and presumably of humans to react to elevated blood glucose concentrations with a transient decrease of their  $\beta$ -cell identity appears to play a key role in protection from dysfunction and/or apoptosis.”

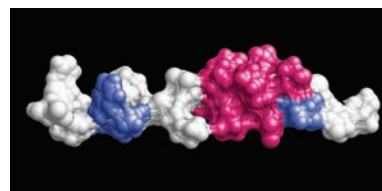
### First-in-Class Synthetic Peptide PATAS Promotes Insulin-Free Glucose Absorption

A peptide called PATAS, for “Peptide derived of PKC Alpha Targeting AlMS,” can trigger insulin-independent glucose absorption in adipocytes, according to Schreyer et al. (p. 2034). They also report that the peptide can reduce whole-body insulin resistance, improve glucose intolerance and fasting glucose, and improve markers of liver health, at least in rodents. On that basis the authors suggest that PATAS is a “first-in-class” treatment for insulin resistance. The findings come from an investigation that originally looked at an ultrarare monogenic disorder called Alström syndrome, in which there is severe insulin resistance (among many other issues). A key cause of the condition is a mutation in a gene called *ALMS1*, which encodes the corresponding protein ALMS1 and is key to intracellular transport of glucose (among others). Working down the pathway associated with ALMS1 inactivation, the authors identified a key protein–protein interaction that likely controls glucose absorption. They found that PKC- $\alpha$  is likely released from ALMS1 when insulin is present, which results in glucose absorption. However, in the case of insulin resistance, that process would not happen. To solve the issue, the authors turned to a synthetic peptide sequence, PATAS, that would activate the dropping of PKC- $\alpha$  from ALMS1 without the presence of insulin. In initial experiments they found that it worked, but a redesign of the structure using “stapling” resulted in even greater glucose absorption, at least in adipocytes. The rest of the investigation set about quantifying the potential of the peptide to modify insulin resistance–related outcomes in vivo in rodents and cells from various species. In short, PATAS appeared to modify many of the targets considered important for reducing the effects of insulin resistance and its comorbidities, such as type 2 diabetes.



UMAP plot of all cells labeled according to cell type.

Gottmann et al. Heterogeneous development of  $\beta$ -cell populations in diabetes-resistant and -susceptible mice. *Diabetes* 2022;71:1962–1978



Modeled three-dimensional structure of PATAS based on peptide helicity from nuclear magnetic resonance analysis.

Schreyer et al. PATAS, a first-in-class therapeutic peptide biologic, improves whole-body insulin resistance and associated comorbidities in vivo. *Diabetes* 2022;71:2034–2047

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