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In This Issue of *Diabetes*

By Max Bingham, PhD

Elastin-Derived Peptides Might Predict Liver Fibrosis and Risk of Nonalcoholic Steatohepatitis

Elastin-derived peptides (EDPs) may play a crucial role in the development of nonalcoholic steatohepatitis (NASH), according to Romier et al. (**p. 1604**). Specifically, EDPs appear to induce a remodeling of hepatic extracellular matrix that leads to fibrosis of the liver. The authors suggest that circulating EDPs might be useful as (relatively) noninvasive biomarkers to diagnose risk for NASH. They also hint that targeting aging and the preservation of elastic fibers in blood vessels might be an option for therapy against the disease. Using a series of mouse models, cell-based experiments, and a clinical investigation, the authors show that increases in neutrophil elastase activity resulting from activation by EDPs lead to an accumulation of free fatty acids, liver triglycerides, and hepatic collagen and impairment of the AMPK pathway. Conversely, pharmacological inhibition of the enzyme reversed the effects and restored AMPK signaling. In human subjects with obesity, they found that participants with type 2 diabetes also had increased circulating levels of EDPs in comparison to participants without diabetes and that EDPs and neutrophil elastase activity correlated with scoring approaches for fatty liver and fibrosis—hence the suggestion that they might be useful as plasma biomarkers. Author Sébastien Blaise told *Diabetes*: "From the point of view of clinical science, many past studies have identified cardiovascular complications induced by nonalcoholic fatty liver disease (NAFLD), but our approach suggests that NAFLD and vascular diseases could be amplified via the induction of a vicious circle. The therapeutic strategy that we suggest, with the use of elastolysis inhibitors in mice, could help to circumvent this circle and facilitate existing treatments against NAFLD or vascular diseases. We also think that our approach (treatment with EDPs) could be a very interesting and original model for future explorations of nonalcoholic steatohepatitis."

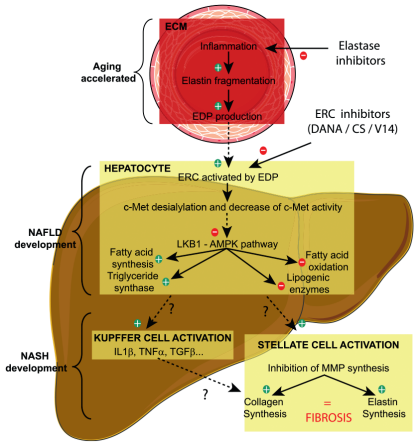

Diagram summarizing the EDP effects on NASH development. ECM, extracellular matrix; ERC, elastin receptor complex.

Romier et al. Production of elastin-derived peptides contributes to the development of nonalcoholic steatohepatitis. Diabetes 2018;67:1604–1615

Sacubitril/Valsartan Combination Therapy for Diabetic Peripheral Neuropathy: Preclinical Study Progress

A combination of sacubitril and valsartan has shown promise in preclinical studies as a potential treatment for diabetic peripheral neuropathy, according to Davidson et al. (**p. 1616**). The authors say there is rationale to continue studies with the combination as a potential therapy, particularly as it is also being evaluated for a range of other diseases. Using a rat model, the authors evaluated six groups of the animals, three groups that remained on a control diet and three groups that received a high-fat diet for 8 weeks followed by streptozotocin to induce hyperglycemia (according to the authors, these rats represented a model of late-stage type 2 diabetes). Then the groups were treated with either valsartan alone, a combination of sacubitril and valsartan, or control at either 4 weeks or 12 weeks after hyperglycemia had been induced to represent an early or late intervention. The authors report that the sacubitril/valsartan combination did demonstrate efficacy in terms of improving vascular and neural function and was superior to valsartan alone. In the early intervention, the combination reportedly slowed the progress of deficits, but with later intervention, it managed to stimulate restoration of vascular reactivity, motor and sensory nerve conduction velocities and sensitivity, and even regeneration of sensory nerves in skin and cornea. They conclude that although the studies suggest that the combination may be an effective treatment, additional studies will still be needed, particularly before any clinical activities can commence. Author Mark A. Yorek commented: "Peripheral neuropathy affects more than 50% of patients with diabetes as well as about 30% of subjects with prediabetes and there is no treatment. Given that this drug combination already has FDA [U.S. Food and Drug Administration] approval, it is my hope that it can achieve the next step and be tested in human subjects and become the first treatment for diabetic peripheral neuropathy."

Davidson et al. Vascular and neural complications in type 2 diabetic rats: improvement by sacubitril/valsartan greater than valsartan alone. Diabetes 2018;67:1616–1626

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Glucagon-Like Peptide 1 Receptor Not Required for Improved Glucose Tolerance Following Vertical Sleeve Gastrectomy Surgery

Much attention has been paid to the potential role of glucagon-like peptide 1 (GLP-1) and its receptor in explaining the improvements in glucose homeostasis following vertical sleeve gastrectomy surgery. However, mixed outcomes from preclinical and human studies mean that it is far from clear what role GLP-1 may play in the dramatic effects of the procedure in obesity and diabetes. According to Douros et al. (**p. 1504**), it seems likely that the procedure does lead to dramatic improvements in glucose tolerance, at least in obese mice, but it does not require β-cell GLP-1 signaling. The authors suggest that the response that leads to enhanced glucose disposition following the procedure is likely much more complex, possibly involving other gut hormones and potentially multiple neural/circulatory factors. The study focuses on a mouse model of the surgical procedure combined with a genetically modified mouse line with tamoxifen-inducible β-cell–specific *Glp1r* knockdown. Following 10–12 weeks on a high-fat diet, mice that had the surgery lost more body weight than controls and had significant improvements in glucose tolerance. Meanwhile, isolated islets from mice who had the surgery had significantly greater insulin responses to glucose than controls. In assessing the role of the GLP-1 receptor, the authors found superior glucose tolerance in mice with and without *Glp1r* knockdown and surgery in comparison to sham-operated controls, effectively ruling out a primary role for GLP-1 in the glucose tolerance improvements following surgery. Author Jonathan D. Douros said: "While increased GLP-1 levels following vertical sleeve gastrectomy may contribute to improved glucose control, our data present a developing picture of bariatric surgeries as not merely GLP-1–enhancing procedures. Rather, these results suggest a more complex model in which bariatric surgeries likely invoke multiple mechanisms to lower glycemia. This raises the intriguing possibility that an effective 'bariatric surgery mimetic' may have to target not one, but multiple, receptors."

Douros et al. Enhanced glucose control following vertical sleeve gastrectomy does not require a β-cell glucagon-like peptide 1 receptor. Diabetes 2018;67:1504–1511

Antigen-Presenting Cells May Pose a Challenge for Antigen-Specific Immunotherapy in Type 1 Diabetes: A Review

In a comprehensive review, Creusot et al. (**p. 1481**) focus on antigen-presenting cells and how their ability to elicit tolerogenic responses that counteract the destruction of β-cells in response to antigen-specific immunotherapy may be hindered. Initially focusing on the features and functions of antigen-presenting cells that are relevant to tolerance and type 1 diabetes, the authors describe a series of events and alterations that are associated with the disease and, for some, how they might contribute to the autoimmune process. They cover a series of biological processes that may be involved, including the development of antigen-presenting cells; their presentation of antigens, activation, and tolerogenic function; and adhesion/homing processes. For each of these processes, they describe a whole series of alterations that have been reported in type 1 diabetes or that may result from susceptibility genes in humans and spontaneous rodent models. In what amounts to a complex series of challenges arising from these alterations, they describe how issues with antigen-presenting cells and other cell types seem to be preventing the successful implementation of antigen-specific immunotherapy. They also describe potential future strategies that might be used to overcome them. Author Rémi J. Creusot commented: "Antigen-specific immunotherapies may involve a variety of antigen-presenting cells at different sites, and we rely on such cells to effectively elicit a tolerogenic T-cell response toward the delivered antigens. Given the relative lack of efficacy achieved so far with these approaches, we ought to know whether those antigen-presenting cells would perform as expected or if the numerous disease-related alterations reported over the course of about three decades indeed contribute to failure to tolerize (just like they may contribute to the disease in the first place). We thought that an up-to-date overview of such alterations was warranted to get a better idea of the scale of the problem and to identify the research that is needed to improve the design and efficacy of antigen-specific therapies."

Creusot et al. Altered function of antigen-presenting cells in type 1 diabetes: a challenge for antigen-specific immunotherapy? Diabetes 2018;67:1481–1494

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