Reg3 Proteins as Gut Hormones? Don't Be Hasty

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The gastrointestinal (GI) tract has historically been defined by its digestive and absorptive functions. However, the interaction with exogenous dietary components uniquely positions the GI tract to communicate nutritional status through a variety of neuronal and hormonal mechanisms. The most compelling evidence of this interaction is exemplified by the incretin system (1). The incretins, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are nutrient-responsive peptides secreted from specialized enteroendocrine cells. Gut-derived GLP-1 appears to signal primarily through neural circuits, whereas GIP acts in an endocrine fashion; both factors regulate numerous processes that are essential for postprandial metabolism. Additionally, GI control of metabolism has evolved to include factors beyond incretin hormones. A number of GI-derived factors are secreted by the gut in response to metabolic demand that control metabolism, inflammatory responses, satiety, and energy expenditure. Moreover, emerging evidence highlights a role for the intestinal microbiome, the collection of bacteria living within the host gut, to elicit numerous actions, metabolic and otherwise (2). Interaction between intestinal microbiota and GI hormone secretion seems likely, but very little evidence exists documenting the impact of this potential relationship toward metabolism.

In the current review, Shin and Seeley (3) highlight the Reg3 family of proteins as potential microbiome-responsive, gut-derived hormones that were originally observed to have antimicrobial functions. The primary function of Reg3 proteins is to act as a barrier defense against microorganisms in the intestine, where Reg3 expression is enhanced in response to a variety of stimuli including bacterial colonization, probiotic treatment, bile acid exposure, bariatric surgery, and inflammatory bowel disease. However, Shin and Seeley (3) explore an expanded role for Reg3 proteins, including hormonal signaling and metabolic regulation. The observation that Reg3 expression occurs in metabolically active tissues including the pancreas, liver, and adipose suggests that this family of proteins may have additional functions beyond barrier protection. Evidence for an expanded role for Reg3 proteins includes regenerative or protective functions in response to cellular damage during pancreatitis, drug-induced liver injury, or a high-fat diet. Thus, the current work presents a theme in which Reg3 expression is stimulated in response to homeostatic insult and exerts simultaneous bactericidal effects on invading pathogens and regenerative or proliferative effects on host tissues.

A number of technical difficulties have limited the interrogation of the metabolic role for the Reg3 system. Methods for detecting circulating levels of Reg3 isoforms are not fully developed, and the receptors for Reg3 proteins have not been established. EXTL3 is a potential receptor for Reg3, and β-cell deletion of *Extl3* diminishes glucose-stimulated insulin secretion both *in vivo* and *ex vivo* (4). Although these actions echo the mechanism by which gut-derived incretin peptides control glucose metabolism, the evidence is far from conclusive that Reg3 proteins are gut hormones that exert metabolic control. On the other hand, many of the actions of Reg3 in metabolic tissues occur in response to cellular damage. Indeed, reviewing the specific actions of Reg3 revealed a limited role in metabolic tissues under homeostatic conditions, which became more prominent after the induction of stress. This effect parallels the effects of GLP-1, where emerging evidence points to a more pronounced

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Abbreviations: GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1.

role in stressed conditions (5). Indeed, the well-described insulinotropic actions of GLP-1 on β-cells are just one example of how the peptide acts to restore homeostasis, in addition to protective effects in the gut, brain, skin, liver, and kidney (6). Applying a similar perspective to Reg3 may reveal that any control of metabolism by this family of proteins may fall under the overall protective role against impaired homeostasis.

Finally, Shin and Seeley (3) highlight an emerging literature regarding the role of Reg3 to regulate systemic metabolism after bariatric surgery. Bariatric surgeries modify the gut anatomy, increase gastric emptying, reduce body weight, improve islet function, increase hepatic insulin sensitivity and, critical to the current discussion, increase GI hormonal secretion (7). In keeping with the previously highlighted theme of increased Reg3 expression in response to homeostatic insult, jejunal Reg3γ and Reg3β expression is increased after bariatric procedures. Elevated prandial secretion of gut peptides, including the incretins, is well documented after surgery. However, the data suggest that elevated GLP-1 secretion after surgery is not necessary for the metabolic benefit observed after these operations (8). It is currently unknown what effect, if any, elevated Reg3 gene expression might exert on prandial secretion of the peptides or systemic metabolism. Similar to GLP-1, the elevation of Reg3 after bariatric surgery may result from the homeostatic imbalance generated by altering the gut anatomy. Whether this effect contributes to the improved metabolic profile resulting from surgery remains to be seen.

The study of Reg3 as a metabolically important gut hormone is in its infancy. The current data suggest Reg3 has protective effects on metabolically important tissues including the pancreas and liver. There is a clear need for improved tools to characterize these peptides' regulation and action. However, the increased intestinal expression of these peptides after bariatric surgery is certainly of interest given the enormous and widespread metabolic benefits of these procedures.

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