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Dysregulated Systemic Factors Underlie Type 1 Diabetic Enteropathy and Impaired Stem Cell Function

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Summary:

Recent breakthroughs in 3-D organoid cultures provide a unique opportunity to model tissue biology and disease in the translational research field. In this issue of Cell Stem Cell, D'Addio et al. leverage this organoid technology to demonstrate that a circulating IGF/IGFBP3 hormonal duo regulates the function of primary human colonic stem cells (CoSCs) in health, as well as in response to disease states such as type 1 diabetes (T1D).

Main Text:

The mechanisms of how tissues adapt to aberrant physiologic states are unclear. Key protagonists in this question are adult stem cells, which drive tissue remodeling and couple organismal metabolic demands to tissue maintenance. Such coordination at the stem cell level relies on an integrated cellular response to local niche factors and to systemic physiologic hormones and growth factors (Mihaylova et al., 2014 and Yilmaz et al., 2012). It is likely that imbalances of these cues in certain metabolic diseases, obesity, and aging contribute to tissues-specific pathologies.

In diabetes, for instance, organismal metabolic status and circulating factors are severely perturbed. Type 1 diabetes (T1D), which occurs from autoimmune-mediated beta-cell depletion, causes insulin deficiency and weight loss. Type 2 diabetes (T2D), on the other hand, often arises as a consequence of obesity-driven metabolic syndrome and is characterized by insulin resistance. Both T1D and T2D are associated with hyperglycemia and result in multi-organ degenerative complications involving the nervous system (diabetic neuropathy), the eyes (diabetic retinopathy), the kidneys (diabetic nephropathy) and the gastrointestinal tract (intestinal enteropathy). It has been proposed that hyperglycemia-mediated increase of hepatic IGFBP3 (insulin-like growth factor binding protein 3) secretion disrupts tissue regeneration during the late stages of diabetes (D'Addio et al., 2015). IGFBP3 is a multifunctional protein predominantly produced by the liver. When it binds to IGF-1, it suppresses the pro-growth effects of IGF-1 and induces apoptosis. IGFBP3 can also act independently of IGF-1 via interaction with its own receptor TMEM219 to induce caspase-8-dependent apoptosis

(Baxter, 2013). Whether IGFBP3 mediates some of the untoward effects of diabetes in tissue maintenance and stem cell function, and, if so, whether it does so by sequestering IGF-1 or through interaction with its receptor is unknown. Until very recently, this translational question has been difficult to address, in part, due to the lack of robust *ex vivo* models that enable interrogation of physiologic cues on tissue structure, composition, and stem cell function.

Recent breakthroughs in mouse and human intestinal cultures have established conditions that allow intestinal crypts to form self-renewing organoid bodies (or “mini-intestines”) (Lancaster et al., 2014). These organoids grow and recapitulate many of the histologic features observed in the intestine and thus represent an ideal platform to study how perturbations in the systemic and local milieu affect intestinal stem cell function. Organoid formation and growth are often used as proxies for intestinal stem cell activity as only stem cells self-renew and differentiate for the long-term into the various intestinal cell types that comprise organoids. In this issue of *Cell Stem Cell*, the Fiorina group utilize this technology to explore how long-term type 1 diabetes (T1D) influences human colon stem cells (CoSCs) function and whether the IGF-1/IGFBP3 dyad represents a possible therapeutic intervention in T1D-mediated diabetic enteropathy (DE)—a clinical syndrome associated with diarrhea, intestinal motility issues, and intestinal mucosal abnormalities (D’Addio et al., 2015). Interestingly, the authors demonstrate that in T1D-end stage renal disease (T1D-ESRD) patients (i.e. patients with chronic disease), CoSCs are reduced in numbers as assessed by stem cell markers (e.g. EphB2 and Lgr5) and have impaired function in the intestinal organoid assay. These changes in CoSCs correlate with hyperglycemia, reduced free serum IGF-1, and increased levels of circulating IGFBP3 shown by serum proteomic analysis (Figure 1A and 1B). Notably, these deleterious effects on CoSCs can be simply mimicked in the organoid assay by exogenous exposure to T1D-ESRD patients’ serum or IGFBP3 protein directly; these inhibitory effects can be reversed by treatments with either Caspase 8 or Caspase9 inhibitors. Although additional IGF-1 is sufficient to rescue some defects of T1D-ESRD-derived organoids, it fails to completely rescue the inhibitory effects that T1D-ESRD serum or exogenous IGFBP3 have on organoid growth, raising the possibility that IGFBP3 possess IGF-1 independent effects on organoid formation and maintenance through acting on its receptor TMEM219.

An important question is whether these changes in intestinal morphology and CoSC function are reversible in patients with T1D-ESRD. Remarkably, restoration of euglycemia in T1D-ESRD subjects by simultaneous pancreas-kidney (SPK) transplantation, normalizes IGF-1 and IGFBP3 levels, improves the structure of the intestinal mucosa, and importantly augments the organoid-forming capacity of CoSCs (Figure 1C, SPK). To interrogate whether inhibition IGFBP3 signaling is sufficient to rescue the T1D-ESRD-mediated intestinal phenotype, the authors engineered a recombinant protein based on the 161-amino-acid TMEM219 extracellular domain (ecto-TMEM219) that could lure excess IGFBP3 and prevent it from binding to its endogenous TMEM219 receptor. Strikingly, in organoid cultures exposed to T1D-ESRD serum and in an *in vivo* preclinical T1D mouse model, ecto-TMEM219 administration reverses the inhibitory effects of T1D serum on organoid growth and restores intestinal

morphology in vivo (Figure 1C, ecto-TMEM219). These findings indicate that elevated IGFBP3 signaling through the TMEM219 receptor potentially contributes to the detrimental effects on CoSCs function and degenerative intestinal mucosa in T1D. Another implication of these findings is that IGFBP3/TMEM219 signaling may represent a new treatment axis for DE that is separate from the insulin/glucose axis, which is what most contemporary treatment interventions target for treating complications of diabetes.

This study provides important insights into how systemic factors couple intestinal homeostasis to organismal physiology and how dysregulation of such factors, like IGFBP3, in T1D impair the function of human CoSCs and contribute to DE. It also provides rationale for targeting elevated levels of circulation IGFBP3 factors in the treatment of T1D-induced DE. However, open questions remain about the binding dynamics and physiological actions ecto-TMEM219 in human patients. In particular, IGF-1R and TMEM219 are broadly expressed throughout the entire gastrointestinal (GI) tract and in many other organs such as the kidneys. Therefore, elucidating how interventions that disrupt IGFBP3/TMEM219 signaling need to be addressed in other tissues in normal physiology and in T1D. Such studies, in fact, may also leverage the use of pancreas or kidney organoid technology (Lancaster et al., 2014). In addition to T1D-mediated hyperglycemia, obesity driven T2D diabetes also is associated with GI complications (Shakil et al., 2008).

Although both T1D and T2D share hyperglycemia, T2D includes an array of other metabolic abnormalities such as insulin resistance in many tissues, dysfunction of growth hormone (GH)-IGF-1 signaling and dyslipidemia. It will be interesting to apply the current experimental paradigm to study how the systemic milieu in T2D patients influences intestinal stem cell function and how obesity and T2D contribute to the increased incidence of gastrointestinal cancers. If the proposed therapeutic treatment of TMEM219 inhibition is relevant for T2D patients then it will need to be compared to the standard first line therapies such as Metformin, which has been shown to decrease IGF-1 levels by increasing amounts of its binding protein IGFBP1. In conclusion, this study translates basic biology by uncovering novel mechanisms for how IGFBP3/TMEM219 signaling mediates T1D intestinal enteropathy to a potential therapeutic intervention and, in doing so, it poses stimulating questions for the field.

Figure Legends

Figure 1. Peripheral IGF-1/IGFBP3 regulates the function of human CoSCs.

(A) In normal physiology, basally low levels of IGFBP3 bind to free IGF-1 and to the TMEM219 receptor, which i) allows excess IGF-1 to bind to IGF-1R to promote CoSCs proliferation and ii) minimize IGFBP3/TMEM219 mediated apoptosis. **(B)** In type 1 diabetes (T1D), hyperglycemia increases circulating IGFBP3 that competitively binds to IGF-1, which i) dampens pro-growth IGF-1/IGF-1R signaling and ii) augments IGFBP3/TMEM219 mediated apoptosis. **(C)** Restoration of euglycemia by simultaneous pancreas-kidney (SPK) transplantation normalizes the levels IGFBP3, while exogenous ecto-TMEM219 sequesters IGFBP3 and prevents it from binding to TMEM219. Both of these interventions shift IGFBP3/TMEM219 mediated apoptosis towards IGF-1/IGF-1R-

activated proliferation in T1D.

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