Methods of Identifying and Using Agents for Treating Diseases Associated with Intestinal Barrier Dysfunction (Yeda)

code: T4-1925

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Summary

The obesity pandemic has reached alarming magnitudes, affecting more than 2 billion people worldwide and accounting for more than 3 million deaths per year. A poorly understood feature of the metabolic syndrome' is its association with dysfunctions of the intestinal barrier, leading to enhanced permeability and translocation of microbial molecules through the intestinal barrier leading to increased risk for mucosal infection and systemic inflammation. This influx of immune-stimulatory microbial ligands into the vasculature, in turn, has been suggested to underlie the chronic inflammatory processes that are frequently observed in obesity, diabetes, and related manifestations. Entry of pathogens through an impaired barrier leads to an enhanced risk of infection in obese and diabetic individuals, particularly at mucosal sites. Beyond metabolic disease, enhanced intestinal permeability has also been linked with systemic inflammation in a variety of conditions, including cancer, neurodegeneration, and aging. **Thus, there is an urgent need to devise strategies to counteract the detrimental systemic consequences of gut barrier dysfunction.**

Applications

? A novel method for treating diseases associated with intestinal barrier dysfunction by downregulating the amount of glucose in intestinal cells.? A method for treating inflammatory bowel disease in individuals presenting comorbidities such as obesity, diabetes, fatty liver disease and pre-diabetes.? A method for identifying agents useful for treating intestinal barrier dysfunction? The therapeutic agent that can selectively downregulate the amount of glucose in intestinal cells vs. non-intestinal cells.

Technology's Essence

The team of Profs. Elinav and Geiger have uncovered that the key driver of gastrointestinal barrier dysfunction in different metabolic diseases such as obesity and diabetes is hyperglycemia. Specifically, the team was able to demonstrate that the intestinal bidirectional glucose transporter GLUT2 was responsible for hyperglycemia-mediated epithelial reprogramming characterized by lower expression of adherence and tight junction genes. In human, using a cohort of 27 individuals, Prof. Elinav's team have shown a strong correlation between hemoglobin A1c (HbA1c), indicative of an individual's 3-month average plasma glucose concentration, and serum levels of PRR (microbial pattern recognition receptor) ligands, symptomatic of enhanced influx of gut commensal-derived products. Collectively, these findings provide a potential molecular explanation for altered barrier functionin the context of the metabolic syndrome and the resultant enhanced mucosal infectionnoted in patients suffering from obesity diabetes mellitus. Furthermore, the link between hyperglycemia and gut barrier alterations may provide a mechanistic basis for a variety of seemingly unrelated inflammatory manifestations and complications, associations with metabolic syndrome, and serve as a potential therapeutic target.

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