An antioxidant protein to fight changes to the intestinal microbiota and control inflammation

Teams from Hôpital Paul-Brousse AP-HP, Inserm and Paris-Sud University have recently evidenced a mechanism which modulates the intestinal microbiota, involving a molecule with antioxidant and anti-inflammatory properties, known as REG3A. The latter is thought to protect the intestinal barrier and the bacteria most sensitive to oxygen forming the microbiota, thus improving "good" bacterial survival and growth. Transplantation of fecal microbiota in mice models of severe colitis or administration of a REG3A recombinant protein to wild type mice evidences a marked reduction in their susceptibility to the disease. These results have been published in the journal *Gastroenterology* and represent a new approach to manipulation of the intestinal microbiota for therapeutic purposes, restoration of host-microbiota symbiosis, and alleviation of intestinal inflammation.

One of the key factors for an imbalanced microbiota composition or "dysbiosis" is intestinal oxidative stress. Combined with immune responses, this is capable of amplifying the production of free radicals, activation of inflammatory cells (macrophages), imbalances of microbiota composition in favor of aerotolerant bacteria, and lesions in the intestinal barrier.

Dr. Jamila Faivre from the Department of Oncology-Hematology at Hôpital Paul-Brousse, AP-HP, and her team from Unit 1193 "Physiopathogenesis and Treatment of Liver Disease" at the Hepatobiliary Center (Inserm/Paris-Sud University) are studying oxidative stress as a therapeutic target to prevent or treat diseases and/or disorders related to dysbiosis.

In this study, the researchers show that a recombinant human protein known as REG3A is capable of modifying the intestinal microbiota by reducing the levels of free radicals. This regulatory mechanism is based on the antioxidant activity of this molecule.

REG3A protects commensal gut bacteria from oxidative stress by trapping free radicals and improving the survival and growth of "good" gut bacteria known to be highly sensitive to oxygen.

In keeping with the data obtained from *in vitro* bacterial cultures, the molecule delivered into the gastrointestinal lumen of transgenic mice modifies intestinal microbiota composition with the over-representation of Gram-positive symbionts, such as Clostridiales, and improves barrier function and resistance of the mice in two models of severe experimental colitis.

With further investigation, the researchers observed that transplantation of fecal microbiota originating from transgenic mice strongly expressing REG3A protects conventional wild type mice, together with germ-free mice colonized with induced severe colitis. Furthermore, intrarectal administration of REG3A recombinant human protein to wild type mice significantly reduces their susceptibility to induced colitis.
These results suggest that biological therapy based on administration of REG3A recombinant protein is a novel approach to (re)modeling the intestinal microbiota, alleviating intestinal inflammation, and, indeed, to preventing colorectal cancer.

Compared to current strategies, this approach is innovative in two respects: using a human protein produced endogenously in the intestine, and increasing the proportion of gut bacteria with anti-inflammatory potential by raising the intraluminal concentration of REG3A to preserve host-microbiota symbiosis and thus fight intestinal, or, indeed, extra-intestinal inflammation more effectively.

Source:

**Enteric Delivery of Regenerating Family Member 3 alpha Alters the Intestinal Microbiota and Controls Inflammation in Mice With Colitis.**

Darnaud M1, Santos AD1, Gonzalez P1, Augui S1, Lacoste C1, Desterke C2, De Hertogh G3, Valentino E1, Braun E1, Zheng J4, Boisgard R4, Neut C5, Dubuquoy L5, Chiappini F1, Samuel D1, Lepage P6, Guerrieri F7, Doré J6, Bréchot C8, Moniaux N1, Faivre J9.

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* Other founder members of Aviesan: CEA, CNRS, CHRU, CPU, INRA, INRIA, Inserm, Institut Pasteur, IRD

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