Abnormal activation of Autophagy-induced crinophagy in Paneth cells from patients with Crohn's disease

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IIntroduction

Intestinal epithelial cells (IEC) have the difficult task to protect the host from potentially harmful luminal content and promoting the uptake of water and nutrients. Specialised IEC such as, Paneth cells, are protective cells located at the small intestine in the crypt base. These cells produce anti-microbial substances such as defensins and lysozyme, but also produce growth factors that are indispensable for the intestinal stem cell niche. Highly secretory cells, such as Paneth cells need to be able to cope with high endoplasmic reticulum (ER)-dependent protein production causing chronic ER stress. As such, micro and macro engulfment of intracellular compartments (e.g. autophagy) is part of the ER stress response to protect cells from noxious ER stress levels.
Defects in Paneth cell function, including impeded defensin production and secretion, have been reported in Crohn's Disease (CD) patients. The mechanisms behind this phenomenon are still largely unknown. However, a recent short report by Thachil et al. in Gastroenterology from January 2012 elegantly shows that this impeded Paneth cell function in CD patients may be due to increased autophagy-related engulfment of the secretory granules, known as crinophagy. This finding further strengthens in the importance of IEC, in particular the Paneth cells, in a normal gut homeostasis.

Key findings

Small intestinal biopsies from therapy naïve paediatric CD patients, where histologically analysed for signs of autophagy. Firstly the authors show that LC3 (autophagy marker) was increased specifically in Paneth cells of the CD patients, irrespective of disease activity or intestinal location. Interestingly, this increase in autophagy was not associated with polymorphisms in autophagy related genes, such as NOD2, IRGM and ATG16L1. Besides, Paneth cells of UC or celiac patients did not show increased LC3 expression.

Since reduced granules and enhanced LAMP1 (lysosomal marker) were detected using additional transmission electron microscopy and immunohistochemistry, the authors concluded that the Paneth cells of CD patients have an elevated active autophagic flux. Subsequent analyses showed that the secretory granules in Paneth cells of these young CD patients are target of autophagolysosomes, which appear to be specific hallmarks for crinophagy.

Overall Conclusion

The authors conclude from their data that the protein secretion in Paneth cells, specifically in CD patients, is impeded due to autophagic secretory granules engulfment known as crinophagy. Accordingly, crinophagy may account for the previously observed granuloma disorganisation in Paneth cells of CD patients.

Overall Conclusion

The authors of the paper did a great effort to reveal the mechanism behind the impeded Paneth cell function associated with CD. The fact that the authors use biopsies from paediatric CD patients that were naïve for any therapy is of great value, since therapies can have an affect on the secretory pathways in Paneth cells. Moreover, it was interesting to see that polymorphisms in the autophagy pathway or the presence of mucosal inflammation were not related to the enhanced autophagy in Paneth cells. This strengthens the hypothesis that there is a continuous existence of (molecular) mucosal activation in CD patients, despite of the absence of clinical or histological inflammation.

The authors solely use observational histologic assessments to determine the Paneth cell specific crinophagy. Although they postulate a possible explanation for the reduced production of antimicrobial peptides, there is no experimental evidence provided that shows that the 30% reduction in granules is indeed reducing the amount of excreted antimicrobial peptides. Besides, no clear attempts were made to explore the observed degradation of the granules (crinophagy). So the question remains if there is something wrong with the granules leading to their degradation. It will be of great interest to further investigate the possible (molecular) trigger, e.g. specific microbes or microbial products, which can initiate crinophagy. Also, by enlarging the patient population will give more definite genetic associations. In order to assess the cellular effect of activated crinophagy, other high productive cells, e.g. goblet cells, pancreatic cells, and gastric epithelial cells, need to be investigated. Moreover, the examination of biopsies from adult CD patients is also missing in this paper. These analyses are important since there are major differences in clinical disease appearance between paediatric and adult CD patients.