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Effects of NOD2/CARD15 and ATG16L1 on Crohn's Pathogenicity

Thomas J Tibbetts SMCC, Elizabeth Ehrenfeld, Ph.D SMCC

Abstract

Crohn's disease is a form of inflammatory diseases of the alimentary canal, usually most affecting the small intestine. This disease may affect over 700,000 people in the United States alone, while the cause remains somewhat of a mystery. This literature review will explore the role of two specific genes (NOD2/CARD15, ATG16L1) and how they may affect the pathogenicity of Crohn's. Both the CARD15/NOD2 and ATG16L1 genes have specific functions in immune and inflammatory response. Studies using both empirical data and in vivo laboratory results the CARD15/NOD2 gene has been found to encode a nucleotide-binding oligomerization domain which identifies a specific component of bacterial cell walls, thus playing an important part in innate immunity. The ATG16L1 gene has been shown to regulate autophagocytosis in cells, a function which likely plays a role in the inflammatory response experienced by most Crohn's patients. The function of both these genes should show a role in how an inflammation of the bowel may occur in patients.

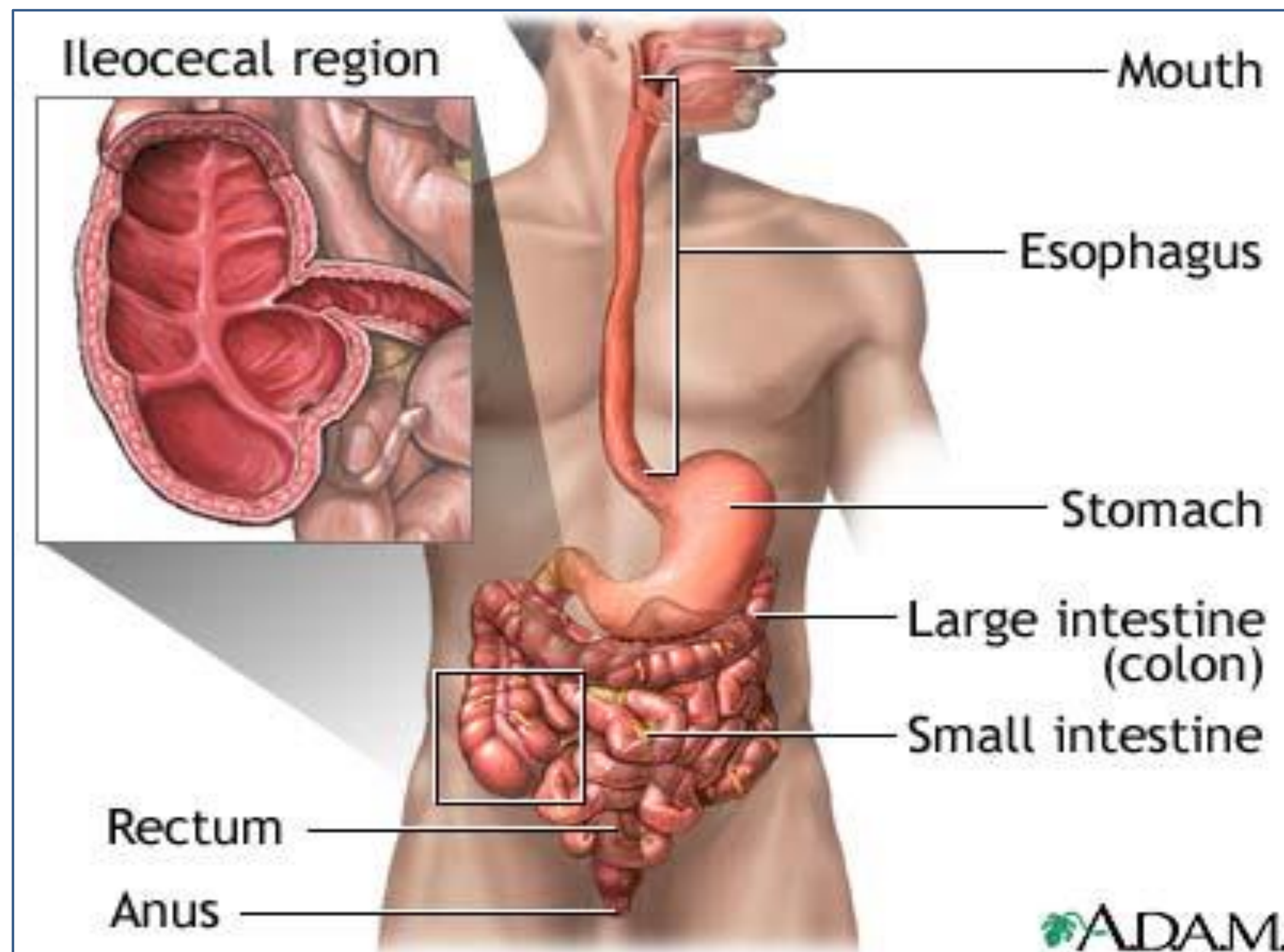


Figure 1: The alimentary canal, Crohn's can affect any part of the alimentary canal but is most common in the beginning of the colon, highlighted here. (Digestive Disease Center)

How Does Crohn's Disease Affect Patients?

- Crohn's disease is characterized by chronic gastrointestinal inflammation.
- This inflammation is caused by an autoimmune response and often leads to ulceration and thickening of alimentary tissue.
- Crohn's most often affects the ileum and beginning of colon, but symptoms can often develop in any part of the alimentary canal.
- Chronic inflammation can lead to tears in the intestinal wall which may fistulate, or create a secondary "tunnel" to other parts of intestine, bladder, vagina, or skin.
- The culmination of effects usually leads to sever abdominal cramping, rectal bleeding, constipation, loss of appetite, and many other clinical signs.

Paneth Cells

- In order to explore the pathogenicity of Crohn's cellular anatomy must be explored.
- Found in the crypts of Lieberkühn
- Critical role in release of defensins, a defense molecule used to disrupt cellular membrane function

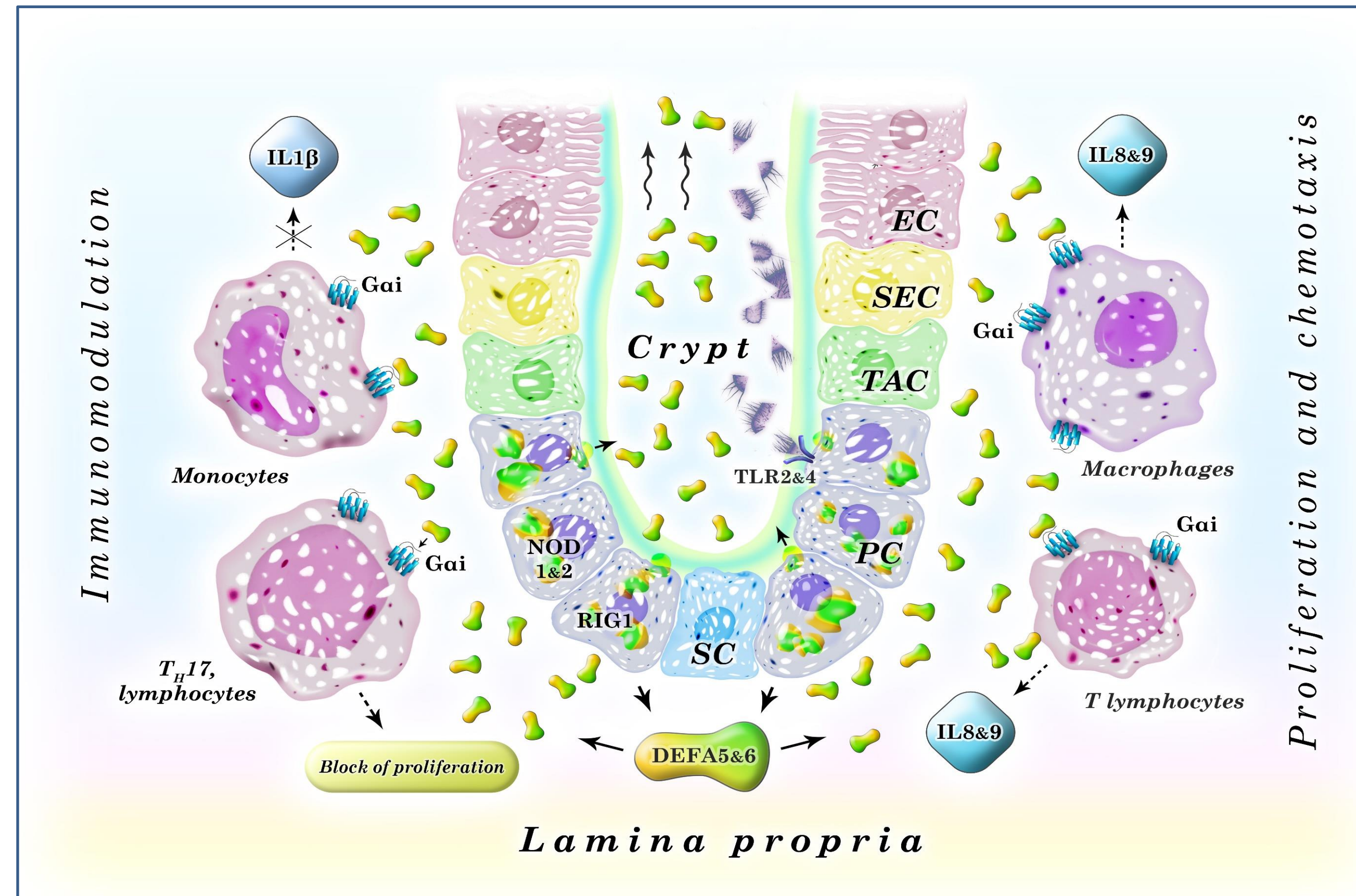


Figure2: This shows Paneth Cells and their complex interactions with both digestion and immunity. This also highlights the role of defensins in pro and anti-inflammatory response. (Lisitsyn, et al, 2012)

The Pathway (Fig3)

- Both ATGL1 and the CARD15/NOD2 act in response to intestinal bacteria
- ATGL1 activates autophagy
- NOD2/CARD15 acts to detect cell wall constituents
- Multiple expressions
- Normal expression leads to appropriate antigen production
- Altered pathway leads to inflammatory response

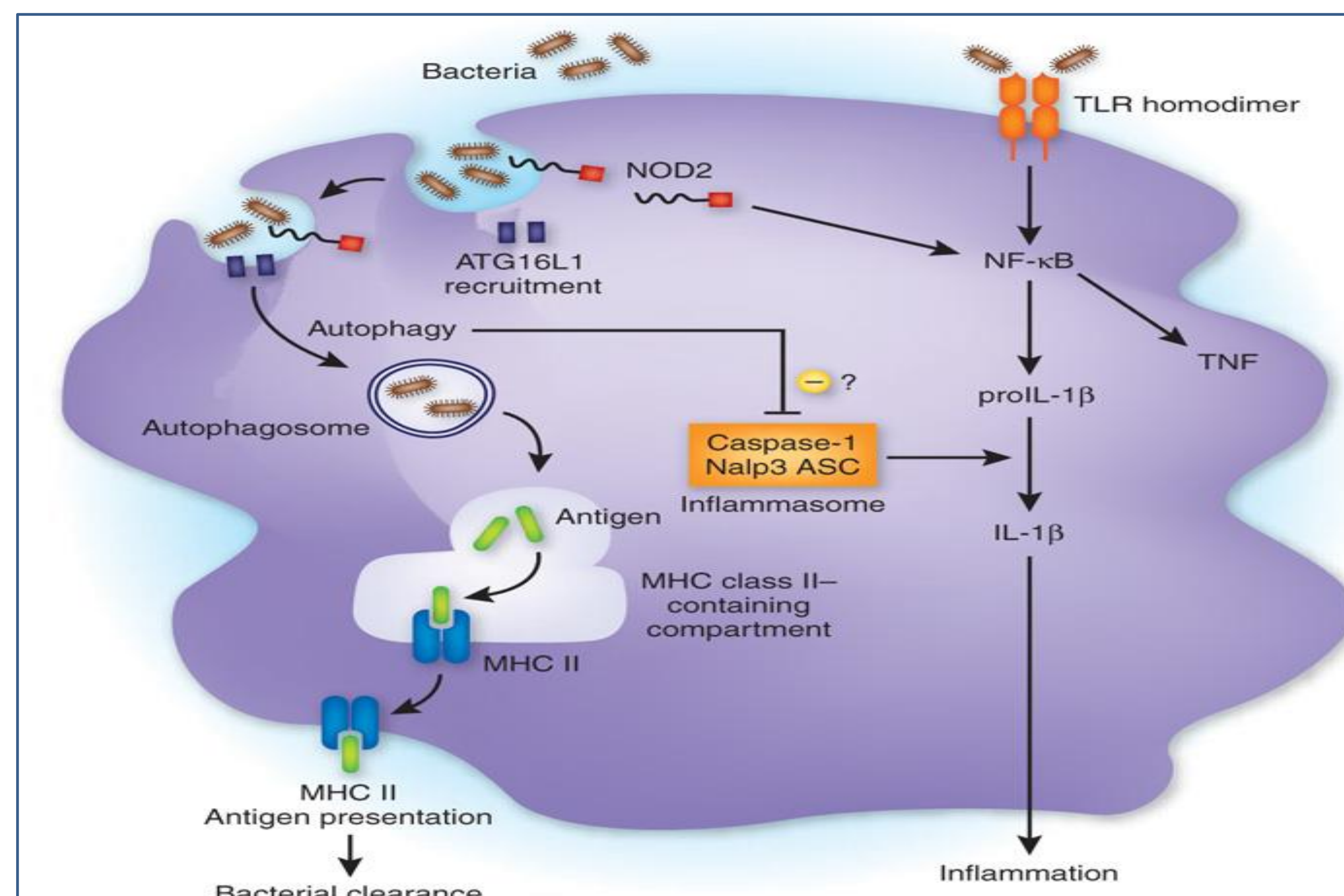


Figure 3: Showing the interaction between NOD2/CARD15 and ATG16L1 (Joosten, Netea 2010)

Results

- Quantitative studies show connection between variants of NOD2/CARD15 and ATG16L1 to higher instances of Crohn's and inflammatory bowel disease
- A study used mice which possessed a mutation in the ATG16L1 genes, this created over expression of certain genes which play a direct role in the intestinal inflammation and injury response (Cadwell, et al. 2008)
- Another study found ATG16L1 autophagy to be essential for clearing bacterial cells from intestinal epithelium (Conway, et al. 2013)
- Impaired CARD15 function was found to be important in the pathogenesis of Crohn's, since the signaling mechanism still activates the inflammation pathway but is unable to sense relevant stimuli (Seidelin, et al. 2009)

Further Research, New Treatments

- Current treatments are limited to management of symptoms and surgery for intestinal repair
- Commonly prescribed medications include: anti-inflammatory drugs to help reduce inflammation and lessen the effects of flare ups, immunosuppressants to help reduce the auto immune effects of Crohn's, and antibiotics to reduce number of harmful gut bacteria which thrive during fistula events.
- Gene therapy: genetic therapy maybe the best solution, reducing a patients number of harmful alleles would greatly increase chances of normal intestinal function
- Another possibility could be a more specific anti-inflammatory, which acted more specifically in the IL-1β inflammation pathway (Fig. 3)

Acknowledgements

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