Editorial

Evidence that the ubiquitin proteasome system plays a prominent role in inflammatory bowel disease: possible pharmacological approaches

Keywords: ubiquitin, proteasome, epithelial, colonic, endopeptidase, genetic, cylindromatosis, pharmacological

Abbreviations: IBD, inflammatory bowel disease; CD, crohn's disease; UC, ulcerative colitis; CYLD, cylindromatosis

Editorial

Inflammatory Bowel Disease (IBD), which exists predominantly as Crohn's Disease (CD) and Ulcerative Colitis (UC) involves genetic and microbial factors, which result in chronic inflammation of the GI Tract.[1] A recent manuscript by Cleynen and colleagues showed that the ubiquitin proteasome system (UPS), which is present in mammalian cells (e.g., intestinal epithelial cells) relevant to Inflammatory Bowel Disease (IBD), is an important contributor to the pathogenesis of intestinal inflammation.[1] Specifically, these authors proposed that Cylindromatosis (CYLD) protein, which is a de-ubiquitinase that acts as a negative regulator of NF-κB signaling, plays a prominent role in IBD.[1] This manuscript also provided good evidence that genetic polymorphisms in CYLD are significantly associated with human CD.[1] Moreover, the authors showed that pathogenic bacteria (*E. Coli* strain LF82) decrease the expression of CYLD, thereby resulting in enhanced NF-kB activation in intestinal epithelial cells.[1] This transcription factor has frequently been cited as a central mediator of inflammation in IBD.[2] Other manuscripts published over the last 10years have also implicated various components of the UPS as being important in the pathogenesis of IBD.

CYLD

In 2006, Zhang, et al.[3] (working at the NIH) showed that CYLD deficient mice were more susceptible to colonic inflammation, as well as developing colitis associated cancer.[3] Subsequent studies by Reilly and co-investigators (including myself) at the Penn State College of Medicine confirmed these murine colitis findings.[4] Moreover, we showed that adoptive transfer of CYLD-/- T cells induced colonic inflammation and symptoms of colitis in recipient mice.[4]

Immuno proteasome subunits (LMP2, LMP7, LMP10)

It is now established that when cells are exposed to pro-inflammatory cytokines (IFN-γ, IL-1β, TNF-α), which are up-regulated during the course of IBD, there is a replacement of constitutive catalytic proteasome subunits with immuno proteasome subunits.[5,6] Results from my laboratory, as well as other investigators, suggest that these immuno proteasome subunits [low molecular mass polypeptide (LMP) 2 (b1i), multi-catalytic endopeptidase complex-like-1 (b2i), and LMP7 (b5i)] are involved in the pathogenesis of experimental colitis and IBD.[5–7]

Novel pharmacological treatments targeting the UPS

A review of the references cited in this editorial implies that modulation of the UPS, particularly by developing drugs that selectively target the immuno proteasome would be a worthwhile endeavor.[1–7] In this regard, targeting the LMP7 subunit with a selective small molecule inhibitor (PR-957, ONX-0914) was shown to be effective in a mouse model of UC.[7] To date, the relevant literature seems to suggest that targeting the LMP7 or LMP2 immuno proteasome subunits may be most beneficial for the treatment of IBD.[5–7] Of note, two recent review papers (published in 2015) provide recent insights, which may further aid in the development of safe and effective drugs that inhibit immuno proteasome activity. Such drugs could be used not only for treating IBD, but also for the treatment of other autoimmune diseases (e.g., Rheumatoid Arthritis).[8,9] Therefore, the transition of immuno proteasome-selective inhibitors into clinical trials for chronic inflammatory diseases seems to be highly warranted in 2016.[9]

Volume 4 Issue 1 - 2016

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Received: January 21, 2016 | **Published:** February 02, 2016

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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Citation: Fitzpatrick LR. Evidence that the ubiquitin proteasome system plays a prominent role in inflammatory bowel disease: possible pharmacological approaches. *Pharm Pharmacol Int J.* 2016;4(1):308–309. DOI: 10.15406/ppij.2016.04.00062