Journal of Infectious Diseases & Therapy
ISSN: 2332-0877

Dupouy-Manescau, et al., J Infect Dis Ther 2022, 10:6

Short Communication Open Access

Role of Proteolytic Dysregulation in Gut Inflammation

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Received: 19-Oct-2022, Manuscript No. JIDT-22-77810; **Editor assigned:** 21-Oct-2022, PreQC No. JIDT-22-77810 (PQ); **Reviewed:** 07-Nov-2022, QC No. JIDT-22-77810; **Revised:** 14-Nov-2022, Manuscript No. JIDT-22-77810 (R); **Published:** 21-Nov-2022, DOI: 10.4172/2332-0877.1000516

Citation: Dupouy-Manescau N, Méric T, Kriaa A, Mariaule V, Jablaoui A, et al. (2022) Role of Proteolytic Dysregulation in Gut Inflammation. J Infect Dis Ther 10: 516.

About the Study

The etiology of Inflammatory Bowel Disease (IBD) remains incompletely understood in both human and dogs. The currently suspected physiopathology relates to excessive activation of the host immune response under genetic and environmental factors. In the review presented by Mariaule, et al., the authors highlight that proteolytic dysbalance has been shown to participate to gut inflammation [1].The paper focuses on metalloproteinases and serine proteases that have been the subject of numerous previous studies.

Matrix Metalloproteinases (MMPs) produced by the host take part to the mucosal homeostasis and are involved in many biological processes such as angiogenesis, immunity and inflammatory response. Dysregulations in the expression or activation of several MMPs have been associated with IBD in many ways. MMPs degrade the extracellular matrix, facilitating the progression of neutrophils. In addition, MMPs stimulate the release of TNF-α that contributes to mucus depletion, destabilization of tight junctions, and increase in epithelial permeability. Also, an increase in MMPs is associated with a decrease in programmaded death-ligand 1 binding to myofibroblasts, suppressing their ability to inhibit Th1/Th17 responses. All these pathogenic pathways supply inflammation.

In the host, serine proteases are mostly released by neutrophils infiltrating the gut: Their granules contain significant levels of elastase, proteinase 3, and cathepsin G. Mast cells also secrete serine proteases, including tryptase, chymase, cat G and granzyme B. In humans suffering from IBD, significant increase in levels of serine protease activity is found in tissue biopsies and fecal samples [2-5]. Serine proteases contribute to mucus degradation and destabilization of the endothelial and epithelial tight junctions by cleaving or phosphorylating junctional proteins, making easier the transmigration of inflammatory cells and microbes. Moreover, serine proteases turn on Protease-Activated Receptors (PAR), that can contribute to pathogenicity in many ways; for example, tryptase-mediated activation of PAR-2/Akt/mTOR pathway in fibroblasts participate to intestinal fibrosis. Serine proteases also alter cytokines processing, as CXCL5 and CXCL8 that lower the chemotactic activity toward neutrophils under physiological conditions. Finally, serine proteases also contributes to metalloproteinases activation.

Identified bacterial proteases are mostly produced by *Bacteroides*, *Streptococcus* and *Clostridium* species. These proteases provide the bacteria with a survival advantage in hostile conditions, and might also directly participate to local inflammation.

At the same time, studies have also shown that protease inhibitors are down-regulated in IBD patients, amplifying the protease-antiprotease imbalance that participate to the genesis of inflammation. These natural protease inhibitors include metalloproteinase inhibitors (tissue inhibitors of metalloproteinases) and serine protease inhibitors, refered as serpins.

For these reasons, inhibition of proteases from both host and microbiota may be a therapeutic avenue of interest, in particular in patients resistent to current medical options. Many synthetic and natural inhibitors have been studied in experimental models (mice and rats) and in humans. So far, clinical benefits have only been suggested in humans with the use of APC-2059: this highly specific tryptase inhibitor has already completed a phase II clinical trial, eliciting clinical improvement without drug intolerance in patients with mild to moderate ulcerative colitis [6]. However, several other inhibitors have proven to be promising candidates *in vitro* or in preclinical studies. These inhibitors include RO28-2653, minocycline, argatroban, silvelestat, TY-51469, nafamostat mesylate for the synthetic inhibitors, or α-1-antitrypsin, elafin, secretory leukocyte protease inhibitor, for the natural inhibitors [7-15].

One of the challenges of these studies targeting such proteases associated with gut inflammation is to identify inhibitors with sufficient specificity and stability to restore the proteolytic balance while minimizing adverse effects. Another approach would be to modulate the gut microbiota to favor bacteria that naturally secrete serpins of interest. Despite this demanding aspect, the authors believe that further characterization of proteases and their inhibitors might lead to relevant therapeutic targets in IBD patients, that may also benefits our canine patients.

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