British Journal of Gastroenterology
2020; 2(3): 185 - 188. doi: 10.31488/bjg.1000118

Review article

In Ulcerative Colitis, The Damage Caused to Gut Cells Is Inflicted by the toxic Effects of Auto Immune Complexes, Neutrophils Nets and Pro Inflammatory Agents, Cationic Histones and Bacteriolyis Which Can All Be Strongly Modulated by Highly Anionic Heparins

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Received: June 15, 2020; Accepted: July 07, 2020; Published: July 09, 2020

Abstract

The hallmark of the autoimmune disorder Ulcerative Colitis which destroys gut cells, is the deposition of immune complexes mediated by highly cationic histones released by neutrophils traps nets (netosis). These poly cations can function not only to kill microorganisms but may also act as potent opsonic agents having properties very similar to antibodies. These can then interact by strong electrostatic forces with negatively - charged domains in immune complexes facilitating their deposition and also their internalization by gut cell. However, the main cause of damage to the gut cells is initially caused by the action of the plethora of highly toxic pro inflammatory agents released by activated neutrophils. These mainly include: oxidants, proteinases, membrane perforating phospholipases and lyso phosphatides which can act in synergy to injure the intestinal cells. Cell damage may also be further aggravated by certain microbial cell wall components released following bacteriolysis induced either by antibiotics or by cationic lysozyme. However, a suppression of tissue damage may be achieved by the administration to patients of highly anionic heparins and heparinoids, which can neutralize histones if also combined with anti oxidants, proteinase inhibitors, inhibitors of phospholipases and by the potent anti inflammatory drugs, steroids, methotrexate, colchicin as well as and by novel anti inflammatory biologics recently certified for human use.

Keywords: ulcerative colitis, inflammation, cationic histones, neutrophils, toxic agents, heparin, bacteriolysis

Introduction

Today, the pathogenesis of ulcerative colitis, a common auto immune intestinal bowl disorder (IBD), is attributed to a dysbiosis, defined as a decrease in gut microbial diversity owing to a shift in the balance between commensal and potentially pathogenic microorganisms [1-9]. Currently, most experts also recognize that intestinal imbalance in the structural and/or functional properties of the gut microbiota can disrupt host-microbe homeostasis, which is integral to the pathogenesis of ulcerative colitis (UC). However, as of today, no specific microbial species have been identified as main causative agents, and the use of antibiotics, has invariably failed to significantly affect UC pathogenicity. Today, UC is also considered as an auto immune phenomenon in which negatively- charged immune complexes are deposited upon gut epithelia, which commences complex interactions with neutrophils products [10-18].

The pivotal role of neutrophils netosis in uc pathogenicity.

A special tribute should however be awarded to pioneering studies which have pointed out the key role of neutrophils and their traps(netosis) [19,20]. These traps are rich in a nucleosome and in highly cationic histones and in additional poly cationic substances incriminated in the pathogenesis of auto immune disorders. It is well accepted that neutrophils (PMNs) have a main biological purpose to kill invading pathogenic microbes and also to promote mucosal healing and resolution mediated by inflammation. However, activated PMNs can also function as double edged swords [16] by causing a severe damage to mucosal architecture by secreting into the surrounding media a plethora of highly toxic pro inflammatory mediators which act in synergy to injure cell and tissues creating a severe relapsing chronic destructive inflammation (summarized in detail in)[17,18].

A novel hypothesis may explain the mechanisms of pathogenicity of auto immune ulcerative colitis.

For the first time the present communication offers a novel approach that may shed a new light and can also clarify the

mechanisms by which auto immune complexes are deposited upon intestinal epithelia such as seen in UC. We postulate that highly cationic histones behave like opsonins similar to antibodies [21]. Such opsonins can now bind by strong electrostatic forces to negatively - charged domains in immune complexes and, similarly to antibodies, can also opsonize microorganisms for phagocytosis. This facilitates their localization, binding and even their internalization by the gut epithelia. This assumption is based on several publications from our laboratories which have shown that if suspentions of negatively charged group A hemolytic streptococci, Candida albicans [22], whole cell nuclei [23], and even entameba [24], which have been pre-coated (opsonized) by cationic poly peptides such as histones and also by poly alpha basic amino acids, could bind to and also undergo endocytosis not only by the professional phagocytes, PMNs, and macrophages, but also by epithelial cells, endothelial cells and even by fibroblasts and possibly also by gut epithelia. The proof that microorganisms and their fragmented cell wall constituents induced following bacteriolysis (see below) could localize intracellulary in macrophages to induce a severe relapsing arthritis which can be verified either by electron microscopy or by measuring muramic acid, an integral specific part of the microbial peptidoglycan.

The possible role of infection and bacteriolysis in uc pathogenicity

Several microbial species in the gut could undergo bacteriolysis due to the activation of their endogenous autolytic wall enzymes [25, 26]. This can be induced either by poly cations such as lysozyme from PMNs [27], or also by certain antibiotics [25,26]. Bacteriolysis can release into the surrounding media toxic cell wall components [28], lipoteichoic acid [29], and peptidoglycan from Gram positive bacteria [25, 26], and also toxic endotoxins from Gram negatives [25,26]. To prevent the binding, deposition and endocytosis of immune complexes, and also of whole bacteria by gut epithelia mediated by the action of cationic opsonins [21], it may be proposed to administer to patients highly negatively-charged heparin[30] and heparinoids [31, 32], which might be able to neutralize the opsonic power of poly cations. . Poly anions may also interfere with the activity of pro inflammatory agents released by neutrophil [33-37], and may also affect chemotaxis by cytokines [38].

Drugs that may help to protect against gut damage

Being a multi factorial disorder, an effective treatment of UC may prove successful by employing multidrug strategies [39], and anionic heparin [30-32]. However, combinations among anti oxidants such as N- acetyl cysteine, ascorbate and glutathione, which can abolish severe oxidation reactions, the anti protease aprotinin to abolish elastase activity, and purified lecithin to suppress PLA2 and lyso phosphatides toxicities [39], may prove beneficial elements. However, this is if these agents are combined with: steroids, methotrexate, colchicine. Such combinations might prove effective to depress inflammation and particularly the PMNs functions chemo taxis and the toxic action of pro- inflammatory agonist. The possible efficacy of antibiotics to suppress inflammation in UC [40], is controversial. Specific microbial pathogens, such as virulent Escherichia coli strains, and Bacteroides species have been linked to the pathogenesis of IBD. Antibiotics may influence the course of UC by decreasing concentrations of bacteria in the gut lumen and altering the composition of intestinal microbiome. Different antibiotics, including ciprofloxacin, metronidazole, the combination of both, rifaximin, and vancomycin regimens have been evaluated in clinical trials for the treatment of inflammatory bowel disease but with limited success. More recently, other drugs proposed to be effective UC, may include: amino salicylates, balsalazide (Colazal), mesalamine (Asacol HD, Delzicol), olsalazine (Dipentum), and sulfasalazine (Azulfidine), methylprednisolone, or prednisone . Screening the recent literature also suggested the use in UC of biologics such adalimumab (Humira), given by subcutaneous injection, golimumab (Simponi), given by subcutaneous injection infliximab (Remicade), given by IV infusion, infliximab-dyb (Inflectra), given by IV infusion and vedolizumab (Entyvio), given by IV infusions [41].Taken together, such proposed treatments may perhaps also alter the pathogenicity of other autoimmune disorders such as lupus nephritis, rheumatoid arthritis and perhaps additional autoimmune disorders.

Conclusions

Several overlapping and successional steps may help the reader to follow the stages of the development and progression of UC.Generation of auto immune complexes.The release from PMNs nets (netosis) of highly cationic toxic histones.Histone may also function as a potent opsonic agent possessing properties similar to antibodies. Opsonic histones, may interact with and bind by strong electrostatic forces to negatively- charged domains in immune complexes, facilitating their deposition and possibly also their internalization by gut cells. PMNs migrating to the gut undergo activation to release into the surrounding media a plethora of toxic pro inflammatory agonists. These mainly include: cationic peptides, oxidants, proteinases, membrane –perforators phospholipase, and fatty acids which may all act synergistically to injure gut ells.Protection against the progressing tissue damage in UC, might be provided to some extent by highly anionic heparin and heparinoids which can neutralize polycations. This is provided that these are also combined with drugs such as, steroids, methotrexate and colchicine and with other drugs which can prevent leukocytes recruitment., chemotaxis and phagocytosis UC may be dealt by non- bacteriolytic antibiotics since these may prevent the release from bacteria of the potent toxic cell wall components, lipotiechoic acid a peptidoglycan and endotoxins. Non - biodegradable microbial cell wall components may persist for long periods in macrophages capable of perpetuating chronic destructive effects. Toxic oxidants and proteinases released by PMNs may be controlled to some extent by multi drug strategies and by the low molecular weight anti- oxidants :glutathione, ascorbate, N- acetyl cysteine as well as by certain plant polyphenols, and also by the anti-proteinase, aprotinin.

Author Contributions

Conceptualization, I.G.; Writing – Original Draft Preparation I.G.; Writing – Review & Editing, I.G. and M.F.; Supervision, I.G.; Funding Acquisition, I.G.

Competing interests

The authors declare that they have no competing interests

Funding

Endowment fund contributed by the late S. M. Robbins of Cleveland, Ohio USA

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To cite this article: Feldman M, Ginsburg I. In Ulcerative Colitis, The Damage Caused to Gut Cells Is Inflicted by the toxic Effects of Auto Immune Complexes, Neutrophils Nets and Pro Inflammatory Agents, Cationic Histones and Bacteriolyis Which Can All Be Strongly Modulated by Highly Anionic Heparins. British Journal of Gastroenterology. 2020; 2:3.