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Stereotyped Tissue Response Promotes Progression of Injury in Bowel Inflammation

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Abstract: Evolving dynamics of vascular blood supply and ulceration of otherwise absorptive mucosal epithelium appear to primarily implicate intercellular adhesion molecules such as cadherin. An increased permeability of mucosa would progress in terms of injury to enterocytes with translocation transcytolically and paracellularly of fluid and macromolecules. Intense congestion with mucosal ulceration would develop as a multiplicity of involvement of blood vessels constituting granulation tissue and ulcer base. Also, a loss of effective epithelial barriers of the gut mucosa would progress largely as increased vascular wall permeability that further damages adjacent mucosal epithelium. Vascularity and disease progression would allow for a delineation of active processes that promote inflammation and ongoing injury to the bowel wall centered particularly on the lamina propria. Cytokine and chemokine derivatives would impair the vascular response patterns to injury of bowel mucosa in terms characteristically of a stereotyped lamina propria response. Variable mucosal injury induces a stereotyped response in attempted repair of the injury that further progresses as a superimposed series of changes in proliferation of enterocytes coupled to vascular permeability effects and transformed adhesion dynamics of epithelial cell junctions.

Key words: Stereotyped tissue, promotes progression, injury in bowel, inflammation

PERINATAL HIV INFECTION AS A SERIES OF NUMERICAL VALUES OF INDEX ACTIVITY IN ONSET AND PROGRESSION

A preventive measure scheme might obviate the need for a vaccine against HIV-1 infection only in so far as it is possible in the first place to counteract dimensional attributes of a transmissibility arising as a sexual behavior pattern[1]. One might indeed view HIV-1 infections as a linked series of events culminating in lymphocyte killing and progressing as immunodeficiency. It is only in so far as it is possible to assume attributes of a retroviral integration in the host cell genome that one might variably consider dynamics of a transmission that is transmucosal and subsequently hematogeneous.

Not only is it possible to assume that perinatal infection is itself an event of transmissible agent production but one might better understand how to control dynamics of an infection that is transmissible in terms other than the infection itself. Indeed, one might speak of a perinatal event whereby the neonate infant is affected by infectious agents of variable virulence and particularly by abundant virion particles. Only in trying to formulate dynamics of such exposure would one have to develop a vaccine program and a vaccination that is bound to development of the infant in the first instance.

EVOLVING STEATORRHEA NOT DUE TO INCREASED MUCOSAL PERMEABILITY IN HIV ENTEROPATHY/DIARRHEA

HIV enteropathy involves increased permeability of the mucosa arising from paracellular dysjunction at the site of tight junctions[2]. One might consider how increased mucosal permeability progresses in the absence of opportunistic infection. It might be valid to consider increased calcium entry in epithelial cells a system that normally operates to induce not only diarrhea but also a full spectrum of malabsorption syndromes that include steatorrhea. Uncontrolled mucosal immune responses may lead to inflammation involving in particular antigen presentation and T lymphocytes[3]. Contraction of actin-myofiber filaments might involve a paracellular permeability that would not only increase fluid loss in the lumen but particularly lipid loss in feces, unrelated to fluid loss. Indeed, steatorrhea is itself a fundamental series of events whereby malabsorption arises in a context that contrasts with increased permeability of the bowel mucosa in HIV enteropathy with a predominant diarrheal component.

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IS IMMUNOODULATION A PROLIFERATIVE RESPONSE IN TERMS OF DIFFERENT PHASES OF ACUTE INFLAMMATORY REACTIVITY?

Hepatocyte loss would appear a central mechanism in directing an acute inflammatory response integral to immunomodulation of stem cell differentiation and oval cell proliferation[4].

One might view the essential features of hepatocyte regeneration as centrally placed pathways of evolving immunomodulation that are transforming in terms of a proliferating pool of stem cells induced as an inflammatory or acute phase reaction.

Acute phase reactivity might apply to various modes of proliferative reactivity involving injured hepatocytes; these are removed by the immunomodulation response. Proliferating stem cells would invade the liver parenchyma as driven by Tumor Necrosis Factor alpha and by expressed gp 340/DMBT1 gene.

Only insofar as modulation of responsiveness of hepatocyte oval cells occurs as an acute phase reaction can immunomodulation be a primary sensor system of loss of hepatocytes that effectively participates in inducing proliferation and differentiation of oval cells.

HIGHLY SPECIFIC EPITHELIAL BARRIER LEAK OF HIV ORIGIN CHARACTERIZING ABSORPTION AND SECRETION DYNAMICS IN HIV ENTEROPATHY

An epithelial barrier leak affecting HIV enteropathy might specifically involve pathways of progression in terms primarily of HIV-1 accumulation within macrophages in the lamina propria[5].

The production of inflammatory cytokines as a response to HIV-1 might perhaps help account for diarrhea and malabsorption that are variably related to a stage-specific progression of the HIV-1 enteropathy. Adenosine, in particular, regulates immunity and inflammation and also modulates intestinal function[6]. These would operate both as a state of infection and also as a reservoir of continually productive systems of HIV-1 organisms.

Perhaps one might relate HIV infection to variable compromise of pathways of absorption and secretion that are integrally reflected in a highly specific form of epithelial barrier leak of HIV-1 origin. Mucosal endothelial cells regulate mucosal immune response and control accumulation of leukocytes in the interstitial compartment[7]. Leukocyte-endothelial adhesion molecules are implicated.

INTERACTIVE CELL ADHESION AS AN AGONIST-ANTAGONIST SYSTEM VIA LIVER-INTESTINE CADHERIN IN INFLAMMATORY STATES

Laterally mobile adhesive functionality of liver intestinal LI cadherin appears one tied up with basolateral attachment of enterocytes and goblet cells, on the one hand and of hepatocytes in a manner that would define their polarized state[8].

One might recognize cytoskeletal attachment via actin as a mode whereby polarization functions in terms of restricted variation in shape of the attached cell.
Homotypic cell-cell interactions would perhaps implicate receptivity as a functional component in intercellular support that progresses as ongoing agonist-antagonist systems.

Hepatocyte interactions might account for inflammatory states of both liver and bowel that characterize many patients as an integral dysfunctional state in many patients with inflammatory bowel disease.

PARAINFECTIOUS NONCONSEQUENTIAL RELATIONSHIPS OF CHOLERA-RELATED DIARRHEA AND BOWEL INFLAMMATION

Constitutive rather than inducible causes of cholera toxin-associated diarrhea might implicate hydroxytryptamine in complex pathways that arise as a consequence of dysfunction of barriers in the gastrointestinal mucosa and submucosa[9]. Pathologic involvement of the bowel wall may be a consequence as well as a cause of further inflammation based on infectious transmission to various different levels of the alimentary tract. Dendritic cells are important antigen-presenting cells in the colon and may directly promote ongoing inflammation[10].

In cases of chronic gut inflammation, post-translational protein modification may be important pathogenically, involving in particular increased expression of the endogenous inhibitor of Transforming Growth Factor beta 1 signaling, Smad 7[11].

Bowel wall dynamics are constitutive mechanisms that in turn determine in non-consequential manner the evolution of diarrhea, whether this is actually inflammation-induced or not. Cholera diarrhea may be a realized consequence also of barrier dysfunction that is parainfectious rather than directly induced by the infecting organism and its cholera toxin.

INTRANEURONAL AND INTESTINAL PROLIFERATION OF VIRUS IN THE ABSENCE OF INFLAMMATORY REACTIVITY

Cytokine action in the absence of inflammatory infiltrates may very well involve neuronal secretory activity that not only provokes an upsurge of possible inflammatory reactivity but also helps define susceptibility traits of the neurons in states of viral replication[12].

Replication of virus appears only secondarily susceptible to inflammatory reactions. It would further appear that susceptibility of neurons constitutes systems of transformation coincident with intraneuronal replication and accumulation of viral particles.

Such a phenomenon may in part account for variability of cytokine production in the essential absence of a discernible inflammatory infiltrate; this would apply also to involvement of bowel mucosa and especially lamina propria in HIV enteropathy. In particular, a recapitulation of embryonic hedgehog signaling may occur in acute epithelial injury and chronic inflammation of the bowel[13].

THE HEMOPHAGOCYTIC SYNDROME

The hemophagocytic syndrome appears to mark a state of immunodeficiency that arises primarily within a context of evolving phagocytosis of antigenically distinct groups of erythrocytes.

The accumulation of multiple red blood cells within the cytoplasm of histiocytes in the bone marrow might actually constitute a process of antigenic processing relative to adsorbed antigenic profiles to the erythrocyte membrane.

The rapidly evolving viral infections often associated with the hemophagocytic syndrome would perhaps refer to a multiplicity of viral antigen types arising particularly within the context of induced immunodeficiency.

Multiple different viral types may cooperatively participate in evolving infectious states and immunodeficiency, to specifically implicate lymphocyte injury and lymphocyte targeting by such viruses.

Epstein-Barr virus in a setting of HIV-induced immunodeficiency might constitute a prototypic mechanism of immunodeficiency that is alternatively lymphoproliferative and carcinogenic or leukemogenic/lymphomagenic in scope.

One might recognize lymphoproliferative states as primarily mechanistic pathways of progressive transformation through various stages of evolving influence in the establishment of an immunodeficiency that is both established and transforming to further proliferative states of a clonal or nonclonal type.

ENDOGENOUS INFLAMMATORY CELLS IN THE LAMINA PROPRIA CONTROL ABSORPTION/TRANSFER OF MACROMOLECULES

Inflammatory bowel disease would constitute a set of circumstances whereby degradation of protein molecules in the gut lumen results in increased antigen presentation to the immune system[14]. Flagellin is a dominant antigen of the Crohn's disease-associated adaptive immune response and it also activates innate immunity[15].

Such dysfunctional increase in antigen presentation might account for a progressive leak in epithelial barrier functionality linked not only to cytokine secretion but especially to a synergistic action between TNFalpha and IFNgamma in increasing both paracellular and transcytolic transfer of macromolecules to the underlying mucosa. Regulatory B lymphocytes might develop in inflammatory bowel disease and would dampen pathogenic immune response by interacting with T cells[16]. One might view inflammatory cells in the lamina propria as an important mechanism that endogenously regulates degrees of such paracellular and transcytolic transfer of macromolecules from the gut lumen.

PROGRESSION OF INFLAMMATION IN ULCERATIVE COLITIS INITIALLY MANIFESTS AS BREAKDOWN IN INTERCELLULAR EPITHELIAL ADHESION

Tight junctions correlate with the onset and prolongation of diarrhea due to ulcerative colitis and would be largely potentiated by evolving dynamics of early ulcer formation[17]. Disruption of epithelial barrier function by interferon-gamma plays an important role in the development of bowel inflammation[18].

This aspect of the pathophysiologic course of inflammatory bowel disease would tend to promote a break in continuity of the gastrointestinal mucosa linked to evolving injury of crypts as well as of surface enterocytes or mucosal epithelial cells. Diarrhea is an integral index of an inflammation that induces breakdown of the mucosal barrier with physical disruption particularly of intercellular tight junctions. Vascular cell adhesion molecule-1 mediates leukocyte-endothelial cell adhesion and plays a co-inflammatory role in various organs[19]. Enzymatic disruption of such a mucosal physical barrier might induce aphthoid ulceration implicating the paracellular space with an intercellular adhesion molecular framework of progression. A molecular diagnostic assay, particularly a peripheral blood mononuclear cell-based gene expression signature, may help considerably in the classification of otherwise indeterminate forms of inflammatory bowel disease[20].

NONABSORPTIVE DYNAMICS OF Na+ FROM ULCERATIVE COLITIS-AFFECTED BOWEL

Nonabsorption of Na+ in the distal colon and rectum in ulcerative colitis would involve a marked diminution of and a transformation of, dynamics of chloride nonabsorption and of impaired basolateral Na+K+ ATPase activity[21].

A global absorptive malfunction of the distal large bowel would transcend inflammatory impairment of Na+ channels per se and dynamics of a malabsorptive ionic exchange series of pathogenic mechanisms.

Mucosal epithelial cells are a reliable point of reference in trying to index activity of an inflammatory process that eventually promotes persistent mucosal ulceration. Inflammation may induce increased translocation of bacteria and toxins across the mucosa and also promotes microcirculatory hypoperfusion or cytopathic hypoxia[22]. Interleukin 13 impairs epithelial barrier function by affecting epithelial apoptosis, tight junctions and restitution velocity[23]. Even when one considers all aspects of a mucosal pathology that culminates in hemorrhagic ulceration of relapsing remitting type, ulcerative colitis would prove both an effect and an integral cause of cycles of progression of Na+ malabsorption culminating in Na+ non-absorption from the bowel lumen.

BARRIER DYSFUNCTION AS BREAKDOWN IN INTERCELLULAR COMMUNICATION IN CROHN'S DISEASE

Increased mucosal epithelial permeability would correlate with mucosal vascular endothelial permeability in terms of relapses of Crohn's disease arising as luminal antigen stimulation of the mucosal immune system[24].

Peroxisome proliferator-activated receptors are metabolic and anti-inflammatory transcription factors and may inhibit the induction of proinflammatory cytokines, adhesion molecules and extracellular matrix proteins[25]. One might view aspects of development of bowel wall inflammation as integral manifestations of increased permeability of vascular and epithelial barriers that progress in the face of potential injury. Angiogenesis, as induced by Vascular Endothelial Growth Factor-A, may be implicated in inflammatory bowel disease that is linked to cell-mediated immune responses[26].

Barrier dysfunction as an invoked series of mechanisms inducing increased permeability of vascular walls would involve a paracellular defect that interrupts intracellular contact and adhesion beyond operative ion conductance. One might view inflammation as a disruption of barrier compartments and also of mechanical communication between cells.

PROXIMITY OF BLOOD VESSELS TO MUCOSA IN CELIAC DISEASE

Occludens attachment of enterocytes appears to be operatively modulated in a manner that induces variable barrier functionality to a small bowel loop or remnant of small bowel after disease or surgery[26].

It is in terms of how glucose flux is prevented in an outward direction that one can better gauge how well such barrier functionality can be controlled.

Celiac sprue is remarkable in that cytokines, particularly Tumor Necrosis Factor-alpha, can induce a series of changes that down-regulate bowel wall permeability; these would operate in terms of increased outflow of fluids and of proximity of blood vessels to mucosa and submucosa. Increased numbers of metalloproteinase-12 positive macrophages may predispose to Coeliac disease due to degradation of the extracellular matrix early in the disease[27].

STRICT PARALLELISM OF DUCTULAR OVAL CELLS AND SOME MARROW STEM CELLS IN SPECIFIC FAT DIFFERENTIATION

Ductular reactive proliferation of small oval cells would constitute a parallel system of regenerative response along with bone marrow-derived stem cell proliferation in replacing injured hepatocytes[28]. Such parallelism might account for oval cell proliferation as an essential fate-determining series of differentiation patterns establishing attributes of the hepatocyte phenotype.

Novel expression of Deleted in Malignant Brain Tumor I appears integral to the hostile environment that is created with injury to hepatocytes either as a result of trauma or in terms of toxicity to these cells. A switching on and off of novel transcript expression would closely parallel the migration and proliferation of stem cells from the bone marrow and the subsequent fate determination in hepatocyte differentiation. Parallelism of dual system responses would play a fundamental role in integrating regeneration in hepatocyte and liver injury or toxicity. Adipocytokines in particular may play an important role in inflammation and serum levels of adiponectin, resistin and active ghrelin rise whilst those of leptin fall in patients with inflammatory bowel disease[29].

Such concepts would perhaps particularly apply to mucosal regenerative attempts in inflammatory bowel disease. Bone marrow cells are the only cells of extra-gastrointestinal origin that contribute to regeneration of the intestinal epithelium[30]. Associated liver disease, in cases of ulcerative colitis, would underlie such parallelism that evolves as dual systems of promotion and progression of the inflammatory state.

DYNAMICS OF INFLAMMATORY RESPONSE AS STEREOTYPED TISSUE INJURY IN PROGRESSION

It is significant that stereotyped inflammatory responses to a wide range of potential pathogenic pathways or agents would evolve within a setting of progressive tissue injury on the part of bowel mucosa and submucosa[31].

Defects in Nod1-dependent peptidoglycan sensing following bacterial infection may contribute to the development of bowel inflammatory states[32]. Bacterially derived DNA in the bowel lumen contributes to perpetuation of chronic inflammation of the bowel[33].

Onset determines progression of inflammatory lesions and involves a variety of tissue components ranging from blood vasculature to lymphatics and stromal proliferation. A specific deficiency of Paneth cell defensins may compromise native immune response in patients with ileal Crohn's disease and would promote perpetuation of the disease[34].

In view of the endless list of potential agents provoking enteropathy in terms of such progression of the inflammatory state, it is significant that ulceration of the mucosa together with relapses and remissions of the disease in ulcerative colitis involve a hemorrhagic component. Anemia is commonly present in patients suffering from inflammatory bowel disease[35]. Crohn's disease, on the other hand, would be viewed as a chronically progressive disorder with fibrosis and lymphangiectasia and as a cause of intestinal obstruction.

In terms of such relapsing-remitting course or of chronically progressive inflammatory reactivity, one might view onset and progression of the inflammation as largely attributable to pathways originating from highly variable causes of tissue injury. Inflammatory bowel disease possibly arises from a dysregulated immune response toward intestinal microflora[36].

Inflammatory states as a response to a heterogeneous group of potentially inciting agents would constitute a stereotyped model of progression of injury to bowel mucosa that underlies various systems or tissues that respond to the injury. Bacteria might trigger and sustain inflammation and colon carcinogenesis in patients with inflammatory bowel disease, particularly within the context of gene mutations in the Transforming Growth Factor-beta signaling pathway[37]. Inflammatory states would be redefined as a progression largely determined at outset by the development of prerequisite systems of injury to tissue components rather than simply to mucosa or submucosa.

In terms of tissue disease reactivity, inflammatory enteropathy would progress as a result of vascularization and as states that couple induced damage to a responsive reactivity to such injury. Epithelial carcinogenesis might be mitigated by anti-inflammatory cells and cytokines in patients with inflammatory bowel disease[38].

These would evolve beyond just onset or progression of the particular disease entity but rather in terms of dynamics of blood flow or stasis. In particular, a paradoxical combination[39] of ischemia and hyperemia to the bowel mucosa and epithelium may contribute to protracted mucosal injury and especially to the initiation and progression of bowel inflammation.

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