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Review Article

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The Human Gut: Inflammatory Remote Manifestations Regulated by the Microbiome

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Abstract

In recent decades, intensified scrutiny of the inflammatory gut disorders has shown that the gut and the periphery tend to handle inflammation in a two-way fashion of reciprocal influence. As an example, among a thousand, food reaching the bowel can well arouse gut inflammation; and, in turn, an inflamed gut can favor the rise of inner neurodegenerative pathology, including motor disturbances such as the Parkinson's syndromes. In analogy to other situations, the study of the multiplex microbiome is beginning to let unfold the knots still paralyzing our understanding of the mode the gut handles inflammation.

Keywords: Microbiota; Parkinson's disease; Inflammatory bowel disease; Food

Introduction

Inflammation makes one of the most efficiently conserved processes in the evolution [1]. The acute presentation (tissue swelling, fever, blood stasis, pain, impaired function) is a classic hallmark of response to life-threatening events. In more modern eras, chronic inflammation phenotypes have prevailed with subacute immune activation, and creeping debilitating disease (often complicated by neuropsychiatric signs) [2].

As a multicellular and multifunctional conduit penetrating the body for some 9 meters from mouth to anus, the alimentary canal does present with most of the features that permit the origin, maintenance and expansion of the chronic inflammatory processes we are describing in this review. Briefly, the gut is nowadays considered the prototype barrier organ [3] with a single line of columnar cells separating the inflammogenic lumen contents from an underneath lymphocyte reactive tissue; the system can maintain a delicate balance provided that a few conditions are met at any time: cell to cell tight junctions remain sealed; wall permeability is controlled; inflammogenic antigens in the lumen are presented to reactive lymphocytes by self-destructing (apoptotic) dendritic cells, whose demise determines response termination [4]. Wrongly checked gut inflammation is not uncommon. The consequences may obviously be an upgraded inflammation, encompassing, according to modern views, a continuum inflammatory "crescendo" from irritable bowel to full-blown inflammatory classics including Crohn's disease and ulcerative colitis; with an equal frequency, but raising perhaps a more exciting interest, the gut perturbations named above can materialize to extra-luminal disorders [5].

Thus, three of those clinical conditions were arbitrarily chosen:

1) The post-prandial syndrome
2) The skin complications
3) A few neurologic disorders

A discussion on these topics cannot avoid becoming embedded into the consideration of the microbiota, the billion-cell population whose consequences on the bodily physiology and pathology are being further characterized at a daily increasing pace. We shall try to conclusively integrate all these notions into a unifying glance at human immune-inflammatory biology.

Data Presentation and Analysis

The post-prandial syndrome

The team of Dror E, et al. [6] has elaborated on the bias that the simple process of feeding is regulated in an inflammatory environment. The cast of characters in this "drama" was supposed to include:

a) The insulin-producing beta cells that are notably rich (and responsive) in receptors for the pro-inflammatory Interleukin (IL)-1 beta cytokine

b) The macrophage-containing omental fat

c) The pro-inflammatory mediator IL-1 beta, as anticipated above

d) The highly immunogenic bacterial lipopolysaccharides

Having set the characters, the drama may be envisaged. In the Dror's E hypothesis, the insulinic response to the (physiologic) post-prandial glucose rise turns out to be an immune inflammatory event where in the Langerhans cells are induced to release insulin upon stimulation of their IL-1 beta receptors; in turn, IL-1 beta would be released by omental macrophages becoming activated by contact with the polysaccharides brought about by digestion of the meal. A few points are worth of note in this ideal metabolic-inflammatory chain [6]:

a) An inflammatory bout may follow all meal in physiologic conditions

b) Digestion and inflammation are intertwined in the digestive system

c) Insulin release may be regulated as an immune-inflammatory event

At least two keystone reflections may be relevant to the arguments set forth above:

a) In an ambivalent fashion, Nature has established the act of feeding as obviously indispensable, yet hardly tolerated in a background of upgraded inflammation. Elaboration of the evidence from the post-prandial syndrome is now enhancing modern concepts on the role of the diet in intestinal physiology and disease [7].

b) In this construct, the bulk of the available glucose is supposed to be sequestered and used by the inflammatory cells engaging a contrast with neural cells with which they share the Glucose Transporter 1 (GLUT-1) receptor (the marker of glucose-avid cell types) [8,9]. The competition for glucose of inflammatory and neuronal cells may end up with obvious detriment of the latter in cases of strong or recurrent inflammation. Investigators of mankind history have agreed on the evidence that pre-historic phases of prevailing inflammation due to weather disasters or clash with prevailing wilderness have coincided with periods of shrinking of volume and weight of the brains of the victims of such adverse events [10]. In modern eras, acute fear of the wild has in fact left room to chronic nervous malaise (anxiety, depression), that many have thought to depend on brisk abandonment of natural life in favor of more artificial lifestyles imposed by industrialization [11]. Efforts to counteract this detrimental tendency have partially been successful in designing anti-inflammatory diets, and, most specifically, in working out scientific programs of regular physical exercise [12]. Interestingly enough, the mechanism of the beneficial effect of physical exercise has been consistently indicated as the muscle-driven release of the complex lactoferrin protein [13].

Thus, initially based on the curiosity for a marginal phenomenon like the "post-prandial syndrome", scrutiny of inflammation has indeed widened our angle of knowledge on gastroenterology, immunology, alimentary and behavioral sciences [14], opening landscapes of basic science and medical practice.

The inflammatory skin complications

Structurally and functionally, the skin can be considered as a barrier organ and the array of its relevant pathology may resemble that of the gut. This category traditionally includes erythema nodosum and pyoderma, and may affect 1-15% of all Inflammatory Bowel Diseases (IBDs) [15]. A very popular hypothesis holds that a cross response may take place to antigens that are shared between the gut flora and the skin. This would evolve into a hypersensitivity reaction with immune complexes forming in blood vessels adjacent to subcutaneous fat [16]. In the case of pyoderma, investigators stress a heightened expression of pro-inflammatory cytokines: IL-8, IL-16, IL-17, Tumor Necrosis Factor (TNF)-alpha [17]. As usual, the influence of a permissive Human Leucocyte Antigens (HLA) expression is invoked: B15 has been associated to development of erythema nodosum [18]; TNF-receptor associated factor 3 (TRAF3) interacting protein 2 (TRAF3IP2) an intermediate of the inflammatory response.

A closer scrutiny: psoriasis: Psoriasis is probably one of the most frequent co-morbidity accompanying IBD, with particular reference to Crohn's disease. This contiguity can now be conveniently discussed on clinical grounds, as well as be explained in terms of genetic immunology. Real-life clinical experience has shown that relevant skin lesions can be revealed in Crohn's disease patients up to seven times more frequently than in the controls [19]; further clinical inquiry showed that 10% of patients with CD are likely to report with a first-degree relative affected by psoriasis [20]. Genetically, psoriasis is no longer considered as the result of an autoimmune reaction against keratinocytes, but rather as the consequence of a wrongly driven recognition of skin microbiota, favored by genetically determined changes of innate immunity. This proposal has received corroboration and detail from the description in psoriasis of 4 peptidoglycan recognition structures, exerting their defense endeavor by binding glycans of Gram+ bacteria [21]. Most researchers now accept that polymorphism of at least two of these sensors (Peptidoglycan Recognition Proteins [PGRP]-3 and -4) on chromosome 1q may lead to skin microbiome misrecognition and hence psoriatic inflammation. This vision would classify the skin and its pathology (psoriasis) in the chapter of the barrier organ diseases in analogy with the gut itself [3]. Similarly, misfunction mutations of Nucleotide-Binding Oligomerization Domain (NOD) sensors have been indicated as the cause of Crohn's disease in Western descent patients.

The neurologic disorders attached to IBD

An exhaustive review of some ten years ago [22] esteemed that the peripheral or the central nervous system can be found affected in a proportion of IBD cases ranging widely between 0.25 and 35.7% in accord with selection bias and disease definition. At least six pathogenetic mechanisms might be invoked as the causes of this neurologic involvement:

1) Malabsorption and deficiency of vitamins of the B and D classes

2) Metabolic agents

3) Immune suppression induced infection

4) Medication side effects, including cyclosporine and metronidazole

5) Thromboembolism

6) Immunological abnormalities

Point 6 now correctly reminds us of the "barrier organ function" delineated above. Relative failure of the barrier at the gut level (allowing undue contact between sub-mucosal reactive tissues and antigenic luminal content) has been indicated as the culprit for fueling out gut inflammation up to IBD. Should the function of the blood-brain barrier [23] fall as well inadequate, gut outflow of inflammogenic material (including bacterial Lipopolysaccharides [LPS]) would reach the inner brain, triggering release of local "defensive" substances (amyloid) with inflammation-dependent neuronal degeneration [24] (with Alzheimer's as the clinical counterpart in the view of many). In this view, gut and brain malfunction are pathogenically unified; gut handling of inflammation would be the core variable, and membrane permeability would play the balance, biasing trans-organ inflammatory

reactions. We deem it now due to enter somewhat more inside the mechanisms of a model disorder: Parkinson's disease.

Parkinson's Disease (PD) and syndromes: In 1817, the English physician James Parkinson described a few patients presenting with shaking palsy [25]; non-motor symptoms [26] typically including depression and dementia were later described, and, steadily worsening, were shown to be the cause of death. Today, PD is included in the degenerative neuropathies. There is no cure. Treatment consists of the daily replacement of the DOPA mediator whose deposits were consistently shown to be curtailed in common with the characteristic mesencephalic lesions. Interestingly, programs of regular aerobic physical exercise (for example daily bouts of brisk walking) have been shown to reduce symptoms, to spare the need for DOPA, and act also on non-motor signs, including depression [27]. It has been shown that exercised muscles release myokines that can direct release of lactoferrin from monocytes. Lactoferrin can then quench inflammatory processes by antagonizing IL-8, re-establishing gut eubiosis, and terminating LPS-induced reactions [reviewed in [28]].

Parkinson's routes intertwined with inflammation and gut pathophysiology? Despite the relevant description dates back to 1817, many aspects of PD continue to elude attempts to reach a clear-cut picture. The mostly discussed point is the possible origin of Parkinson's from gut (mal) function, based on three orders of fascinating yet deceptive facts:

a. Clinical disease onset may be preceded by years of constipation [29]

b. Similarly, smell attenuation may be a long-time harbinger [30]

c. Patients who had received troncular vagotomy seem to be protected against Parkinson's [31]

d. Chronic uncontrolled parodontitis has been strongly suspected to induce the disease [32].

The discovery and characterization of the marker alpha-synuclein might have provided the missing link to organize this mixed evidence. Alpha-synuclein is a 14kD prion-like protein with a likely meaning of reaction against infection of the nervous tissue [33]. Release of this prion-like substance has been shown to follow infection of the enteric nervous system sustained by an array of virus or bacterial invaders; initially beneficial, however, a synuclein response may be unleashed by continuing infection; on these premises, excess protein might migrate cranially, and reach the mid-brain structures finally causing the hallmark of PD: decrease or abolition of DOPA secretion, which is the base for the extra-pyramidal signs (reviewed in [34]). Recently published smart work has succeeded in ascribing a role for *Helicobacter pylori* (*H. pylori*) in this story, by showing that PD may be 3-4 times more frequently infected than controls [35].

Alzheimer's disease: Though apparently unrelated, the results of recent studies are telling a similar story for Alzheimer's disease. The severely invalidating symptoms of this neurodegenerative affection have long been placed in relationship with the presence of excess amyloid in the brains of autopsied patients [36]. With time however, the strength of this observation began to faint, in view of the frequent finding of similar amyloid deposits in the brains of unaffected subjects. Current speculation holds that one of the primary events in inducing Alzheimer's is the age-favored damage of the blood-brain barrier [37], leading to uncontrolled trespass of gut toxins including bacterial polysaccharide belonging to the overwhelming flora and ensuing inflammation and neural damage; rather than the mediator of the damage, excess amyloid should be seen as a tentative defensive response.

Considering their epidemic-like diffusion and the recalcitrance to cure, PD and Alzheimer's are correctly named as dreadful threats hanging upon today's mankind. At least, the design of a unifying pathogenic hypothesis may humbly be pretended to make an initial leap forward. Wrapping together the wealth of mixed data so far available, we have liked to stress that both disorders seem to derive from an undue invasion of the bodily specificity by the outer world gut contents (either extraneous infection or indwelling species); wrong membrane permeability and inflammation are the effectors of the damage.

The importance of the gut microbiome stems now clears from the premises; we then choose to concentrate on this topic as a tentative way to close the narrative circle.

The gut microbiome: two issues relevant to the presentation above

The term "microbiome" [38] is commonly used to indicate any microbe population that indwells the so-called barrier organs. Because of the huge number of bacteria, fungi and bacteriophages in the bowel, the multiplex functions of the gut, and the involvement of its disorders into a huge series of human diseases, the gut-associated microbiome has received a particular attention. We now know that the gut microbiome components encompass ten times the number of human cells in the body, and the relevant genetic material is 100 times larger [39]. The importance of the gut microbiome is simply demonstrated by the changes shown by animal offspring if grown in "germ free" conditions, as emphasized below. The number of the effects of the gut microbiome in health and disease is continuously rising: we have chosen to concentrate on two aspects that are related to the main topic of this review.

Microbiota can affect central nervous system and brain function: The autonomic nervous system may be influenced *via* activation of the vagus nerve: experimental animals receiving *Lactobacillus rhamnosus* exhibited less stress-induced cortisone production and reactive anxiety and such effects were abolished by vagotomy [40].

Short Chain Fatty Acids (SCFA) are a sort of multifunction product of a few microbial species; if large amounts of SCFA derived from gut microbiota encounter a "leaky membrane", they can enter brain structures, and start out a series of epigenetic changes including inhibition of histone deacetylase impacting the hypothalamus-pituitary-adrenal axis [41].

Some microbiota species can influence cerebral neurotransmitter handling by enhancing tryptophan metabolism with release of kynurenine and serotonin; again this reactive chain is enhanced by SCFA [42].

The gut microbiota can influence central nervous system performances through an immune associated process depending on IL-6 and IL-1beta. Certain microbiota strains can also concur in destruction or restoration of microglia [41].

Because of their individual and social burden, the pervasive personality disorders such as autism have always met with the interest and professional commitment of the medical community, and those involved with the study of microbiome could not deny their attention to the (often pediatric) autistic patients with their seriously challenged families. The working hypothesis that dysbiosis may affect these psychiatric disorders was partially confirmed; further, animal studies showed that germ-free conditions at birth can disturb social functions, with damage being possibly reverted by probiotics. Autistic individuals have been shown to harbor various strains of *Clostridium*

tetani whereas *Lactobacillus reuteri* seemed to be beneficial in reducing stereotypic behavior [43]. Therapeutic trials on autism are of course being designed and conducted rapidly, under the pressure of patients and families.

A "healthy" microbiome is required for correct gut immunity: At gut level, a correct immune balance can be maintained only on the background of a "normal" composition of the microbiome. Abnormal communication between gut microbial communities and the mucosal immune system has been identified as the core defect that leads to chronic inflammation [44]. An alteration in the diversity and composition of the gut microbiome (dysbiosis), rather than the presence of specific pathogens, likely plays a critical role in IBD pathogenesis: several studies have shown that there is a significant reduction in the diversity of the stool microbiome of individuals with IBD: 25% fewer genes were detected in the fecal samples of IBD patients than in those of control patients. The majority of IBD susceptibility genes (for example NOD2, ATG16L1, IL23R genes) are linked to pathways involved in immune-microbe interactions [45].

Concluding Remarks

Dominated by inflammation, and endowed with a relatively limited genomic wealth, mankind would succumb to the daily antigenic invasion conveyed by feeding (see the post-prandial syndrome described at the beginning). The balance may be re-established by the presence of the microbiome with its huge genome in continuous change according to diet i.e., socio-economic drift [46]. This merging of human and microbiome messages advises to interpret the phenotypes of health and disease in a socio-economic key.

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