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Editorial

One, Two, Three Inflammatory Bowel Diseases or More? A Microbial Point of View

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Abstract

The role played from intestinal microbiota on the onset and on the evolution of inflammatory bowel diseases has been and is widely investigated during the last two decades. Also, with the techniques most recently applied, however, no final result seems to be reached and the uncertainty rises between gastroenterologists and general practitioners also in the classification of the disease.

Keywords: *Inflammatory Bowel Diseases; Intestinal Microbiota*

Abbreviations

IBD: Inflammatory Bowel Disease; HMA: Human Micro-Biota Associated; UC: Ulcerative Colitis; CD: Crohn's Disease; VEOIBD: Very Early Onset IBD; IBS: Irritable Bowel Syndrome; HTG: Horizontal Transfer Gene

Alisa Hart and David T. Rubin published in 2022 on Gastroenterology a paper titled "Entering the Era of Disease Modification in Inflammatory Bowel Disease" (IBD) [1]. This title reflects a substantial change in the knowledge from1909 when Hawkins H.P. first wrote that "the active bacterial agents in ulcerative colitis should be known"? [2]. One century and thirteen years later the forecast of a possible microbial etiology for IBD, the new "Era" should mean the identification of a new microbe or at least of a well identified bacterial community responsible of IBD. The truth is however different. Nevertheless, many progresses both in cultural techniques and in cultural-independent techniques such as Next-Generation Sequencing [3] and Meta-genomic techniques [4] we are a long way far from this end-point. While intestinal dysbiosis in IBD seems, today, undoubted, we do not really know whether the microbial alterations as the primary cause or an effect of intestinal inflammation [5].

Probably the only data suggesting that micro-biota could be an etiologic agent in IBD are the experimental models developed in rats. It was demonstrated that chemical or genetic induction of IBD in "germ-free "rats do not develop or develops a low-grade disease. These positive results, also confirmed by researchers were however published over 10 years ago [6]. Furthermore, other researches inquiring the implications of the transplantation of human micro-biota to rats ("human micro-biota-associated rodents (HMA)" present important limits and the results obtained seem to be overwhelmed [7], being also to understand what could be considered the healthy man intestinal microbiota [8-10]. The new "Era" in IBD could be restricted to new classification perspectives of the disease, related to the discovery of different inflammatory pathways, to their impairment and/or to the most recent epidemiological acquirement.

In this perspective in fact, it is possible to obtain a significant change with the past. While in medicine we try to downgrade complexity, on the basis of the theory "one-size-fits-all", in the era of the ongoing change in IBD classification we could think to speak instead of two

different diseases as Ulcerative Colitis (UC) and Crohn's Disease (CD), of up to 13 different diseases following an inflammation proximity axis of "IBD continuum" [1]. Thirteen different diseases are the number of diseases that we reach taking care of different criteria such as the onset age together with genetic polymorphism, i.e. the very early onset IBD (VEOIBD) and the different locations of the disease as rectum, perianal zone, pouches differentiated in sub classifications. It is significant to observe how in this classification the CD limited to colon could be considered for its clinical and genetic characteristics to UC and that CD classification on the basis of the severity of inflammation could not be applied because of the unpredictable behavior of the disease.

Also, this classification however presents uncertain areas due to IBD extra-intestinal localizations involving skin, eyes, bones. A more complete classification, comprehensive of extra-intestinal localizations, can be reached considering IBD in the widest field of autoimmune illnesses [11]. This implies to change the point of view from an "Organ-Based Concept "to a "Cytokine–Based Concept" of classification. The cytokines to be considered as hubs of inflammatory pathways are Interleukin-17, Interleukin-23, Interleukin-1 and Interleukin-6.

If the IBD are seen under a physiopathology point of view instead, at least two other different classifications are possible. The first one suggests that T effector lymphocytes could lose their ability to antigenic response for the so called "T cells exhaustion". The IBD patients with a higher inflammatory response exhaustion could have a better prognosis for relapses and new flares [12]). In this way we can distinguish IBD patients in two groups IBD1 e IBD2 through a blood test using the transcriptional signal of CD8 T-lymphocytes [13]. The second one raises from the observation that the micro biota of CD colon limited patients differs from the micro biota of CD located in the ileum and is similar to the micro biota of UC patients [1]. According to these hypotheses it is possible to introduce a "dysbiosis index" considering the ratio between *F. prausnitzii* and *Escherichia coli* (FE index) able to distinguish irritable bowel syndrome (IBS) from different phenotypes of IBD [14]. It's evident how this classification models cannot be considered during the daily routine practice also from experienced gastroenterologists [15] Probably, the perspective of the new "era" will be possible with the use of artificial intelligence (AI) permitting the evaluation of the "BIG DATA" with self-learning techniques in the field of precision medicine (PM) [16]. The "machine-learning" could be useful for the right stratification of patients, in evaluating disease progression with upcoming complications and extra-intestinal manifestations, in the choice between different inflammatory pathways blocking systems through biological agents, downgrading possible complications and therapeutic costs [17].

Beside this, the question about the cause for which the intestinal bacteria, nevertheless a 0,2 kilos weight mass [18], had a controversial role both on pathophysiological and therapeutic side, remains unsolved [19]. Frequently the reason of this failure is ascribed to the complexity of the laboratory techniques for taxonomic identification of intestinal bacteria. As an example, the identification of the different members of microbiota is strongly limited from the high number of uncharacterized different species, or from the taxonomy determination based only on highly conserved portions of 16SrRNA or from the use of short-read sequences [20]. Nevertheless, also the new bio-informatic approaches based on "-omic" techniques considering functions as the metatranscriptome and the metabolome instead of the bacterial identity has negative aspects [21]. In this second case completely lacks the functional characterization of the majority of the bacterial genes. The reason of the failure is probably due to causes more important than simple technical difficulties. In order to correctly define the multiple bacterial functions is possible to consider new horizons linked to ecologic evolutive theories alternative to those observed in higher eukaryote communities [21]. Significantly, the Horizontal Transfer Gene (HTG) and the rapid evolution of bacterial communities in humans create a mismatch of timescales of the observations applied to eukaryote. As an example, the theory of the geographic biodiversity of bacteria predicts how an oral probiotic (Bifidobacterium longum) can colonize the human intestine less frequently in the subjects yet presenting in their microbiota the same bacteria. The theoretical hypotheses Black Queen recognizes that bacteria have the possibility to quickly loose the genes functionally unsuccessful and complicates the picture of the fast acquisition of genes of HTG. The increase of density, that in the eukaryote system determines negative effects, in the microbial systems instead has a positive effect on fitness. In the microbiome exists an upgraded mutualism with production of public goods, a cross-feeding where a species depends on the degradation products of the nutrients of another species and also a cell-to-cell communication socially useful to bacterial community, defined as quorum sensing [22]. The picture is also complicated for the presence of bacteriophages, prokaryotic viruses, able to infect bac-

teria, whose clinical significance in IBD in unknown and for the presence of pathobionts, commensal bacteria that in some circumstances can became pathogens [5].

In conclusion, nevertheless new machine-learning techniques [23] and the sure role of faecal transplantation in IBD [24], a new era in IBD-microbiota relationship is already not raised.

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