Comparative Immunology, Microbiology and Infectious Diseases 62 (2019) 88–100

Contents lists available at ScienceDirect

Comparative Immunology, Microbiology and Infectious Diseases

journal homepage: www.elsevier.com/locate/cimid

Review

Chronic regional intestinal inflammatory disease: A trans-species slow infection?

Ana Balseiro[a], Valentin Perez[b], Ramon A. Juste[c,*]

[a] Centro de Biotecnología Animal, Servicio Regional de Investigación y Desarrollo Agroalimentario (SERIDA), 33394 Gijón, Asturias, Spain
[b] Departamento de Sanidad Animal, Instituto de Ganadería de Montaña (CSIC-ULE), Facultad de Veterinaria, Universidad de León, 24071 León, Spain
[c] Direccion. Servicio Regional de Investigación y Desarrollo Agroalimentario (SERIDA), 33300 Villaviciosa, Asturias, Spain

ARTICLE INFO

Keywords:
Chronic regional inflammatory intestinal disease
Inflammatory bowel disease
Mycobacterium avium subsp. *paratuberculosis*
Histopathological pattern
Mammal enteritis

ABSTRACT

Crohn's disease and ulcerative colitis in humans and paratuberculosis in domestic and wild ruminants can be defined as chronic regional intestinal inflammatory diseases (CRIID). This review is a literature overview on these diseases in humans, non-human primates, dogs, cats, rabbits, equids and ruminants with a focus on pathological and microbiological features aimed identifying common characteristics that could lead to a unified pathological classification for a better understanding of their mechanisms and causes. The result is a framework of inflammatory forms throughout the different species indicative of common mechanisms of the slow infection type characterized by a time course varying from weeks to months or even years, and where the inflammatory component would be more prominent in the intestinal interphase between host and environment and be morphologically characterized by an infiltrate ranging from lymphoplasmacytic to histiocytic. This should provide new insights for causation demonstration and therapeutic approaches in human IBD.

1. Introduction

Inflammatory bowel disease (IBD) is a term commonly applied to a multifactorial intestinal disorder for which a definitive etiology is still unknown, but that includes a convergence of genetic predisposition, intestinal microbiota changes, external environmental factors and host immunological responses [1,2]. In humans, there are different clinical IBD syndromes of which Crohn´s disease (CD) and ulcerative colitis (UC) are the most frequent and best known. IBD has also been reported in non-human primates, dogs, cats and horses [3–6].

In domestic and wildlife ruminants this type of disorder corresponds to a chronic granulomatous enteritis that is recognized as a frequent, widespread and often of big population impact disease called paratuberculosis or Johne´s disease. Paratuberculosis is a chronic infectious disease caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP) first reported in a cow in 1895 [7]. MAP are acid fast bacilli which belong to the *Mycobacterium avium* complex (MAC) group of slow growth mycobacterial species. The disease is relatively well studied in domestic ruminants (cattle, sheep and goat), but there are relatively few reports in wildlife, although it has been repeatedly reported in free-ranging deer [8–12]. MAP has also been isolated from dogs, wild boar (*Sus scrofa*), foxes (*Vulpes vulpes*), stoats (*Mustela erminea*), weasels (*Mustela nivalis*), badgers (*Meles meles*), wood mice (*Apodemus sylvaticus*), rats (*Rattus norvegicus*), brown hares (*Lepus europaeus*), jackdaws (*Corvus monedula*), rooks (*Corvus frugilegus*), crows (*Corvus corone*), and wild rabbits (*Oryctolagus cuniculus*) among other domestic and wildlife animals [10,13–19].

Both IBD and paratuberculosis can be included in the concept of "chronic regional intestinal inflammatory diseases (CRIID)", based on the clinical course, pathological presentation and inflammatory infiltrate composition, variants of which can be found in almost any mammal species. In general terms, CRIIDs would be associated with dysfunction of the gastrointestinal tract due to infiltration of the mucosa and submucosa with populations of lymphocytes, macrophages, plasma cells and few eosinophils and basophils [20–22].

In spite of their obvious morpho-clinical similarities pointing out to a common primitive type of innate immune response typical of slow infections, association with an obvious bacterial agent or not in the first descriptions of these diseases in each species led to two separate approaches. Where no bacterial agent was observed, the disease was defined exclusively by its morphological aspects and further classified according to its histopathological features. It is the type found in monogastric species. Where MAP is isolated, the disease is named according to its mycobacterial etiology and defined as paratuberculosis and its variants and classified according to the extension, the cellular inflammatory infiltrate and the amount of mycobacteria present in the histological lesions.

* Corresponding author.
E-mail address: rajuste@serida.org (R.A. Juste).

https://doi.org/10.1016/j.cimid.2018.12.001
Received 11 October 2018; Received in revised form 27 November 2018; Accepted 7 December 2018

Table 1
Historical main events of chronic regional inflammations (CRIIDs). Most relevant milestones are included from 1509 to present day.

Year	Author	Main finding
1502	Benivieni, Bologne [24]	First series of human enteritis
1643	Petitfils, 2008, Paris [48]	Louis XIII as a case of well studied granulomatous regional enteritis
1769	Morgagni, Florence [25]	Description of a case of granulomatous enterocolitis in his De sedibus et causis morborum per anatomen indicatis
1793	Baillie, London [49]	Description of regional enteritis in his Anatomia Morbida
1859	Wilks, London [27]	Pathological descriptions of regional enteritis
1895	Johne and Frothingam, Dresden [7]	First case of paratuberculosis in a cow
1898	Berg, Stockholm (cited by Kirsner) [50,34]	Report on a case of human ileitis inflammatory disease
1904	Lesniowsky, Warsaw [51]	Report on a case of human ileitis inflammatory disease
1912	Twort and Ingram, London [37]	Isolation of *Mycobacterium enteriditis chronicae pseudotuberculosae* bovis on media supplemented with dead mycobacteria
1913	Dalziel, Edinburgh [28]	Pathological similarities between human and ruminant regional enteritis
1923	Moschcowitz and Wilensky, New York [32]	Inespecific granulomas in the intestine, distal ileum thickening and fistulization
1932	Crohn, Ginzburg, Oppenheimer, New York [29]	Regional ileitis; a pathologic and clinical entity
1960	Lockhart-Mummery and Morson, London [33]	25 cases of CD (regional ileitis) and distinction from ulcerative colitis
1975	Marshak, New York [34]	Definition and differentiation of regional enteritis and ulcerative colitis
1975	Morson, London [35]	Initial pathologic descriptions of ulcerative colitis
1984	Chiodini et al., New York [36]	First isolation of MAP in human CD cases
1990	Carrigan and Seaman, New South Wales [38]	First description of diffuse lymphocytic lesions with few mycobacteria in ovine, resembling the CD pattern
2003	Greenstein, Nueva York [43]	Evaluation of mycobacterial etiology in CD
2004	Naser et al., Florida [40]	Isolation of MAP in blood from patients with Crohn's disease
2007	Clancy et al., New South Wales [41]	Increased values of tumor necrosis factor-alpha and presence of MAP in intestine of patients with CD
2007	Abubakar et al., Norwich [42]	Significantly associated meta-analysis between MAP and Crohn's disease
2008	Juste et al., Bilbao [43]	Presence of DNA from MAP in healthy blood donors
2009	Juste et al., Bilbao [44]	First significantly associated meta-analysis between inflammatory enteritis and immune response against mycobacteria
2014	Vázquez et al., Bilbao [22]	Epidemiopathogenic forms of paratuberculosis defined
2014	Küpper et al., Gieben [45]	Genetic association between NOD2 polymorphism and infection status by MAP in German Holstein cattle
2018	Juste et al., Villaviciosa [55]	Genetic risk for paratuberculosis epidemiopathogenic forms
2018	Girardelli et al., Trieste [46]	Genetic profile of patients with early onset inflammatory bowel disease

CD: Crohn's disease; MAP: *M. avium* subspecies *paratuberculosis*.

In this paper, we will review the literature on both groups and discuss similarities and differences in order to go back to mechanisms that might point out to similar etiological roots and to its implications regarding new strategies for causation demonstration and therapeutic approaches.

2. History of CRIIDs

Apart from very general descriptions of intestinal disease in old Greek and roman medicine books [23], the first series of enteritis cases in humans was reported by Benivieni in Bologna in 1502 [24] (Table 1). A more specific form of disease that could be assimilated to what we now know as IBD was first described by Morgagni Giovanni Battista Morgagni in 1769 [25], although Gullielmus Fabricius Hildenus in 1612 had noted ulcerated cecum contracted and invaginated into the ileum in a boy who died after persistent abdominal pain and diarrhea [26]. Samuel Wilks in 1859 also described ulcerative colitis in London in an old woman who died after several months of diarrhea and fever [27]. Perhaps the first more important milestone in terms of IBD identification and etiology association was the 1913 paper of Dalziel where the similarities between chronic interstitial ileitis and Johne´s mycobacterial intestinal disease of cattle was pointed out [28], shortly after the bovine chronic enteritis had been first described by Johne and Frothingham [7]. Finally, the entity currently known as Crohn's disease was defined in 1932 when Burril Bernard Crohn, an American gastroenterologist, submitted to a meeting of the American Society of Gastroenterology a paper describing a series of 14 cases of terminal regional ileitis surgically treated at the Mount Sinai hospital by several colleagues [29]. This seminal paper led to the coining of the Crohn´s disease eponym and its quick worldwide acceptance. After that, many studies and findings have been published along the years [30,31], of which the more relevant to this paper approach are included in Table 1 [7,24,25,27,28,32–51].

3. Etiological and microbiological aspects of CRIIDs

The incidence of human IBD has been increasing worldwide during the last century, but it seems to have stabilized now [2]. Great efforts have been made throughout the XXth century trying to find a specific cause. As a consequence, numerous biological and chemical agents have been proposed as causative agents without a definitive etiology identification. At this moment, it only seems clear that an interaction of genetic factors, intestinal microbiota changes, external environmental factors and host immunological responses is involved [1,2,52] but no single factor or specific combination has been identified. Regarding genetic factors, certain genes (i.e. NOD2/CARD15, SLC11A1, TLRs or ILRs) are involved in IBD susceptibility, some of which have also been related to paratuberculosis [45,46,53–58]. For instance, the recent development of metagenomics has allowed to identify changes in the composition of the intestinal microbiota such as increased populations of Enterobacteriacea or decreased of Bacteriodales [59]. More specifically, infectious pathogens, such as virus (Cytomegalovirus) and bacteria (*Chlamidia trachomatis*, *Aerobacter aerogenes*, *Campylobacter fetus jejuni*, *Escherichia coli* or *Yersinia enterocolitica*) have been proposed as possible IBD causal agents throughout time [30,31,60]. Most of them have been only superficially studied, but due to CD and paratuberculosis pathological and clinical similarities and the relevance of a zoonotic transmission, MAP has received more prolonged attention as a potential cause of CD [61]. However, up to now, convincing evidence to support the role of a specific microorganism in IBD is still missing and, therefore a comparative pathology approach discussion can be worthwhile.

In this perspective, focusing on the main suspect, MAP, it can be pointed out that it is an intracellular pathogenic microorganism that can survive up to a year into the environment after having been excreted in the feces of infected animals due to the particular characteristics of its mycobacterial cell wall [62]. Thus, pastures contaminated

by paratuberculous animals can accumulate bacteria that not only keeps them contagious, but also allows washing down to water courses and subsequent infection of susceptible hosts at a distance. Additionally, since MAP can survive in milk and its derivatives, even after pasteurization [63], humans might be more or less frequently exposed to MAP through contamination of food and water, and probably aerosols too [64].

Chiodini et al. [36] were the first microbiologists to successfully isolate MAP from three patients with CD in 1984, thus opening great expectations on a quick and solid demonstration of the mycobacterial etiology of human CRIID. However, current published data on the potential role of MAP in CD causation are still contradictory, although in the last years the balance has shifted towards considering MAP as the possible microbiological causative agent in at least fraction (30%–50%) of CD patients [65]. The prevalence of MAP in patients with CD is highly variable, with estimates ranging from 0 to 35% [66] to 92% [67,68]. Naser et al. [40,69] were able to isolate MAP from the breast milk and peripheral blood macrophages of patients with CD, even though without visual observation of neither colonies nor bacilli. Singh et al. [70] also found high prevalence of MAP ('Indian bison type') in animal attendants suffering from gastrointestinal complaints working with goat herds endemic for paratuberculosis in India. Different studies have additionally found significant associations between MAP and CD patients using PCR assays and culture [67,71–73]. These associations, however, do not fully comply with Koch´s postulates since MAP can also often be detected in blood, tissues and feces from healthy individuals [43,44,67,74,75]. Koch´s postulates require for causation that (i) the bacteria must be present in every case of the disease, (ii) the bacteria must be isolated from the host with the disease and grown in pure culture, (iii) the specific disease must be reproduced when a pure culture of the bacteria is inoculated into a healthy susceptible host and (iv) the bacteria must be recoverable from the experimentally infected host [76]. However, this is not a critical argument against a MAP etiology given that these postulates were developed for acute infectious diseases while in chronic diseases like paratuberculosis most individuals in an infected environment also become infected albeit remaining in a latent subclinical form without developing clinical disease despite of having positive culture and/or PCR results [11,22,77–79]. This is also well known in the other big mycobacterial disease, tuberculosis, where it is estimated that the ratio of healthy infected carriers to new progressive disease patients is about 219 to 1 [80].

Another point in favor of MAP causation is that a substantial proportion of people with active CD get better when are treated with drug combinations (i.e. rifabutin and clarithromycin) which are active against MAP infections [81,82].

The implication of MAP in patients with UC has received less attention and is less supported by culture results data [65], although MAP has also been isolated from patients with this form of disease [71].

4. Immunopathological aspects of CRIIDs and the “slow” infection model

CRIIDs have similar immunopathological characteristics in the initial stage, course, latency and development of the disease (see section on pathological forms). The similarities in latency suggest that if a pathogen is involved, it would use the same signaling pathways to dysregulate the immune response and establish a persistent infection, that eventually, over time, would drive a growing spiral of tissue inflammation leading to development of clinical disease once a certain quantitative threshold has been crossed [83]. The immune response, thus, would exert a certain control of the pathogen. In some cases this would make infection nearly undetectable, but in others it will allow massive multiplication within the macrophagic cells. In both cases the agent would provide a constant stimulus to the more primitive unspecific cellular element of the immune system that is unable to prime the more evolved specific immune response. The triggers for transition from latent infection to clinical illness are unknown and are likely related to host genetic factors, lack of efficacy of phagocytosis and altered innate immune response [84]. According to this immunopathological model of paratuberculosis, in about half of a farm population, the innate immune response is efficient and capable of dead stop the infection before causing any visible lesion [84]. But if that innate immune response is inefficient, the disease progresses to subclinical delimited focal or multifocal forms, and, in few animals, to diffuse patent forms (lymphocytic or histiocytic) with a specific humoral immune response. A similar phenomenon is seen in other infectious diseases in humans and animals such as tuberculosis, Maedi-Visna, mycoplasmosis or Q fever, between others. For instance, tuberculous granulomas are observed in active, latent and reactivation stages of tuberculosis. The tuberculous lesion is highly dynamic and shaped both by the pathogen and the host defense elements [85]. The initial/latent tuberculous granuloma successfully contains (but do not eliminate) the infectious focus in more than 90% of cases, whereas 10% of individuals progress towards tuberculosis disease as a consequence of an unbalanced inflammatory reaction. In this model, the granuloma is capable of restricting the growth of the mycobacteria, but also provides to them a good environment from which the bacteria may disseminate.

The features of CRIIDs fully fall within the concept of “slow infection” originally proposed by Sigurdsson in 1954 for diseases such as sheep Maedi-Visna, pulmonary adenocarcinoma and paratuberculosis [86]. Some common features of those diseases are the chronicity (from long to very long clinical course) and the irregular and unpredictable time sequence. In these infections, the host immune system is unable to fully control the pathogen and therefore a long and dubious battle between aggressor and defender ensues. In the long intervening period between pathogen entrance into the body and development of clinical signs, these diseases are active but inducing only minimal pathological changes that keep the disease at a subclinical level [86]. This could correspond to a standoff between injury and response caused by an inability to switch from innate to adaptive immunity [84]. As Sigurdsson pointed out [86], realizing that there is a group of slow infections sharing a number of characteristics would help us to recognize and understand other infections belonging to the same class. According to this, CRIIDs may be included within the “inflammatory slow infection” group with a time course varying from weeks to months or even years, and where the inflammatory component affects primarily the lymphoid tissues being particularly prominent in the intestinal interphase between host and environment as an infiltrate ranging from lymphoplasmacytic to histiocytic and always linked to the regional lymph nodes. In this sense, these infections could be viewed essentially as diseases of the organized lymphoid tissue, where the real battle takes place, that have a tropism for a specific port of exit with diffuse lymphoid tissue for dissemination.

5. CRIIDs Pathological forms in different species

Since the identification of patterns is a critical step to understand disease mechanism, here will review the pathological forms observed in both monogastric and ruminant species affected by CRIIDs in an attempt to see whether or not there are common characteristics throughout mammal species that could lead to a unified pathological classification like the one defined for paratuberculosis: *focal, multifocal, diffuse histiocytic, diffuse intermediate* and *diffuse lymphoplasmacytic* (Table 2, Fig. 1). The individual form presentation in an individual will depend on the interaction of factors such as time since effective contact with the agent, individual´s genetic resistance or susceptibility, age at the time of infection and on previous exposure to the same or other environmental mycobacteria [84]. In general, CRIIDs are usually classified as histiocytic or multibacillary and lymphoplasmacytic/lymphocytic or paucibacillary according to the composition of the

Table 2
Pathological forms described in monogastric and ruminant species affected by chronic regional inflammation disease (CRIID) according to the pertinent scientific literature. Last column contains the currently proposed pathological unified terms.

Mycobacterium avium sbsp. *paratuberculosis* etiology							
SHEEP	GOATS	CATTLE	FALLOW DEER	CAMELIDS	RABBIT	Cell types in order of abundance	Extension
Type I	Focal	Focal	Focal	–	Focal	Macrophages Lymphocytes Langhans giant cells	Isolated small clusters
Type II and IIIa	Multifocal	Multifocal	Multifocal	–	Multifocal	Macrophages Lymphocytes Langhans giant cells	Multiple small and middle size foci
Type IIIb	Diffuse Multibacillary	Diffuse Multibacillary	Diffuse Multibacillary	Diffuse Multibacillary	Diffuse Multibacillary	Macrophages Epithelioid cells Lymphocytes Langhans giant cells	Large contiguous areas
–	Diffuse mixed	Diffuse Intermediate	Diffuse Intermediate	–	Diffuse Intermediate	Macrophages Epithelioid cells Lymphocytes Langhans giant cells	Large contiguous areas
Type IIIc	Diffuse Lymphocytic	Diffuse lymphocytic	–	–	–	Lymphocytes Epithelioid cells Macrophages Langhans giant cells	Large contiguous areas

Mycobacterium avium sbsp. *paratuberculosis* etiology		Unknown etiology					Pathological unified terms
SHEEP	AFB	HORSE	DOG/CAT	HUMAN	NON-HUMAN PRIMATES	RODENT MODELS	ALL SPECIES
Type I	None / Rare	–	–	Focal (KIDS)	–	–	FOCAL
Type II and IIIa	Few	–	–	–	–	–	MULTIFOCAL
Type IIIb	Many	Histiocytic	–	Histiocytic	–	–	DIFFUSE HISTIOCYTIC
–	Moderate	–	–	–	–	Diffuse Intermediate	DIFFUSE INTERMEDIATE
Type IIIc	Sporadic / Rare	Lymphoplasmacytic	Lymphoplasmacytic	Lymphoplasmacytic	Lymphoplasmacytic	–	DIFFUSE LYMPHOPLASMACY-TIC

AFB: Acid fast bacilli.

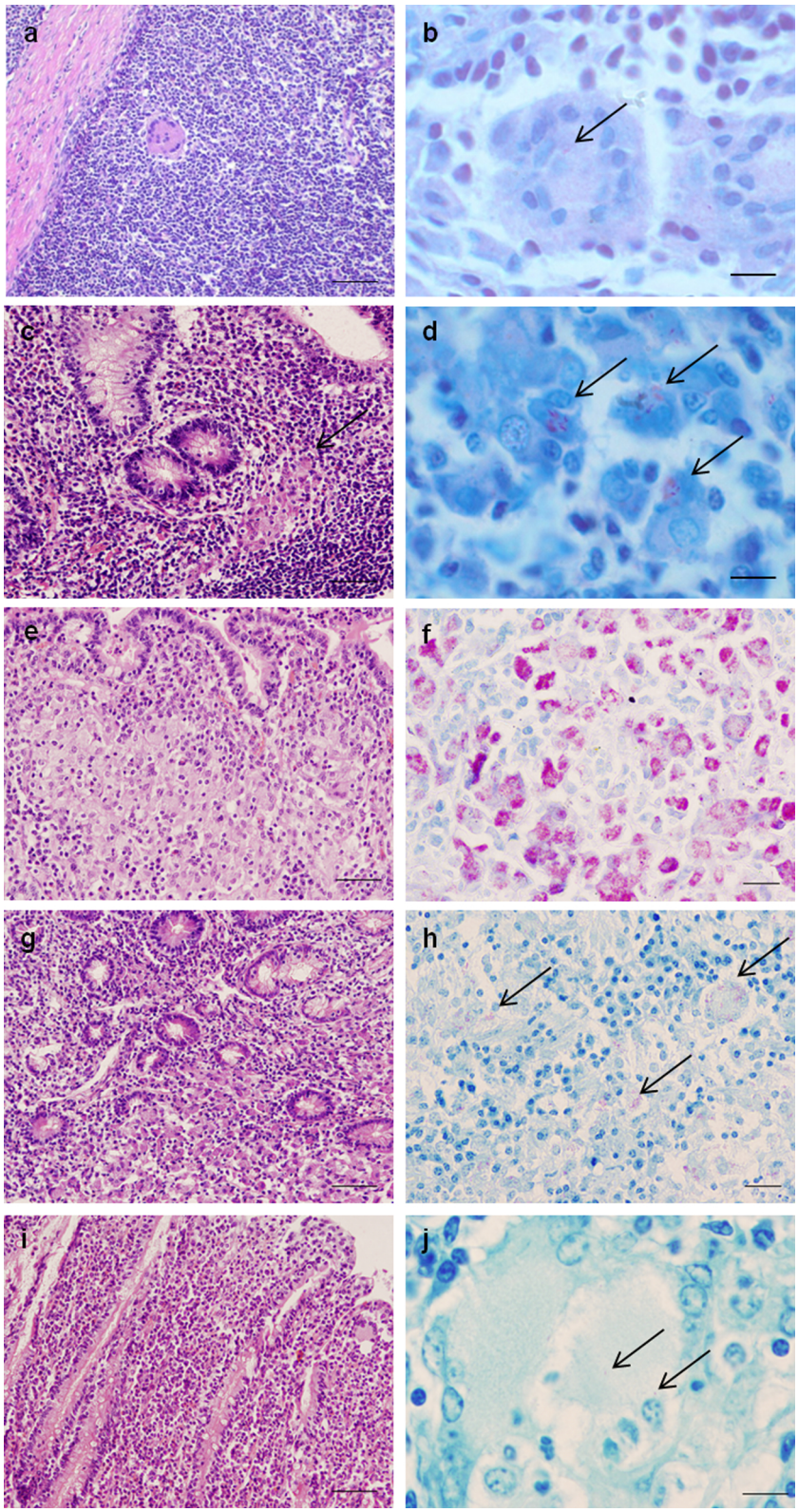

Fig. 1. Paratuberculosis unified pathological forms. Cattle, Haematoxylin-eosin (a, c, e, g, i) and Ziehl-Neelsen (b, d, f, h, j) staining. Focal: a) Isolated granuloma (arrow); single location, no gross lesions (bar = 50 microns); b) Only one acid fast bacillum (AFB) is observed (arrow) within a Langhans giant cell (bar = 10 microns). Multifocal: c) Middle size granuloma (arrow) mainly consisting of macrophages and lymphocytes; several locations, no gross changes (bar = 50 microns); d) Few AFBs (arrows) are observed within Langhans giant cells (bar = 10 microns). Diffuse histiocytic: e) Inflammatory infiltrate formed mainly by macrophages; large areas affected with thickening of the mucosa, grossly visible (bar = 50 microns); f) Many AFBs are observed (bar = 20 microns). Diffuse intermediate: g) The infiltrate contains macrophages, lymphocytes and scant Langhans giant cells; large segments of the intestine affected that grossly appears thickened (bar = 50 microns); h) Moderate number of AFBs (arrows) are observed inside some Langhans giant cells (bar = 20 microns). Diffuse lymphoplasmacytic: i) The infiltrate is composed mainly of lymphocytes that extends through broad areas and is clearly visible to the naked eye (bar = 50 microns); *j*) Rare AFBs (arrows) are observed (bar = 10 microns).

inflammatory infiltrate and the amount of mycobacteria present in lesions. In the histiocytic types, macrophages would be the main and more characteristic cellular type and numerous mycobacteria would be present in lesions. In lymphoplasmacytic types, lymphocytes would be the main cellular type generally associated with few, if any, mycobacteria (Table 2).

5.1. Monogastric species

Scientific literature on IBD in monogastric species varies a lot. Obviously the most abundant corresponds to humans, followed by dogs, cats and horses since those are the species that get more medical care.

Rodents are a particular case since rats and mice are often used as models of human disease.

5.1.1. Humans

IBD in humans includes UC and CD, and is clinically characterized by both chronic and acute disease states, with periods of improvement, latency and relapse [87]. Both entities differ in clinical presentation, distribution of inflamed areas in the gastrointestinal tract, progression of disease, and response to interventions, either medical or surgical. UC is almost always confined to the colon and CD may occur in any part of the gastrointestinal tract from the mouth to the rectum. The histological features of IBD are those of a chronic active colitis. In the chronic stages, a *lymphoplasmatyc* infiltrate can be observed, while in active stages *neutrophils* in the lamina propria, epithelium or within crypt lumens are present [21]. In more severe forms, necrosis, ulceration and inflammatory polyps can be additionally found. In children affected by UC, inflammatory changes are typically confined to the mucosa, whereas in CD the inflammatory process may be "focal" with inflamed areas bordered by normal crypts, or with focal granulomas located in deep submucosa, lymphoid follicles or lymph nodes [88], resembling initial or latent stages of paratuberculosis in animals (see ruminant species section). The presence of an excess of histiocytes, epithelioid granulomas, pigmented macrophages and a few Langhans giant cells is also commonly observed in CD patients´ affected sections of the intestine [21,88,89].

Acid fast bacilli are not seen in human CRIID, however, MAP isolation or DNA detection has been repeatedly reported. Instead, even though etiological hypothesis are dominated by autoimmunity, also include bacteria as *Escherichia coli* or psicrophyllic species and virus such as measles or just dysbiosis [59].

5.1.2. Non-human primates

Non-human primates have been used as models of human disease, and therefore have received considerable medical attention. Both natural outbreaks of enteritis and experimentally induced inflammatory disease have been studied. Chronic idiopathic enterocolitis is the leading cause of natural morbidity in colonies of captive rhesus macaques (Macaca mulatta), and is in part, associated with a variety of enteric pathogens such as *Campylobacter* spp. or *Escherichia coli* [90]. Chronic inflammation of the colon in rhesus monkeys resembles not only clinically but also immunologically IBD of a human patient [90]. Histologically, multifocal lymphoplasmacytic inflammation ranging from mild to moderate in both the small and large bowel is characteristic of this disease [6].

MAP has been involved in some natural cases [91], but a solid and general hypothesis is missing.

5.1.3. Dog

IBD in dogs is the third most studied type of IBD. Canine phenotypic IBD disease classifications include lymphoplasmacytic enteritis (LPE), granulomatous colitis (GC), eosinophilic gastroenteritis, eosinophilic colitis and neuronal hyperplasia [92–94]. Neither breed nor sex seems to affect presentation and cases do not seem to follow an infectious pattern since most dogs taken to clinics live alone in different households.

LPE is the most frequently described type of IBD in dogs, characterized histologically by infiltration of lymphocytes and plasma cells in the lamina propria of the small intestine. The etiology remains still unknown, and immune response dysregulation at local level is considered the most likely cause [93,95,96]. For GC *Escherichia coli* has been proposed as the causative agent [97].

MAP has not been reliably detected in dogs except for a description of a clinical case of paratuberculosis with positive culture in a single dog [18]. A re-emerging debate about the link between MAP and CD has increased awareness of public health concerns about the occurrence of MAP infections in pets [98]. In 19% of dogs with biopsies indicative of IBD with mild degree of inflammation and cellular infiltrate, MAP-specific DNA was detected [5]. However, as in other species MAP is also identified in healthy individuals [99]. No other causes beyond autoimmunity have been postulated.

5.1.4. Cat

Cat IBD has drawn some medical attention because this species is a common pet. Feline IBD comprises a heterogeneous group of immunologically mediated disorders of the digestive tract, commonly presented as a chronic LPE mainly affecting the small intestine, although also affecting stomach and colon [3,100,101]. Lymphocytic/plasmacytic infiltrates commonly are limited to the lamina propria in biopsy specimens from all regions of the gastrointestinal tract.

No specific pathogens have been associated with feline IBD, and the most common etiological hypothesis are related to autoimmunity or just considered of an idiopathic origin [100].

5.1.5. Horse and ass

IBD in the horse with histologic similarities to CD in humans was first reported in 1974 by Cimprich [102]. In this species, different cases of IBD have been described for which no etiology has been identified. This would include granulomatous enteritis (GE), multisystemic eosinophilic epitheliotropic disease (MEED), lymphocytic-plasmacytic enterocolitis (LPEC) and idiopathic eosinophilic enterocolitis (EC) [4]. Microscopic lesions for GE consists of aggregates of macrophages and epithelioid cells with occasional giant cell macrophages. LPEC consist of infiltration of the lamina propria with lymphocytes and plasma cells and MEED infiltration of mucosa and submucosa with eosinophils, lymphocytes and macrophages.

The etiology of IBD in horses is unknown and bacterial pathogens are not consistently cultured from specimens. MAP has been isolated from one donkey with GE [103] and from a miniature donkey with massive diffuse granulomatous enteritis involving large quantities of acid-fast organism mainly in macrophages [104]. Foals experimentally infected with MAP developed granulomatous enteritis resembling those of GE in the gut [105].

5.1.6. Rabbit

Rabbit is a domestic species that is bred for meat in large numbers in some countries. In these systems, digestive diseases are a big hurdle and a chronic enteritis, mucoid enteritis, is one of the main concerns of the industry. This disease, however, has very specific features that clearly differentiates it from the type of chronic enteritis we are dealing with here. In fact, rabbit is considered a species susceptible to paratuberculosis and lesion classifications have been reported for rabbits with this disease. According to that, there are two lesion classifications of paratuberculosis in rabbits, one by Beard *et al.* [15], in which lesions were divided in mild and severe, and the other one by Maio et al. [106], in which lesions were classified on the basis of their location, intensity and inflammatory cell type, and mycobacteria abundance, in four categories: focal, multifocal, diffuse multibacillary and diffuse intermediate. *Focal lesions* were those formed by small, well-demarcated granulomas, located exclusively in the intestinal lymphoid tissue and in the mesenteric lymph nodes, and consisting of macrophages and, frequently, lymphocytes and multinucleated Langhans giant cells. *Multifocal lesions* consisted of well-demarcated granulomas in the intestinal lymphoid tissue and lamina propria with few mycobacteria. *Diffuse multibacillary lesions* showed an infiltrate consisting of epitheliod cells, macrophages, lymphocytes and numerous multinucleated Langhans giant cells, with large numbers of mycobacteria. In the *diffuse intermediate* lesions, the infiltrate, however, contained epitheliod cells, macrophages, lymphocytes and few Langhans giant cells with smaller numbers of mycobacteria. Paucibacillary *diffuse lymphocytic* lesions have not been described in this species.

Rabbit was used early on as an experimental animal for infectious diseases and made the key contribution to medicine when its use

demonstrated the infectious nature of tuberculosis [107]. This has yielded an amount of medical literature on this species and thus, there are reports on natural and experimental enteritis. Success of this species in tuberculosis and other infectious diseases research led to some attempts to experimentally reproduce paratuberculosis in this species that were not rewarded with clear success. The first report on paratuberculosis in rabbits was made in Spain in 1987 after isolation of the agent from wild rabbit pellets [108]. Later, in Scotland, extensive studies suggested that rabbits play a role in the epidemiology of paratuberculosis, acting as a wildlife reservoir for cattle [16]. Naturally infected rabbits had histopathological changes within the lymph nodes and intestines compatible with ruminant paratuberculosis, demonstrating that MAP not only replicates but can also produce disease in rabbits [13]. A study in wild rabbits in Spain also showed several cases of paratuberculosis-like intestinal lesions [106], confirming previous reports of isolation from rabbit feces [108]. A recent review provides comprehensive information on natural and experimental mycobacterial infections in rabbit and shows that although clear evidences of infection can be obtained, typical paratuberculosis cannot be experimentally reproduced in full in this species [19].

5.1.7. Rat and mouse models

There are no reports on cases of natural CRIIDs in rats and mice. However, these species have been widely used for experimental studies of CRIIDs. One of these species advantages is that there are many experimental genetically modified transgenic animals that are very useful in examining basic pathogenic mechanisms of disease as well as in developing and evaluating new types of biological therapies [109]. Characteristic histopathological changes in those animal models include severe and extensive mucosal ulceration and severe inflammatory cell infiltration. In general histopathological changes consist of cellular infiltrates of mixed cells into the mucosa and submucosa, in which lymphocytes predominate, but also another cells such as neutrophils, plasma cells and macrophages [109–112]. These models are usually caused by chemical challenge, the most popular being dextran sulphate sodium (DSS) and trinitrobenzene sulfonic acid (TNBS), but they only persist while the irritant persist and fail to elicit a full immune response [113].

5.1.8. Pig

Pigs suffer a proliferative enteropathy caused by *Lawsonia intracellularis* which has some clinical similarities to paratuberculosis, such as diarrhea, anorexia or poor growth, but that can be easily differentiated histologically [114,115].

Pigs are frequently infected by *M. avium* subspecies that seem to be easily exchanged with humans, i.e. *M. avium hominissuis*. MAP has been isolated and identified from pigs and wild boars lymph nodes and feces, but never has been associated to chronic enteritis [10,116].

5.2. Ruminant species

Most of the literature on chronic regional enteritis in ruminants is that associated with paratuberculosis with a mean ratio of nearly 9 to 1 [117]. Actually, there are no other chronic regional enteritis in ruminants other than paratuberculosis, with the exception of a terminal ileitis of lambs [118,119]. The characteristic pathology of paratuberculosis led to propose many classifications related to tuberculosis and leprosy in different attempts to find explanatory patterns for treatment, prevention or control. Thus, classifications of paratuberculosis forms have been described in sheep [38,77,120], goats [78,121], cattle [22,79,122], red deer [12,123] and fallow deer [11]. The immune response plays an important role in determining the histopathological type of paratuberculosis. Whereas paucibacillary types might be associated with a peripheral cellular immune response, multibacillary types are associated with a predominantly humoral immune response [11,22,78,79,124–126]. The lesions in all species have been usually classified on the basis of their location, intensity and inflammatory cell type, and the amount of mycobacteria in them.

5.2.1. Sheep

Ovine paratuberculosis was first described in 1911 [127]. Stamp and Watt in 1954 published the first case series with a classification of paratuberculosis forms into four types according to both the lesion gross and microscopic features and the bacillary load [120]. Later in 1961 Rajya and Singh classified lesions in three types [128]. But it was in 1990 when Carrigan and Seaman first introduced in the classification lesions with a clearly diffuse lymphocytic pattern with very few mycobacteria, resembling in severity, in the histopathological characteristics and in the low or undetectable mycobacteria load to the lesions described in CD [38]. Six years later, Pérez et al. [77] described small “tuberculoid” granulomas in the ileocaecal lymphoid tissue (Peyer´s patches) with no detectable acid-fast bacilli. This type of lesion, also referred to as a “focal lesion”, was later reported in goats [78], cattle [79] and fallow deer [11]. A multibacillary form, in which macrophages were filled with numerous mycobacteria, was also described in those species [11,38,77–79,129].

The Pérez et al. classification for sheep paratuberculosis, which has been the most influential one, included five categories [77]. *Type I* lesions consisted of small granulomas formed by macrophages and were located exclusively in the ileocaecal Peyer's patch. In *type II* lesions granulomas were also observed in the mucosa associated with Peyer's patches. *Type III* lesions were characterized by granulomas in areas of the mucosa both associated and adjacent to the Peyer's patches. Three subtypes of type III lesions were recognized. In *subtype IIIa* multifocal granulomas appeared in different areas of the lamina propria. *Subtype IIIb* consisted of large numbers of macrophages, widespread in the lamina propria; in *subtype IIIc* lymphocytes were the main inflammatory cell, with some macrophages scattered amongst them. Mycobacteria could be demonstrated in tissue sections from all the samples with subtype IIIb lesions and in almost all of those with type II and IIIa lesions; these organisms were absent or sparse, however, in type I and IIIc lesions. Gross lesions were clearly visible only in sheep with type IIIb and IIIc lesions. Control by vaccination is highly successful in some major sheep industry countries like Spain and Australia.

5.2.2. Goat

Noel-Pillers in 1924 first described paratuberculosis in goats [130] and forty years later Mohiyuddeen and Malaki described histopathologycally the disease in naturally infected goats [131]. Soon afterwards a broad classification of its forms in four groups was proposed [121]. Later Corpa et al. [78] divided lesions observed in a large set of goat paratuberculosis cases into four categories roughly corresponding to those of sheep, but with some substantial differences. *Focal lesions* consisted of small granulomas in the ileocaecal Peyer's patches or related lamina propria. *Diffuse multibacillary lesions* consisted of a granulomatous enteritis, affecting different intestinal sites. Numerous macrophages containing abundant mycobacteria were present, resulting in gross changes in the normal gut morphology. In *diffuse lymphocytic lesions*, the lymphocyte was the main inflammatory cell, with some macrophages (containing few if any mycobacteria). In *diffuse mixed lesions* the infiltrate consisted of numerous lymphocytes and macrophages, with small numbers of mycobacteria. The three types of diffuse lesion were often associated with necrosis in the lymph vessels of the mucosa, mesentery and lymph nodes, and with greater thickening of the jejunum than of the ileum. Control by vaccination is highly successful wherever it has been used.

5.2.3. Cattle

The very first ever description of paratuberculosis as we know it was made by Johne and Frothingham on pathological grounds back in 1895 [7]. Different classifications of paratuberculosis have been proposed for cattle [79,122], since it was first described. González et al. [79] divided

lesions into five categories. *Focal lesions* consisted of small granulomas in the ileal and jejunal lymph nodes or the ileocaecal lymphoid tissue. In the *multifocal type*, small granulomas or scattered giant cells appeared in some intestinal villi, as well as in the lymph nodes. *Diffuse multibacillary lesions*, associated with severe granulomatous enteritis affecting different intestinal locations and lymph nodes, were formed by macrophages containing large numbers of acid-fast bacilli. In *diffuse lymphocytic lesions*, lymphocytes were the main inflammatory cells, with some macrophages or giant cells containing few if any mycobacteria. In *diffuse intermediate forms*, the infiltrate was formed by abundant lymphocytes and macrophages, and mycobacteria were present to varying degrees related to the number of macrophages. Clinical signs and gross lesions were mainly associated with diffuse forms.

A more recent study proposed to re-group the original immunopathological types into two broader paratuberculosis epidemiopathogenic forms or states: *latent* and *patent* [22]. The former term would define infections with *focal* lesions and might constitute an apparent resilience status. The latter would group those cases with *multifocal* and *diffuse* inflammatory lesions with higher mycobacterial load and viability suggestive of a more immediate epidemiological risk. Control by vaccination is highly efficient, but is restricted in many countries and regions because of an over-simplistic fear of interference with tuberculosis eradication schemes.

5.2.4. Free-ranging deer

There are many descriptions of paratuberculosis in free-ranging deer worldwide, mainly affecting red deer and fallow deer [132]. Clark et al. [12,123] classified lesions in red deer in paucibacillary and multibacillary forms with different degrees of severity. In the 70 s of the last century, Riemann et al. [133] reported and described paratuberculosis in fallow deer in United States. In 2008, the lesions in that species were divided by Balseiro et al. into four categories - *focal*, *multifocal*, *diffuse multibacillary* and *diffuse intermediate lesions* – following the same criteria that those proposed for bovine paratuberculosis [11]. Changes were found from the proximal jejunum to the ileocaecal valve, but lesions were always particularly severe in the distal jejunum. Paucibacillary *diffuse lymphocytic* lesions have not been described in fallow deer. Control by vaccination has been successful wherever it has been used.

5.2.5. Camelids

The apparent prevalence of paratuberculosis in South-American camelid populations (llamas, alpacas and guanacos) is low and there are few histopathological descriptions of the disease [134–136]. However, there are unpublished reports indicating the disease is important in dromedaries and that it has required control measures based on vaccination. Similar to cattle, camelid paratuberculosis infections may proceed undetected for a prolonged period of time. The major histopathological lesions are extensive infiltration of macrophages, epithelioid cells and lymphocytes into mucosa and submucosa of ileum and of mesenteric and ileocaecal lymph nodes, containing numerous acid fast bacilli [136,137]. It has also had some relevance in alpaca herds in United States, Australia and South America [135,138–140].

5.2.6. Zoo species

Apart from sporadic cases of regional enteritis, paratuberculosis with similar characteristic of those in domestic ruminants regarding clinical signs, pathology and MAP detection has been reported in many zoo ruminant species in which control has been established with the use of vaccination, which is a highly efficient measure in species where individual preservation is important and are not subjected to tuberculosis control programs based on culling [141].

5.3. General histopathological pattern

This review of CRII literature in different species shows a series of shared histopathological features that can be best visualized in a summary table where upon the more complete framework of paratuberculosis in domestic ruminants, CRIIDs from other species can be aligned (Table 2). Known features (cell composition and extension of inflammatory lesion) in each species allow fitting their corresponding CRIID into the different histopathologic forms of paratuberculosis thus predicting an AFB load in each non-paratuberculosis CRIID and showing a large number of missing forms. It can be seen that most of the forms are associated to low numbers of mycobacteria, thus making likely that their presence can be overlooked. In that context, lack of a specific causative agent will lead to failing to identify as subclinical forms those similar to paratuberculosis focal forms where the agent is present but where minimal histological lesions can be seen. Since these latent forms might not have drawn pathologists attention, and therefore might have escaped study, an interesting prediction from this study is that finding the missing forms would confirm or at least lend additional support to the hypothesis that etiology would be the same. However, this prediction on mycobacterial burden seems to fail for the human histiocytic forms that should show large amounts of mycobacteria if they were caused by these pathogens. Since it is clear that there are no reports of high AFB burdens in these forms, it is still possible that some unknown factors might prevent mycobacteria to display typical acid-fast staining in human IBD. Actually, this possibility has been addressed with the hypothesis that MAP in humans is in a wall-deficient form that would be not acid fast and much more difficult to grow in artificial media [142]. Anyway, even if etiological considerations are left apart, we think that the summary presented in Table 2 might become a reference to pathologists for characterizing and classifying histopathological lesion description in order to standardize criteria throughout species and thus to more objectively address both description and understanding of pathologic mechanisms.

6. Epidemiologic and therapeutic aspects

When looking for hints to etiology, there is further evidence that can be considered in order to match pathological entities with a recognized etiology to those without it, in order to eventually verify or falsify the hypothesis of a common pathogenesis and, thus, a similar etiology. Some of that evidence can be found looking to the following aspects:

6.1. Geographic distribution

Although some regional differences in prevalence have been pointed out regarding CD, human CRIID is found everywhere throughout the world [2] and the same can be said of paratuberculosis. Even though some countries or regions claim freedom of paratuberculosis, the infection has been found in all continents, latitudes and climates in different species. Although not necessary, if human IBD is caused by MAP, a route from animals to humans has been clearly established when MAP has been detected in commercial milk and beef and has also been found in drinking water [63,64].

6.2. MAP detection

MAP is a difficult to grow mycobacteria and for some time some sheep strains could not be grown on artificial media [143,144]. There are also reports of extremely slow growth where colonies were not observed until after 12 months of incubation. Both growing features cause strong controversies on the association of MAP with clinical cases in some species that are further complicated by the finding of the bacteria on healthy subjects. Modern molecular and immunohistochemical (IHC) techniques have not brought clarification to human CRIID since these methods also fail to detect MAP or any other specific pathogen in all patients, but have increased the frequency of healthy individuals with a positive result to MAP [43,44,67,74,75].

6.3. Immune response

It is estimated that only 25% of paratuberculosis infected cattle can be detected with specific serological tests [84]. That roughly corresponds with the frequency of patent forms of paratuberculosis, so most of latent infections do not show any specific response. In humans, there is evidence throughout the world that IBD patients have increased antibody responses to mycobacterial and more specifically to MAP antigens [44,73,145]. Additionally, CD patients had increased antibody response against MAP, along with increased basal levels of IFN-g, while they had decreased MAP-specific IFN-g release compared to healthy controls and a lower frequency of MAP DNA detection [44].

6.4. Genetic factors

A genetic component has long been suspected as an essential factor in the pathogenesis of CRIIDs. In humans, several polymorphisms have been associated with CD [46,57,58,146]. A genome wide study showed that genes associated to mycobacterial infection susceptibility are involved in CD causation [147]. In ruminant paratuberculosis, until now only weak associations have been found [22]. However the definition of epidemiopathogenic forms has led to the proposal of groups of infection progression risk associating certain combinations of single nucleotide polymorphisms (SNPs) with epidemiopathogenic forms of paratuberculosis [55]. Some of these SNPs (CD209, SLC11A, TLR2) occur on genes that are the orthologs of those associated with human IBD.

6.5. Therapeutics

Treatment of diseased animals is out of question in the livestock industry because of the costs and epidemiological risks. In humans, until recently, IBD treatment relied exclusively on anti-inflammatory and immunosupressive drugs based on its empirical effects. However it seems that at least some of those, such as sulfasalazine, have an anti-MAP effect *in vitro* which suggests that their anti-inflammatory activity could be due to the control of mycobacterial (more specifically MAP) growth [148]. Given the suspected role of infectious bacteria in the etiology of IBD, antibiotic regimens, some of them following MAP-specific treatments (rifabutin and clarithromycin), have been used to treat CD with clinical improvements or remission in numerous studies [81,149]. Meta-analysis studies of randomized placebo controlled trials showed benefits from treatment with antibiotic therapies using anti-mycobacterial combinations (i.e. rifamycin, ciprofloxacin or matronidazole) which can induce remission in active CD [150].

The pathogenesis course modification caused by paratuberculosis vaccination suggests that circumvention of blocking at some point in the immune defense mechanisms might be critical to prevent paratuberculosis inflammation and likely its human counterpart. In this sense, it might be the training effect of mycobacterial antigens what can cause macrophage function enhancement leading to unspecific control of both paratuberculosis and other inflammatory processes likely related to blocking of transition from innate immunity to adaptive specific immunity [84,151].

7. Conclusion

In this paper we have revised the forms of CRIID in different species in order to determine whether or not a trans-specific common pattern for this type of intestinal diseases can be found. In addition, since causation is a critical point in the knowledge of any disease, we have examined pathologic, epidemiologic and immunological aspects of the corresponding disease in ruminants whose etiology is universally accepted that could apply to human CRIID. Classical infectious causation is demonstrated by fulfillment of Koch postulates. However, it has been shown beyond any doubt and even recognized by Koch himself that these postulates do not hold true for all types of infectious disease causation. Precisely, paratuberculosis is one where several of these postulates are not fulfilled. Therefore, this could be assumed too for CRIIDs and therefore other causation criteria need to be tested.

In our opinion there are the following criteria that support MAP causation beyond Koch postulates:

- Clinical and pathological features fit within the same frame as paratuberculosis.
- There is microbiological evidence, both bacterial and immune, of the implication of MAP in a similar way as in paratuberculosis where subclinical carriers amount to about 40% of the healthy population.
- The putative agent, MAP, is widespread but of low pathogenicity.
- There are common genetic factors associated to the risk of infection progression towards disease.
- Treatment with some antiinflamatory drugs has *in vitro* effect on MAP which might account for clinical improvement.

All these observations and considerations points out that CRIIDs might be a particular case of inflammatory slow infection affecting the environment/organism interface at the intestinal level, and is most likely caused by the recognized etiological agent – MAP – in animal species. The common characteristics of CRIIDs that might include them in the modified slow infection pathogenesis model would be the following: (a) low virulence agent involved, (b) susceptibility linked to individual genetic factors, (c) intestine as the location of the environment-organism interphase, (d) prominent macrophagic and lymphocytic inflammation as innate local immune response, (e) specific immune response absent or inefficient, (f) onset at early-adulthood with a high ratio of healthy carriers to cincal cases, and (g) slow clinical course-wasting to death.

Pathological studies can contribute to confirm common causality by verifying predictions filling out the gaps, mostly regarding latent and subclinical forms, related to focal and multifocal pathological forms and their corresponding agent abundance, in monogastric species (see Table 2).

If that is the case, an alternative unspecific “trained”-type response [151] induction at the right time could become an efficient prevention-treatment rather than current ones exclusively focused on blocking the inflammatory pathways.

Author contributions

Juste RA designed the review; Balseiro A developed the idea, revised the literature and wrote the initial manuscript; Perez V verified and commented on the accuracy of the pathological concepts and supervised the successive versions; Balseiro A and Juste RA rewrote and re-organized the advanced versions; all authors reviewed and approved the final manuscript as submitted.

Conflict-of-interest statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] A. Kaser, S. Zeissig, R.S. Blumberg, Inflammatory bowel disease, Annu. Rev. Immunol. 28 (2010) 573–621, https://doi.org/10.1146/annurev-immunol-030409-101225.
[2] C.N. Bernstein, Review article: changes in the epidemiology of inflammatory bowel disease-clues for aetiology, Aliment. Pharmacol. Ther. 46 (2017) 911–919, https://doi.org/10.1111/apt.14338.
[3] J. Hart, E. Shaker, A. Patnik, M. Garvey, Lymphocytic-plasmacytic enterocolitis in cats: 60 cases (1988-1990), J. Am. Anim. Hosp. Assoc. 30 (1994) 505–515.
[4] J. Schumacher, J.F. Edwards, N.D. Cohen, Chronic idiopathic inflammatory bowel diseases of the horse., J. Vet. Intern. Med. 14 (n.d.) 258–265. http://www.ncbi.nlm.nih.gov/pubmed/10830538 (Accessed 11 July 2018).

[5] B. Glanemann, H. Schönenbrücher, N. Bridger, A. Abdulmawjood, R. Neiger, M. Bülte, Detection of Mycobacterium avium subspecies Paratuberculosis-specific DNA by PCR in intestinal biopsies of dogs, J. Vet. Intern. Med. 22 (2008) 1090–1094, https://doi.org/10.1111/j.1939-1676.2008.0147.x.
[6] K.A. Rice, E.S. Chen, K.A. Metcalf Pate, E.K. Hutchinson, R.J. Adams, Diagnosis of amyloidosis and differentiation from chronic, idiopathic enterocolitis in rhesus (Macaca mulatta) and pig-tailed (M. nemestrina) macaques, Comp. Med. 63 (2013) 262–271 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/23759529.
[7] H.A. Johne, L. Frothingham, Ein eigenthümlicher Fall von Tuberculose beim Rind, Dtsch. Zeitschrift Fur Tiermedicin Und Vergleichende Pathol. 21 (1895) 438–454.
[8] I. Pavlik, J. Bartl, L. Dvorska, P. Svastova, R. du Maine, M. Machackova, W. Yayo Ayele, A. Horvathova, Epidemiology of paratuberculosis in wild ruminants studied by restriction fragment length polymorphism in the Czech Republic during the period 1995-1998, Vet. Microbiol. 77 (2000) 231–251 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/11118709.
[9] I. Marco, M. Ruiz, R. Juste, J.M. Garrido, S. Lavin, Paratuberculosis in free-ranging fallow deer in Spain, J. Wildl. Dis. 38 (2002) 629–632, https://doi.org/10.7589/0090-3558-38.3.629.
[10] J. Alvarez, L. De Juan, V. Briones, B. Romero, A. Aranaz, J.F. Fernández-Garayzábal, A. Mateos, Mycobacterium avium subspecies paratuberculosis in fallow deer and wild boar in Spain, Vet. Rec. 156 (2005) 212–213 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/15747660.
[11] A. Balseiro, J.F. García Marín, P. Solano, J.M. Garrido, J.M. Prieto, Histopathological classification of lesions observed in natural cases of paratuberculosis in free-ranging fallow deer (Dama dama), J. Comp. Pathol. 138 (2008) 180–188, https://doi.org/10.1016/j.jcpa.2008.01.003.
[12] R.G. Clark, J.F.T. Griffin, C.G. Mackintosh, Johne's disease caused by Mycobacterium avium subsp. Paratuberculosis infection in red deer (Cervus elaphus): an histopathological grading system, and comparison of paucibacillary and multibacillary disease, N. Z. Vet. J. 58 (2010) 90–97, https://doi.org/10.1080/00480169.2010.65263.
[13] A. Greig, K. Stevenson, V. Perez, A.A. Pirie, J.M. Grant, J.M. Sharp, Paratuberculosis in wild rabbits (Oryctolagus cuniculus), Vet. Rec. 140 (1997) 141–143 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/9050174.
[14] P.M. Beard, M.J. Daniels, D. Henderson, A. Pirie, K. Rudge, D. Buxton, S. Rhind, A. Greig, M.R. Hutchings, I. McKendrick, K. Stevenson, J.M. Sharp, Paratuberculosis infection of nonruminant wildlife in Scotland, J. Clin. Microbiol. 39 (2001) 1517–1521, https://doi.org/10.1128/JCM.39.4.1517-1521.2001.
[15] P.M. Beard, S.M. Rhind, D. Buxton, M.J. Daniels, D. Henderson, A. Pirie, K. Rudge, A. Greig, M.R. Hutchings, K. Stevenson, J.M. Sharp, Natural paratuberculosis infection in rabbits in Scotland, J. Comp. Pathol. (2001), https://doi.org/10.1053/jcpa.2001.0466.
[16] M.J. Daniels, D. Henderson, A. Greig, K. Stevenson, J.M. Sharp, M.R. Hutchings, The potential role of wild rabbits Oryctolagus cuniculus in the epidemiology of paratuberculosis in domestic ruminants, Epidemiol. Infect. 130 (2003) 553–559 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/12825741.
[17] J.L. Corn, E.J.B. Manning, S. Sreevatsan, J.R. Fischer, Isolation of Mycobacterium avium subsp. paratuberculosis from free-ranging birds and mammals on livestock premises, Appl. Environ. Microbiol. 71 (2005) 6963–6967, https://doi.org/10.1128/AEM.71.11.6963-6967.2005.
[18] M.A. Miller, S.C. Davey, L.S. Van Helden, F. Kettner, S.M. Weltan, R. Last, J.D. Grewar, L. Botha, P.D. Van Helden, Paratuberculosis in a domestic dog in South Africa, J. S. Afr. Vet. Assoc. 88 (2017), https://doi.org/10.4102/jsava.v88i0.1441.
[19] R. Arrazuria, R.A. Juste, N. Elguezabal, Mycobacterial infections in rabbits: from the wild to the laboratory, Transbound. Emerg. Dis. 64 (2017) 1045–1058, https://doi.org/10.1111/tbed.12474.
[20] T. Tams, Chronic diseases of the small intestine, in: T. Tams (Ed.), Handb. Small Anim. Gastroenterol. WB Saunders, Philadelphia, 1996, pp. 267–319.
[21] M. Alimchandani, J.-P. Lai, P.P. Aung, S. Khangura, N. Kamal, J.I. Gallin, S.M. Holland, H.L. Malech, T. Heller, M. Miettinen, M.M. Quezado, Gastrointestinal histopathology in chronic granulomatous disease: a study of 87 patients, Am. J. Surg. Pathol. 37 (2013) 1365–1372, https://doi.org/10.1097/PAS.0b013e318297427d.
[22] P. Vazquez, J.M. Garrido, E. Molina, M.V. Geijo, N. Gomez, V. Perez, I.A. Sevilla, M. Alonso-Hearn, A. Cortes, R.A. Juste, Latent infections are the most frequent form of paratuberculosis in slaughtered friesian cattle, Span. J. Agric. Res. 12 (2014) 1049–1060, https://doi.org/10.5424/sjar/2014124-5978.
[23] S. of Ephesus, On acute and chronic diseases, in: C.C. Mettler (Ed.), Hist. Med. 1947 Blakiston, Philadelphia.
[24] A. Castiglioni, Antonio Benivieni, Encicl. Treccani, Istituto della Enciclopedia, Italiana, Roma, 1949 p. 646.
[25] G. Morgagni, The seats and causes of disease investigated by anatomy, in: A. Millar, C. T (Eds.) Five Books Contain. a Gt. Var. Dissections with Remarks (Translated from Lat. John Baptist Morgagni by Benjamin Alexander). Three Vol., London, 1769.
[26] J.F. Fielding, Crohn's disease and Dalziel's syndrome. A history. (Fabry W. Ex scirrho et ulcere cancioso in intesrino cocco exorta iliaca passio. In Opera, observation LXI, Centuriae, I. Frankfort: 31 J.L. Dufour, 1682:49, J. Clin. Gastroenterol. 10 (1988) 279–285 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/2980763.
[27] S. Wilks, Morbid appearances in the intestine of miss Bankes, London Med. Gaz. (1859) 264–265.
[28] T.K. Dalziel, Chronic interestitial enteritis, Br. Med. J. (Clin. Res.) 2 (1913) 1068.
[29] B.B. Crohn, L. Ginzburg, G. Oppenheimer, Regional enteritis a pathologic and clinical entity, JAMA. 99 (1932) 1323–1329.
[30] J.B. Kirsner, Historical aspects of inflammatory bowel disease, J. Clin. Gastroenterol. 10 (1988) 286–297 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/2980764.
[31] J.B. Kirsner, Historical origins of current IBD concepts, World J. Gastroenterol. 7 (2001) 175–184 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/11819757.
[32] E. Moschcowitz, A. Wilensky, Nonspecific granulomas of the intestine, Am. J. Med. Sci. 166 (1923) 48–66.
[33] H.E. Lockhart-Mummery, B.C. Morson, Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis, Gut 1 (1960) 87–105 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/14417801.
[34] R.H. Marshak, Granulomatous disease of the intestinal tract (Crohn's disease), Radiology 114 (1975) 3–22, https://doi.org/10.1148/114.1.3.
[35] B. Morson, Pathology of ulcerative colitis, in: J. Kinsner, R. Shorter (Eds.), Inflamm. Bowel Dis. Lea and Febiger, Philadelphia, 1975.
[36] R.J. Chiodini, H.J. Van Kruiningen, R.S. Merkal, W.R. Thayer, J.A. Coutu, Characteristics of an unclassified Mycobacterium species isolated from patients with Crohn's disease, J. Clin. Microbiol. 20 (1984) 966–971 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/6511878.
[37] F.W. Twort, G.L.Y. Ingram, A method for isolating and cultivating the Mycobacterium enteriditis chronicae pseudotuberculosae bovis, Johne, and some experiments on the preparation of a diagnostic vaccine for pseudo-tuberculous enteritis of bovines, R. Soc. Proc. Biol. 84 (1911) 517–542.
[38] M.J. Carrigan, J.T. Seaman, The pathology of Johne's disease in sheep, Aust. Vet. J. (1990), https://doi.org/10.1111/j.1751-0813.1990.tb07693.x.
[39] R.J. Greenstein, Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease, Lancet Infect. Dis. 3 (2003) 507–514 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/12901893.
[40] S.A. Naser, G. Ghobrial, C. Romero, J.F. Valentine, Culture of Mycobacterium avium subspecies paratuberculosis from the blood of patients with Crohn's disease, Lancet. 364 (2004) 1039–1044, https://doi.org/10.1016/S0140-6736(04)17058-X.
[41] R. Clancy, Z. Ren, J. Turton, G. Pang, A. Wettstein, Molecular evidence for Mycobacterium avium subspecies paratuberculosis (MAP) in Crohn's disease correlates with enhanced TNF-alpha secretion, Dig. Liver Dis. 39 (2007) 445–451, https://doi.org/10.1016/j.dld.2006.12.006.
[42] I. Abubakar, D.J. Myhill, A.R. Hart, I.R. Lake, I. Harvey, J.M. Rhodes, R. Robinson, A.J. Lobo, C.S.J. Probert, P.R. Hunter, A case-control study of drinking water and dairy products in Crohn's Disease–further investigation of the possible role of Mycobacterium avium paratuberculosis, Am. J. Epidemiol. 165 (2007) 776–783, https://doi.org/10.1093/aje/kwk067.
[43] R.A. Juste, N. Elguezabal, J.M. Garrido, A. Pavon, M.V. Geijo, I. Sevilla, J.-L. Cabriada, A. Tejada, F. García-Campos, R. Casado, I. Ochotorena, A. Izeta, R.J. Greenstein, On the prevalence of M. avium subspecies paratuberculosis DNA in the blood of healthy individuals and patients with inflammatory bowel disease, PLoS One 3 (2008) e2537, https://doi.org/10.1371/journal.pone.0002537.
[44] R.A. Juste, N. Elguezabal, A. Pavón, J.M. Garrido, M. Geijo, I. Sevilla, J.L. Cabriada, A. Tejada, F. García-Campos, R. Casado, I. Ochotorena, A. Izeta, Association between Mycobacterium avium subsp. paratuberculosis DNA in blood and cellular and humoral immune response in inflammatory bowel disease patients and controls, Int. J. Infect. Dis. 13 (2009) 247–254, https://doi.org/10.1016/j.ijid.2008.06.034.
[45] J.D. Küpper, H.R. Brandt, G. Erhardt, Genetic association between NOD2 polymorphism and infection status by Mycobacterium avium ssp. paratuberculosis in German Holstein cattle, Anim. Genet. 45 (2014) 114–116, https://doi.org/10.1111/age.12097.
[46] M. Girardelli, F. Basaldella, S. Della Paolera, J. Vuch, A. Tommasini, S. Martelossi, S. Crovella, A.M. Bianco, Genetic profile of patients with early onset inflammatory bowel disease, Gene 645 (2018) 18–29, https://doi.org/10.1016/j.gene.2017.12.029.
[47] B.B. Crohn, L. Ginzburg, G.D. Oppenheimer, Regional ileitis: a pathologic and clinical entity. 1932, Mt. Sinai J. Med. 67 (2000) 263–268 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/10828911.
[48] J. Petitfils, Louis XIII, (2008).
[49] M. Baillie, The Morbid Anatomy of Some of the Most Important Parts of the Human Body, London Publishers, London, 1793.
[50] J. Kirsner, Origins and directions of inflammatory bowel disease, Early Studies of the "Nonspecific" Inflammatory Bowel Disease, Kluwer Acadmic Publishers, Dordrecht, 2001.
[51] A.M. Lichtarowicz, J.F. Mayberry, Antoni Lésniowski and his contribution to regional enteritis (Crohn's disease), J. R. Soc. Med. 81 (1988) 468–470 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/3047387.
[52] J.C. Uzoigwe, M.L. Khaitsa, P.S. Gibbs, Epidemiological evidence for Mycobacterium avium subspecies paratuberculosis as a cause of Crohn's disease, Epidemiol. Infect. 135 (2007) 1057–1068, https://doi.org/10.1017/S0950268807008448.
[53] J. Wagner, N.A. Skinner, A.G. Catto-Smith, D.J.S. Cameron, W.P. Michalski, K. Visvanathan, C.D. Kirkwood, TLR4, IL10RA, and NOD2 mutation in paediatric Crohn's disease patients: an association with Mycobacterium avium subspecies paratuberculosis and TLR4 and IL10RA expression, Med. Microbiol. Immunol. 202 (2013) 267–276, https://doi.org/10.1007/s00430-013-0290-5.
[54] P. Vázquez, O. Ruiz-Larrañaga, J.M. Garrido, M. Iriondo, C. Manzano, M. Agirre, A. Estonba, R.A. Juste, Genetic association analysis of paratuberculosis forms in Holstein-Friesian cattle, Vet. Med. Int. 2014 (2014) 1–8, https://doi.org/10.1155/

2014/321327.
[55] R.A. Juste, P. Vazquez, O. Ruiz-Larrañaga, M. Iriondo, C. Manzano, M. Agirre, A. Estonba, M.V. Geijo, E. Molina, I.A. Sevilla, M. Alonso-Hearn, N. Gomez, V. Perez, A. Cortes, J.M. Garrido, Association between combinations of genetic polymorphisms and epidemiopathogenic forms of bovine paratuberculosis, Heliyon 4 (2018) e00535, https://doi.org/10.1016/j.heliyon.2018.e00535.
[56] L.A. Sechi, M. Mura, E. Tanda, A. Lissia, G. Fadda, S. Zanetti, Mycobacterium avium sub. paratuberculosis in tissue samples of Crohn's disease patients, New Microbiol. 27 (2004) 75–77.
[57] L.A. Sechi, M. Gazouli, J. Ikonomopoulos, J.C. Lukas, A.M. Scanu, N. Ahmed, G. Fadda, S. Zanetti, Mycobacterium avium subsp. paratuberculosis, genetic susceptibility to Crohn's disease, and Sardinians: the way ahead, J. Clin. Microbiol. 43 (2005) 5275–5277.
[58] L.A. Sechi, M. Gazouli, L.E. Sieswerda, P. Molicotti, N. Ahmed, J. Ikonomopoulos, A.M. Scanu, D. Paccagnini, S. Zanetti, Relationship between Crohn's disease, infection with Mycobacterium avium subspecies paratuberculosis and SLC11A1 gene polymorphisms in Sardinian patients, World J. Gastroenterol. 12 (2006) 7161–7164.
[59] D.C.M. Rapozo, C. Bernardazzi, H.S.P. de Souza, Diet and microbiota in inflammatory bowel disease: the gut in disharmony, World J. Gastroenterol. 23 (2017) 2124–2140, https://doi.org/10.3748/wjg.v23.i12.2124.
[60] J. Wagner, W.H. Sim, K.J. Lee, C.D. Kirkwood, Current knowledge and systematic review of viruses associated with Crohn's disease, Rev. Med. Virol. 23 (2013) 145–171, https://doi.org/10.1002/rmv.1720.
[61] M. Feller, K. Huwiler, R. Stephan, E. Altpeter, A. Shang, H. Furrer, G.E. Pfyffer, T. Jemmi, A. Baumgartner, M. Egger, Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis, Lancet Infect. Dis. 7 (2007) 607–613, https://doi.org/10.1016/S1473-3099(07)70211-6.
[62] R.J. Whittington, D.J. Marshall, P.J. Nicholls, I.B. Marsh, L.A. Reddacliff, Survival and dormancy of Mycobacterium avium subsp. paratuberculosis in the environment, Appl. Environ. Microbiol. 70 (2004) 2989–3004 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/15128561.
[63] I.R. Grant, E.I. Hitchings, A. McCartney, F. Ferguson, M.T. Rowe, Effect of commercial-scale high-temperature, short-time pasteurization on the viability of Mycobacterium paratuberculosis in naturally infected cows' milk, Appl. Environ. Microbiol. 68 (2002) 602–607 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/11823197.
[64] S.W.F. Eisenberg, M. Nielen, A.P. Koets, Within-farm transmission of bovine paratuberculosis: recent developments, Vet. Q. 32 (2012) 31–35, https://doi.org/10.1080/01652176.2012.659870.
[65] S.A. Naser, S.R. Sagramsingh, A.S. Naser, S. Thanigachalam, *Mycobacterium avium* subspecies *paratuberculosis* causes Crohn's disease in some inflammatory bowel disease patients, World J. Gastroenterol. 20 (2014) 7403, https://doi.org/10.3748/wjg.v20.i23.7403.
[66] J.L.E. Ellingson, J.C. Cheville, D. Brees, J.M. Miller, N.F. Cheville, Absence of Mycobacterium avium subspecies paratuberculosis components from Crohn's disease intestinal biopsy tissues, Clin. Med. Res. 1 (2003) 217–226 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/15931311.
[67] T.J. Bull, E.J. McMinn, K. Sidi-Boumedine, A. Skull, D. Durkin, P. Neild, G. Rhodes, R. Pickup, J. Hermon-Taylor, Detection and verification of Mycobacterium avium subsp. paratuberculosis in fresh ileocolonic mucosal biopsy specimens from individuals with and without Crohn's disease, J. Clin. Microbiol. 41 (2003) 2915–2923 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/12843021.
[68] M.A. Behr, V. Kapur, The evidence for Mycobacterium paratuberculosis in Crohn's disease, Curr. Opin. Gastroenterol. 24 (2008) 17–21, https://doi.org/10.1097/MOG.0b013e3282f1dcc4.
[69] S.A. Naser, D. Schwartz, I. Shafran, Isolation of Mycobacterium avium subsp paratuberculosis from breast milk of Crohn's disease patients, Am. J. Gastroenterol. 95 (2000) 1094–1095, https://doi.org/10.1111/j.1572-0241.2000.01954.x.
[70] A.V. Singh, S.V. Singh, P.K. Singh, J.S. Sohal, M.K. Singh, High prevalence of Mycobacterium avium subspecies paratuberculosis ('Indian bison type') in animal attendants suffering from gastrointestinal complaints who work with goat herds endemic for Johne's disease in India, Int. J. Infect. Dis. 15 (2011) e677–683, https://doi.org/10.1016/j.ijid.2011.04.013.
[71] V.J. Timms, G. Daskalopoulos, H.M. Mitchell, B.A. Neilan, The Association of Mycobacterium avium subsp. paratuberculosis with Inflammatory Bowel Disease, PLoS One 11 (2016) e0148731, https://doi.org/10.1371/journal.pone.0148731.
[72] L.A. Sechi, A.M. Scanu, P. Molicotti, S. Cannas, M. Mura, G. Dettori, G. Fadda, S. Zanetti, Detection and isolation of Mycobacterium avium subspecies paratuberculosis from intestinal mucosal biopsies of patients with and without Crohn's disease in Sardinia, Am. J. Gastroenterol. 100 (2005) 1529–1536, https://doi.org/10.1111/j.1572-0241.2005.41415.x.
[73] S. Zamani, M.R. Zali, H.A. Aghdaei, L.A. Sechi, M. Niegowska, E. Caggiu, R. Keshavarz, N. Mosavari, M.M. Feizabadi, Mycobacterium avium subsp. paratuberculosis and associated risk factors for inflammatory bowel disease in Iranian patients, Gut Pathog. 9 (2017) 1, https://doi.org/10.1186/s13099-016-0151-z.
[74] A.V. Singh, S.V. Singh, G.K. Makharia, P.K. Singh, J.S. Sohal, Presence and characterization of Mycobacterium avium subspecies paratuberculosis from clinical and suspected cases of Crohn's disease and in the healthy human population in India, Int. J. Infect. Dis. 12 (2008) 190–197, https://doi.org/10.1016/j.ijid.2007.06.008.
[75] A. Tuci, F. Tonon, L. Castellani, A. Sartini, G. Roda, M. Marocchi, A. Caponi, A. Munarini, G. Rosati, G. Ugolini, L. Fuccio, M. Scagliarini, F. Bazzoli, A. Belluzzi, Fecal detection of mycobacterium avium paratuberculosis using the IS900 DNA sequence in Crohn's disease and ulcerative colitis patients and healthy subjects, Dig. Dis. Sci. 56 (10) (2011) 2957–2962, https://doi.org/10.1007/s10620-011-1699-6.
[76] R.B. Koch, Koch's Postulates, Wikipedia, (1890) https://en.wikipedia.org/wiki/Koch%27s_postulates.
[77] V. Perez, J.F.G. Marin, J.J. Badiola, Description and classification of different types of lesion associated with natural paratuberculosis infection in sheep, J. Comp. Pathol. 114 (1996) 107–122, https://doi.org/10.1016/S0021-9975(96)80001-6.
[78] J.M. Corpa, J. Garrido, J.F. García Marín, V. Pérez, Classification of lesions observed in natural cases of paratuberculosis in goats, J. Comp. Pathol. 122 (2000) 255–265, https://doi.org/10.1053/jcpa.1999.0368.
[79] J. González, M.V. Geijo, C. García-Pariente, A. Verna, J.M. Corpa, L.E. Reyes, M.C. Ferreras, R.A. Juste, J.F. García Marín, V. Pérez, Histopathological classification of lesions associated with natural paratuberculosis infection in cattle, J. Comp. Pathol. 133 (2005) 184–196, https://doi.org/10.1016/j.jcpa.2005.04.007.
[80] E.L. Corbett, C.J. Watt, N. Walker, D. Maher, B.G. Williams, M.C. Raviglione, C. Dye, The growing burden of tuberculosis: global trends and interactions with the HIV epidemic, Arch. Intern. Med. 163 (2003) 1009–1021, https://doi.org/10.1001/archinte.163.9.1009.
[81] J. Hermon-Taylor, Treatment with drugs active against Mycobacterium avium subespecies paratuberculosis can heal Crohn's disease: more evidence for a neglected public health tragedy, Dig. Liver Dis. 34 (2002) 9–12 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/11926580.
[82] J. Hermon-Taylor, T. Bull, Crohn's disease caused by Mycobacterium avium subspecies paratuberculosis: a public health tragedy whose resolution is long overdue, J. Med. Microbiol. 51 (2002) 3–6.
[83] W.C. Davis, On deaf ears, Mycobacterium avium paratuberculosis in pathogenesis Crohn's and other diseases, World J. Gastroenterol. 21 (2015) 13411–13417, https://doi.org/10.3748/wjg.v21.i48.13411.
[84] F. Bastida, R.A. Juste, Paratuberculosis control: a review with a focus on vaccination, J. Immune Based Ther. Vaccines 9 (2011) 8, https://doi.org/10.1186/1476-8518-9-8.
[85] S. Ehlers, U.E. Schaible, The granuloma in tuberculosis: dynamics of a host-pathogen collusion, Front. Immunol. 3 (2012) 411, https://doi.org/10.3389/fimmu.2012.00411.
[86] B. Sigurdsson, RIDA, a chronic encephalitis of sheep: with general remarks on infections which develop slowly and some of their special characteristics, Br. Vet. J. 110 (1954) 341–354, https://doi.org/10.1016/S0007-1935(17)50172-4.
[87] J. Cosnes, C. Gower–Rousseau, P. Seksik, A. Cortot, Epidemiology and natural history of inflammatory bowel diseases, Gastroenterology 140 (2011) 1785–1794.e4, https://doi.org/10.1053/j.gastro.2011.01.055.
[88] G.P. Jevon, R. Madhur, Endoscopic and histologic findings in pediatric inflammatory bowel disease, Gastroenterol. Hepatol. (N. Y.) 6 (2010) 174–180 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/20567564.
[89] C.A. Seldenrijk, B.C. Morson, S.G. Meuwissen, N.W. Schipper, J. Lindeman, C.J. Meijer, Histopathological evaluation of colonic mucosal biopsy specimens in chronic inflammatory bowel disease: diagnostic implications, Gut 32 (1991) 1514–1520 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/1773958.
[90] K. Sestak, C.K. Merritt, J. Borda, E. Saylor, S.R. Schwamberger, F. Cogswell, E.S. Didier, P.J. Didier, G. Plauche, R.P. Bohm, P.P. Aye, P. Alexa, R.L. Ward, A.A. Lackner, Infectious agent and immune response characteristics of chronic enterocolitis in captive rhesus macaques, Infect. Immun. 71 (2003) 4079–4086 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/12819098.
[91] S.V. Singh, A.V. Singh, P.K. Singh, A. Kumar, B. Singh, Molecular identification and characterization of Mycobacterium avium subspecies paratuberculosis in free living non-human primate (Rhesus macaques) from North India, Comp. Immunol. Microbiol. Infect. Dis. 34 (2011) 267–271, https://doi.org/10.1016/j.cimid.2010.12.004.
[92] M.J. Day, T. Bilzer, J. Mansell, B. Wilcock, E.J. Hall, A. Jergens, T. Minami, M. Willard, R. Washabau, Histopathological standards for the diagnosis of gastrointestinal inflammation in endoscopic biopsy samples from the dog and cat: a report from the world small animal veterinary association gastrointestinal standardization group, J. Comp. Pathol. 138 (2008) S1–43, https://doi.org/10.1016/j.jcpa.2008.01.001.
[93] M. García-Sancho, F. Rodríguez-Franco, A. Sainz, C. Mancho, A. Rodríguez, Evaluation of clinical, macroscopic, and histopathologic response to treatment in nonhypoproteinemic dogs with lymphocytic-plasmacytic enteritis., J. Vet. Intern. Med. 21 (n.d.) 11–7. http://www.ncbi.nlm.nih.gov/pubmed/17338144 (Accessed 11 July 2018).
[94] M. Wdowiak, A. Rychlik, A. Kołodziejska-Sawerska, Biomarkers in canine inflammatory bowel disease diagnostics, Pol. J. Vet. Sci. 16 (2013) 601–610 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/24195302.
[95] A.E. Jergens, F.M. Moore, J.S. Haynes, K.G. Miles, Idiopathic inflammatory bowel disease in dogs and cats: 84 cases (1987-1990), J. Am. Vet. Med. Assoc. 201 (1992) 1603–1608 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/1289345.
[96] W. Guilford, Idiopathic inflammatory bowel diseases, in: D. Strombeck (Ed.), Strombeck's Small Anim. Gastroenterol, WB Saunders, Philadelphia, 1996, pp. 451–486.
[97] A.C. Manchester, S. Hill, B. Sabatino, R. Armentano, M. Carroll, B. Kessler, M. Miller, B. Dogan, S.P. McDonough, K.W. Simpson, Association between granulomatous colitis in French Bulldogs and invasive Escherichia coli and response to fluoroquinolone antimicrobials, J. Vet. Intern. Med. 27 (2013) 56–61, https://doi.org/10.1111/jvim.12020.

[98] O. Chacon, L.E. Bermudez, R.G. Barletta, Johne's Disease, Inflammatory bowel disease, and Mycobacterium paratuberculosis, Annu. Rev. Microbiol. 58 (2004) 329–363, https://doi.org/10.1146/annurev.micro.58.030603.123726.
[99] K.S. Kukanich, J. Vinasco, H.M. Scott, Detection of Mycobacterium avium subspecies paratuberculosis from intestinal and nodal tissue of dogs and cats, ISRN Vet. Sci. 2013 (2013) 323671, https://doi.org/10.1155/2013/323671.
[100] A.E. Jergens, Feline idiopathic inflammatory bowel disease: what we know and what remains to be unraveled, J. Feline Med. Surg. 14 (2012) 445–458, https://doi.org/10.1177/1098612X12451548.
[101] S. Sabattini, E. Bottero, M.E. Turba, F. Vicchi, S. Bo, G. Bettini, Differentiating feline inflammatory bowel disease from alimentary lymphoma in duodenal endoscopic biopsies, J. Small Anim. Pract. 57 (2016) 396–401, https://doi.org/10.1111/jsap.12494.
[102] R.E. Cimprich, Equine granulomatous enteritis, Vet. Pathol. 11 (1974) 535–547, https://doi.org/10.1177/030098587401100608.
[103] F. van Ulsen, Johne's disease in a pygmy ass (Equus asinus form. dom.), Tijdschr. Diergeneeskd. 95 (1970).
[104] B. Stief, P. Möbius, H. Türk, U. Hörügel, C. Arnold, D. Pöhle, [Paratuberculosis in a miniature donkey (Equus asinus f. asinus)]., Berl. Munch. Tierarztl. Wochenschr. 125 (n.d.) 38–44. http://www.ncbi.nlm.nih.gov/pubmed/22372323 (Accessed 18 July 2018).
[105] A.B. Larsen, H.W. Moon, R.S. Merkal, Susceptibility of horses to Mycobacterium paratuberculosis, Am. J. Vet. Res. 33 (1972) 2185–2189 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/5081479.
[106] E. Maio, T. Carta, A. Balseiro, I.A. Sevilla, A. Romano, J.A. Ortiz, M. Vieira-Pinto, J.M. Garrido, J.M.P. de la Lastra, C. Gortázar, Paratuberculosis in European wild rabbits from the Iberian Peninsula, Res. Vet. Sci. 91 (2011) 212–218, https://doi.org/10.1016/j.rvsc.2010.12.014.
[107] J.A. Villemin, Études sur la tuberculose, Bailliére et fils, Paris, 1868.
[108] O. Fuentes, J. Cebrian, El conejo de monte ¿reservorio de la paratuberculosis ovina y caprina? I Symposium de Patología Ovina y Caprina, Zaragoza, June 9–10, 1988, p. 32.
[109] S. Prattis, A. Jurjus, Spontaneous and transgenic rodent models of inflammatory bowel disease, Lab. Anim. Res. 31 (2015) 47, https://doi.org/10.5625/lar.2015.31.2.47.
[110] D. Kontoyiannis, M. Pasparakis, T.T. Pizarro, F. Cominelli, G. Kollias, Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies, Immunity 10 (1999) 387–398 (Accessed 11 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/10204494.
[111] S.S. Kang, S.M. Bloom, L.A. Norian, M.J. Geske, R.A. Flavell, T.S. Stappenbeck, P.M. Allen, An antibiotic-responsive mouse model of fulminant ulcerative colitis, PLoS Med. 5 (2008) e41, https://doi.org/10.1371/journal.pmed.0050041.
[112] L.P. Hale, P.K. Greer, A novel murine model of inflammatory bowel disease and inflammation-associated colon cancer with ulcerative colitis-like features, PLoS One 7 (2012) e41797, https://doi.org/10.1371/journal.pone.0041797.
[113] J.A. Jiminez, T.C. Uwiera, G. Douglas Inglis, R.R.E. Uwiera, Animal models to study acute and chronic intestinal inflammation in mammals, Gut Pathog. 7 (2015) 29, https://doi.org/10.1186/s13099-015-0076-y.
[114] J.J. Kroll, M.B. Roof, L.J. Hoffman, J.S. Dickson, D.L.H. Harris, Proliferative enteropathy: a global enteric disease of pigs caused by Lawsonia intracellularis, Anim. Heal. Res. Rev. 6 (2005) 173–197 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/16583781.
[115] R.M.C. Guedes, M.A. Machuca, M.A. Quiroga, C.E.R. Pereira, T.P. Resende, C.J. Gebhart, Lawsonia intracellularis in pigs: progression of lesions and involvement of apoptosis, Vet. Pathol. 54 (2017) 620–628, https://doi.org/10.1177/0300985817698206.
[116] J.-M. Kim, B.K. Ku, H. Lee, I.-Y. Hwang, Y.-B. Jang, J. Kim, B.-H. Hyun, S.C. Jung, Mycobacterium avium paratuberculosis in wild boars in Korea, J. Wildl. Dis. 49 (2013) 413–417, https://doi.org/10.7589/2012-01-001.
[117] R.A. Juste, Intestinal inflammatory disease in animals and humans as a slow infection, Proc. 30th Meet. ESVP (2012) 57–58.
[118] G.A. Chalmers, P.N. Nation, J. Pritchard, Terminal ileitis in lambs, Can. Vet. J. = La Rev. Vet. Can. 31 (1990) 292–295 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/17423561.
[119] L.E. Green, et al., Terminal ileitis in lambs, Vet. Rec. (1990).
[120] J.T. Stamp, J.A. Watt, Johne's disease in sheep, J. Comp. Pathol. 64 (1954) 26–40 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/13130717.
[121] O.P. Paliwal, B.S. Rajya, Evaluation of paratuberculosis in goats: pathomorphological studies, Indian J. Vet. Pathol. 6 (1982) 29–34.
[122] C.D. Buergelt, C. Hall, K. McEntee, J.R. Duncan, Pathological evaluation of paratuberculosis in naturally infected cattle, Vet. Pathol. 15 (1978) 196–207, https://doi.org/10.1177/030098587801500206.
[123] R.G. Clark, J.F.T. Griffin, C.G. Mackintosh, Modification to histopathological lesion severity score in red deer (Cervus elaphus) affected by Johne's disease, N. Z. Vet. J. 59 (2011) 261–262, https://doi.org/10.1080/00480169.2011.596261.
[124] C.J. Clarke, I.A. Patterson, K.E. Armstrong, J.C. Low, Comparison of the absorbed ELISA and agar gel immunodiffusion test with clinicopathological findings in ovine clinical paratuberculosis, Vet. Rec. 139 (1993) 618–621 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/9123786.
[125] V. Pérez, J. Tellechea, J.J. Badiola, M. Gutiérrez, J.F. García Marín, Relation between serologic response and pathologic findings in sheep with naturally acquired paratuberculosis, Am. J. Vet. Res. 58 (1997) 799–803 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/9256958.
[126] V. Pérez, J. Tellechea, J.M. Corpa, M. Gutiérrez, J.F.G. Marín, Relation between pathologic findings and cellular immune responses in sheep with naturally acquired paratuberculosis, Am. J. Vet. Res. 60 (1999) 123–127 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/9918160.
[127] S. Stockman, Johne's disease in sheep, J. Comp. Pathol. 24 (1911) 66–69.
[128] B.S. Rajya, C.M. Singh, Studies on the pathology of Johne's disease in sheep. III. Pathologic, Am. J. Vet. Res. 22 (1961) 189–203 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/13739235.
[129] C.J. Clarke, The pathology and pathogenesis of paratuberculosis in ruminants and other species, J. Comp. Pathol. 116 (1997) 217–261 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/9147244.
[130] G.W. Dunkin, Paratuberculosis of cattle and sheep: (section of comparative medicine), Proc. R. Soc. Med. 30 (1936) 83–90 (Accessed 12 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/19990945.
[131] S. Mohiyuddeeen, A. Malaki, Histopathological study of Johne's disease lesions in a naturally infected goat, Indian Vet. J. 44 (1967) 743–745 (Accessed 18 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/5626640.
[132] D.A. Jessup, E.S. Williams, Paratuberculosis in free-ranging wildlife in North America, in: M.A. Fowler, R.E. Miller (Eds.), Zoo Wild Anim. Med. Curr. Ther. WB Saunders, Philadelphia, Pennsilvania, USA, 1999, pp. 616–620.
[133] H. Riemann, M.R. Zaman, R. Ruppanner, O. Aalund, J.B. Jorgensen, H. Worsaae, D. Behymer, Paratuberculosis in cattle and free-living exotic deer, J. Am. Vet. Med. Assoc. 174 (1979) 841–843 (Accessed 18 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/500426.
[134] E.B. Belknap, D.M. Getzy, L.W. Johnson, R.P. Ellis, G.L. Thompson, W.P. Shulaw, Mycobacterium paratuberculosis infection in two llamas, J. Am. Vet. Med. Assoc. 204 (1994) 1805–1808 (Accessed 17 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/8063605.
[135] S.E. Ridge, J.T. Harkin, R.T. Badman, A.M. Mellor, J.W. Larsen, Johne's disease in alpacas (Lama pacos) in Australia, Aust. Vet. J. 72 (1995) 150–153 (Accessed 11 September 2018), http://www.ncbi.nlm.nih.gov/pubmed/7646382.
[136] K.B. Alharbi, A. Al-Swailem, M.A. Al-Dubaib, E. Al-Yamani, A. Al-Naeem, M. Shehata, M.E. Hashad, K.A. Albusadah, O.M. Mahmoud, Pathology and molecular diagnosis of paratuberculosis of camels, Trop. Anim. Health Prod. 44 (2012) 173–177, https://doi.org/10.1007/s11250-011-9905-2.
[137] A.M. Alluwaimi, Paratuberculosis infection in camel (Camelus dromidarius): current and prospective overview, Open J. Vet. Med. 5 (2015) 153–160.
[138] S.M. Stehman, Paratuberculosis in small ruminants, deer, and South American camelids, Vet. Clin. North Am. Food Anim. Pract. 12 (1996) 441–455.
[139] M.E. Fecteau, J. Ross, B.S. Tennent-Brown, P.L. Habecker, S. Sreevatsan, R.W. Sweeney, R.H. Whitlock, Mycobacterium avium ssp. paratuberculosis high shedding in an adult female alpaca, and its implications for the rest of the herd, J. Vet. Intern. Med. 23 (2009) 1311–1314, https://doi.org/10.1111/j.1939-1676.2009.0401.x.
[140] M. Salgado, I. Sevilla, C. Rios, J. Crossley, C. Tejeda, E. Manning, Presence of Mycobacterium avium subsp. paratuberculosis in alpacas (Lama pacos) inhabiting the Chilean Altiplano, J. Zoo Wildl. Med. 47 (2016) 12–16, https://doi.org/10.1638/2012-0255.1.
[141] T.L. Burgess, C.L. Witte, B.A. Rideout, Early-life exposures and Johne's disease risk in zoo ruminants, J. Vet. Diagn. Invest. 30 (2018) 78–85, https://doi.org/10.1177/1040638717735350.
[142] K. Hulten, H.M. El-Zimaity, T.J. Karttunen, A. Almashhrawi, M.R. Schwartz, D.Y. Graham, F.A. El-Zaatari, Detection of Mycobacterium avium subspecies paratuberculosis in Crohn's diseased tissues by in situ hybridization, Am. J. Gastroenterol. 96 (2001) 1529–1535, https://doi.org/10.1111/j.1572-0241.2001.03751.x.
[143] R.A. Juste, J.C. Marco, C. Sáez de Ocáriz, J.J. Adúriz, Comparison of different media for the isolation of small ruminant strains of Mycobacterium paratuberculosis, Vet. Microbiol. 28 (1991) 385–390 (Accessed 11 September 2018), http://www.ncbi.nlm.nih.gov/pubmed/1949552.
[144] N. Elguezabal, F. Bastida, I.A. Sevilla, N. González, E. Molina, J.M. Garrido, R.A. Juste, Estimation of Mycobacterium avium subsp. paratuberculosis growth parameters: Strain characterization and comparison of methods, Appl. Environ. Microbiol. 77 (2011) 8615–8624, https://doi.org/10.1128/AEM.05818-11.
[145] A. Di Sabatino, D. Paccagnini, F. Vidali, V. Rosu, P. Biancheri, A. Cossu, S. Zanetti, G.R. Corazza, L.A. Sechi, Detection of Mycobacterium avium subsp. paratuberculosis (MAP)-specific IS900 DNA and antibodies against MAP peptides and lysate in the blood of Crohn's disease patients, Inflamm. Bowel Dis. 17 (2011) 1254–1255, https://doi.org/10.1002/ibd.21461.
[146] N. Elguezabal, S. Chamorro, E. Molina, J.M. Garrido, A. Izeta, L. Rodrigo, R.A. Juste, Lactase persistence, NOD2 status and Mycobacterium avium subsp. paratuberculosis infection associations to inflammatory bowel disease, Gut Pathog. 4 (2012) 6, https://doi.org/10.1186/1757-4749-4-6.
[147] L. Jostins, S. Ripke, R.K. Weersma, R.H. Duerr, D.P. McGovern, K.Y. Hui, J.C. Lee, L.P. Schumm, Y. Sharma, C.A. Anderson, J. Essers, M. Mitrovic, K. Ning, I. Cleynen, E. Theatre, S.L. Spain, S. Raychaudhuri, P. Goyette, Z. Wei, C. Abraham, J.-P. Achkar, T. Ahmad, L. Amininejad, A.N. Ananthakrishnan, V. Andersen, J.M. Andrews, L. Baidoo, T. Balschun, P.A. Bampton, A. Bitton, G. Boucher, S. Brand, C. Büning, A. Cohain, S. Cichon, M. D'Amato, D. De Jong, K.L. Devaney, M. Dubinsky, C. Edwards, D. Ellinghaus, L.R. Ferguson, D. Franchimont, K. Fransen, R. Gearry, M. Georges, C. Gieger, J. Glas, T. Haritunians, A. Hart, C. Hawkey, M. Hedl, X. Hu, T.H. Karlsen, L. Kupcinskas, S. Kugathasan, A. Latiano, D. Laukens, I.C. Lawrance, C.W. Lees, E. Louis, G. Mahy, J. Mansfield, A.R. Morgan, C. Mowat, W. Newman, O. Palmieri, C.Y. Ponsioen, U. Potocnik, N.J. Prescott, M. Regueiro, J.I. Rotter, R.K. Russell, J.D. Sanderson, M. Sans, J. Satsangi, S. Schreiber, L.A. Simms, J. Sventoraityte, S.R. Targan, K.D. Taylor, M. Tremelling, H.W. Verspaget, M. De Vos, C. Wijmenga, D.C. Wilson, J. Winkelmann, R.J. Xavier, S. Zeissig, B. Zhang, C.K. Zhang, H. Zhao,

M.S. International IBD Genetics Consortium (IIBDGC), M.S. Silverberg, V. Annese, H. Hakonarson, S.R. Brant, G. Radford-Smith, C.G. Mathew, J.D. Rioux, E.E. Schadt, M.J. Daly, A. Franke, M. Parkes, S. Vermeire, J.C. Barrett, J.H. Cho, Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease, Nature 491 (2012) 119–124, https://doi.org/10.1038/nature11582.

[148] R.J. Greenstein, L. Su, A. Shahidi, S.T. Brown, On the action of 5-amino-salicylic acid and sulfapyridine on M. avium including Subspecies paratuberculosis, PLoS One 2 (2007) e516.

[149] K. Hultén, A. Almashhrawi, F.A. El-Zaatari, D.Y. Graham, Antibacterial therapy for Crohn's disease: a review emphasizing therapy directed against mycobacteria, Dig. Dis. Sci. 45 (2000) 445–456 (Accessed 18 July 2018), http://www.ncbi.nlm.nih.gov/pubmed/10749316.

[150] K.J. Khan, T.A. Ullman, A.C. Ford, M.T. Abreu, A. Abadir, A. Abadir, J.K. Marshall, N.J. Talley, P. Moayyedi, P. Moayyedi, Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis, Am. J. Gastroenterol. 106 (2011), https://doi.org/10.1038/ajg.2011.72.

[151] R.A. Juste, M. Alonso-Hearn, J.M. Garrido, N. Abendaño, I.A. Sevilla, C. Gortazar, J. de la Fuente, L. Dominguez, Increased lytic efficiency of bovine macrophages trained with killed mycobacteria, PLoS One 11 (2016) e0165607, https://doi.org/10.1371/journal.pone.0165607.