Aluminum Is a Potential Environmental Factor for Crohn's Disease Induction

Extended Hypothesis

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ABSTRACT: Aluminum (Al) is a common environmental compound with immune-adjuvant activity and granulomatous inflammation inducer. Al exposure in food, additives, air, pharmaceuticals, and water pollution is ubiquitous in Western culture. Crohn's disease (CD) is a chronic relapsing intestinal inflammation in genetically susceptible individuals and is influenced by yet unidentified environmental factors. It is hypothesized, in the present review, that Al is a potential factor for induction or maintaining the inflammation in CD. Epidemiologically, CD incidence is higher in urban areas, where microparticle pollution is prevalent. Al immune activities share many characteristics with the immune pathology of CD: increased antigen presentation and APCs activation, many luminal bacterial or dietary compounds can be adsorbed to the metal and induce Th1 profile activity, promotion of humoral and cellular immune responses, proinflammatory, apoptotic, oxidative activity, and stress-related molecule expression enhancement, affecting intestinal bacterial composition and virulence, granuloma formation, colitis induction in an animal model of CD, and terminal ileum uptake. The Al–bacterial interaction, the microparticles homing the intestine together with the extensive immune activity, put Al as a potential environmental candidate for CD induction and maintenance.

KEYWORDS: aluminum; Crohn's disease; environmental factor; intestine; mucosal immunology; inflammation

INTRODUCTION

The incidence of inflammatory bowel disease (IBD) is rising in the developed countries and is becoming more common in formerly low-incidence areas in the underdeveloped ones. In the United States, the illness is not associated

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with Caucasians alone; it is spreading to Hispanics and African Americans, suggesting that environmental factors play a role in disease expression. It is clear from twin studies that genetic determinants account for at most 50% of Crohn's disease (CD) susceptibility. On the other hand, cigarette smoking, appendectomy, and enteric infections are the best characterized environmental factors. The ordinarily balanced ecosystem between epithelial cells, immune system, and resident flora is disrupted in CD, resulting in chronic, relapsing intestinal inflammation. The dysregulated immune reaction and the loss of tolerance toward the commensal microbiota or to some of its constituents are the current hypotheses for the development of CD.[1]

These aberrant immune reactions could be primary or secondary processes. However, it is also possible that environmental factors could initiate such inflammatory reaction. For many years, exposure to xenobiotic-like metals was suggested to induce an immune response in different diseases including autoimmune conditions.[2,3] For example, mercury induces antibodies against renal antigens and inhibits $RT6^+$ T cells.[4] The same metal is at the origin of murine mercury-induced autoimmune disease.[5] Exposure to cobalt, aluminum (Al), tin, zirconium, and beryllium has been associated with lung inflammation[6,7] and granulomatous pneumonitis.[7] Zirconium lactate was implicated in causing specific cell-mediated granulomatous skin reaction.[8] Podoconiosis, an endemic, nonfilarial form of elephantiasis results from absorption of microparticles of silica and alumino-silicates through bare feet and metals, such as silica, titanium, and Al are present in microgranulomata within the inguinal lymph nodes.[9] Silver taken up into cells via transferring receptors results in the presence of selected $CD4^+$ T cells[10] and T cell clones from patients with chronic beryllium disease are major histocompatibility complex (MHC) class-2 restricted.[11] In those lines, Al phosphate and hydroxide, used as adjuvants, enhance immune response to an antigen, activate complement, prime helper T cells for IgE production, and induce antibodies production.[12,13] The widespread use of Al was enhanced by the belief that it is not toxic and quickly excreted from the body by urine. It turned out, however, that Al has some pathologic effects on human health. Postdialysis encephalopathy, degenerative brain disorders, osteomalacia, cholestasis, ototoxicity, normo- or microcytic anemia, hemolytic anemia, disturbed erythropoiesis process, and inhibition of macrophage and leukocyte defensive mechanism were extensively described.[14] It is possible that this metal-induced immune activation could occur in the intestine of CD patients.

Recently, Perl *et al.*[15] put forward the hypothesis that due to bacterial–metal interactions, Al and other metals are potential environmental factors, having a role in CD induction. They proposed that the metal-related trace element uptake and/or regulatory system of either the putative mycobacteria or of the human host, or both, are involved in the pathogenesis of CD. The metal uptake/regulatory system allows access to mycobacteria of Al, resulting in an alteration in the organism's virulence and/or the host's ability to contain it. Once the Al-loaded organism is incorporated into the host, Al enhances

the organism's ability to induce a prominent granulomatous immune response, thus giving rise to the pathologic features of CD. Extensive data have been gathered on Al and the terminal ileum in normal and CD patients,[16] on effects of Al on humoral and cellular immunity and on intestinal flora and the new observation on Al enhancing colitis. The present review extends the bacterial–metal hypothesis and focuses on Al as a potential environmental mineral, an inducer of colitis. The review expands on Al and the immune system, the animal and human intestine, and the ensuing harmful immune effects of the metal. The bacterial–aluminum interaction, extensively reviewed by Perl *et al*.,[15] will not be dealt presently.

The objectives of the present paper are to describe, on the basis of the current knowledge, the potential harmful effect of Al on the human intestinal lumen and mucosa, and hypothesize possible mechanisms for Al-induced CD immune colitis.

SOURCES OF ALUMINUM EXPOSURE

Al is the most widely distributed metal in the environment and is extensively used in daily life. It composes 8.3% of the earth's crust and its main source of intake is food.[17,18] Although it has no known biological function, it is consistently introduced into living systems through soil, water, food, and pharmaceutical agents. In the environment, higher soil concentration exists in waste sites near certain industries, such as coal combustion, Al mining and melting, and car manufacturing. Flux of dust is a large source of airborne Al. In the atmosphere, it is mainly found as aluminosilicates and the background levels of Al range from 0.005 to 0.18 mg/m^3. In urban areas, Al levels in the drinking water are higher and acid rain contributes significantly to its environmental exposure. Worldwide, it is estimated that 70% of the cultivable lands are acidic enough for Al toxic effects.

The main dietary source of Al is food grown in Al-containing soil. An acidic pH contributes to its solubility resulting in accumulation in plant roots. Food additives, such as processed cheese, baked goods, grain products, cake and pancake mixes, vending machine powdery milk and cream powder substitute, sugar, frozen dough, etc., add substantial amount to Al intake. Silicates and aluminiumsilicates are usually added to food products at 0.1–1%(w/w) to enable free flow. Preservatives, coloring and levering agents, soy-based milk formulae and products, cola drinks, coffee and tea leaves, and Al cooking utensils are additional sources. Spices and aromatic herbs and the more recently described high Al content of tobacco and cannabis are additional potential human exposures.[19] Water purification procedures increase the content of soluble, low molecular weight, chemically reactive, and more readily absorbed Al species. Different substances when added to the water affect Al bioavailability and toxicity in aqueous organisms resulting in facilitating Al entry into the food chain.[20]

Certain occupational groups, for example, workers of Al refining, metal, printing, publishing, and automotive industries are confronted with higher exposure. Al is considered an occupational hazard in relation to exposure to Al dusts and fumes. Antiperspirants containing Al chlorohydrate are an additional potential hazard.

Iatrogenically, Al potential exposure was described from high Al dialysate or intravenous solutions, consumption of Al-containing phosphate binders or antacids and stress ulcer prophylaxis, buffered aspirins, antidiarrheal products, alum irrigation in the urinary bladder, Al-containing bone cement, and the controversial Al-containing adjuvants used routinely in vaccines.[21,22] An average individual's intake amounts to $>10^{12}$ microparticles/day and the daily consumption of Al sodium silicate is estimated as 0.5 mg/person per day in the United Kingdom.[16] It was estimated that the mean Al intake by an adult male is 10 mg/day whereas that by an adult female is 7 mg/day.[18]

ALUMINUM ABSORPTION AND DISTRIBUTION

The highly polarized Al^{3+} ion is absorbed from the gastrointestinal tract mainly in its hydrated form by solvent drag through paracellular passive diffusion. On top of its absolute amount ingested, the key notion for this metal absorption is bioavailability determined by its solubility and diffusibility.[23] Solubility above pH 4 depends on luminal presence of ligands. The more the Al^{3+} ion is bound into stable complex, the less it is able to dissociate water to precipitate along with the hydroxide anion in the form of the insoluble Al $(OH)_3$. Diffusibility, however, is determined by ligands neutralization of Al electrical charge. Organic dietary components, such as citrate, succinate, tartrate, glutamate, gluconate, and lactate,[23–26] enhance Al bioavailability. Luminal mucins regulate Al hydroxipolymerisation and thus impact its bioavailability.[27] Intestinal absorption of Al per se is very poor, below 1%.[28] In healthy human volunteers, the most recent estimates of fractional intestinal Al absorption were in the range of 0.06–0.1%.[29] Recently, in intensive care unit patients, the mean absorption of enteral Al from sucralfate was only 0.019%.[21] The total body burden of Al in healthy human subjects is approximately 30–50 mg, in flux between different systemic compartments. Following bone, the organ order of increased Al levels in exposed animals was the kidney > liver > testes > skeletal muscle > heart > brain. Al also occurs in the lower gastrointestinal tract and lymph nodes.[18] In rats, the passive and paracellular Al absorption occurs in the small intestine and more distally in the colon.[30] Once absorbed, it is mainly transported by transferrin at the sites left vacant by iron, and to a far less degree by albumin.

Inside the cell, Al is accumulated in the lysosome, nucleus, and chromatin but has been found in cytosole and mitochondria. More recently, after gastric

loading of Al chloride, selective concentration and precipitation of the Al salt was observed as nonsoluble form in enterocytes of the proximal intestine, localized in the apical part of the enterocytes. In addition, the precipitation in duodenal enterocytes allows the element absorbed as soluble form to be eliminated as an insoluble form along with the desquamation of the apoptotic enterocyte.[31]

IMMUNE EFFECTS OF ALUMINUM

Antigen Presentation

It is unlikely that Al adjuvants act via a toll-like receptor (TLR), like many microbial molecules, such as lipopolysaccharide (LPS) and bacterial DNA. Nevertheless, evidence suggests that Al compounds can directly activate antigen-presenting cells (APC). Al adjuvants had two direct effects on APC: enhanced uptake of antigens and increased interleukin (IL)-1 production that may explain enhanced antigen-specific T cell responses. This immune activation can operate through five potential pathways: (1) A much better proliferative response by autologous T cells was observed by pulsing human peripheral blood monocytes with aluminum hydroxide-absorbed tetanus toxoid than monocytes pulsed with soluble tetanus toxoid alone. This correlated with increased uptake of the pulsing agent and increased IL-1 secretion. (2) Al particles are <10 μm in diameter, thus they may be more efficiently taken up by phagocytosis than soluble antigens. Antigen internalization by dendritic cells is enhanced by Al adsorption and by the aggregate size of less then 10 micron in diameter.[32] (3) Alternatively, a more efficient uptake of soluble (desorbed) antigen can be enhanced by direct activation of APC by Al. Most recently, the desorption of Al adjuvant from the protein antigens was observed within hours.[33] (4) Al hydroxide increased the expression of MHC and several co-stimulatory molecules on peripheral blood monocytes, accompanied by increased expression of IL-4, IL-1, IL-6, and tumor necrosis factor (TNF).[34] In contrast, Rimaniol *et al*. demonstrated that peripheral blood mononuclear cells (PBMC)-derived macrophages could also be activated by Al hydroxide (endotoxin free) to become CD83/CD1a-positive DCs. These cells appear to have specifically upregulated MHC class II and CD86 without involving IL-4.[35] (5) In addition, intramuscular injection of Al adjuvants causes tissue necrosis. Recently, it was suggested that necrotic cells release a yet to be identified molecule that activates dendritic cells,[36] thus potentiating antigen presentation. Direct cytotoxicity of Al to the APC may cause bystander activation of dendritic cells. Endogenous mediators, such as interferons (IFN), IL-12, IL-15, TNF, and IL-1, have been proposed to activate DC and show adjuvant activity themselves or taking part in the activity of certain adjuvants.[37]

Humoral Immunity

Generation of maximal T cell responses requires B-cell antigen presentation and the differential expression of co-stimulatory molecules by B cells may affect polarization of naïve T cells to Th1 or Th2 phenotypes. Surprisingly, immunization with alum or alum/LPS-induced unregulated ICOS-B7RP-1 on antigen-specific T and B cells following Th1 induction, contrary to the original implication of this receptor-ligand pair in Th2 generation.[38]

The complement cascade is activated by Al hydroxide and complement plays an important role in B-cell response regulation. B cells and follicular dendritic cells have two distinct receptors, CD21 and CD35, respectively, for C3 and C4 products. CD21 forms a complex with CD19 on B cells, facilitating signal transduction via the membrane immunoglobulin receptor resulting in enhanced immune response. The CD35 receptor on follicular dendritic cells, on the other hand, binds immune complexes and retains these in undegraded form for several months, enabling the generation and maintenance of memory B cells. In summary, Al adjuvant, by activating the complement, enhances the humoral immune response by targeting antigens to B cells and follicular dendritic cells.[39]

Cellular Immunity

It is well documented that Al adjuvants selectively stimulate a type 2 immune response and do not induce cytotoxic T cell-mediated immunity. This mode of action is appropriate for vaccines against extracellular pathogens, bacterial exotoxins, and helminth parasites but inappropriate for vaccines against intracellular pathogens, such as viruses, mycobacteria, and certain protozoa. Strategies to modify the formulation of Al compounds to overcome the induced immune response of Th2 polarization toward Th1 activation have been recently described:[39]

1. Jankovic *et al*.[40] demonstrated that presentation of IL-12 on alum enhances its immunomodulatory effects, promoting humeral-specific antibodies and type 1 cytokine response. Because IL-12 was >98% adsorbed to alum prior to injection to the mice, it was suggested that the release of IL-12 over time may have increased its biological half-time. Moreover, IL-12 redirected murine immune responses to aluminum-phosphate–adsorbed antigen toward Th1 and $CD4^{+}$CTL responses.[41] The adsorbed antigen decreased the optimal dose of IL-12 required to enhance antigen immunogenicity and shift responses toward a Th1-like profile. Of note, other metals, mercury and rIL-12, were proven to deviate a classical Th2 toward Th1 response in murine mercury-induced autoimmunity.[5] It is worth mentioning that IL-12 is a cytokine secreted by dendritic cells,

macrophages, and B cells in response to bacteria, intracellular parasites, and viruses, and plays a pivotal role in driving the differentiation of naïve T cells toward the Th1 phenotype. This action is potentiated when adsorbed to Al. IL-12 overcomes the Th2 polarizing effect of Al compounds. Are such interactions occurring in the intestine of some CD predisposed individuals?

2. Synthetic CpG oligonucleotides, such as bacterial DNA, are potent inducers of IL-12, dendritic cell maturation, and Th1-type immune responses. Co-administering with alum and antigen results in a marked increase of antigen-specific antibody response of both IgG1 and IgG2a subclasses, in comparison with either CpG oligonucleotides alone or aluminum hydroxide alone, indicating a strong synergistic effect.[42] Alum-adsorbed CpG is as effective as Alum-adsorbed IL-12 for priming Th1 lymphocytes in cattle immunized with rickettsial antigen.[43] Moreover, Alum has a strong affinity for bacterial DNA.[44] The relationships between the human intestinal flora DNA or CpG elements and luminal Al compounds were not elaborated.
3. The classical alum-induced Th2 profile can be switched toward Th1 polarization by mixing it with γ-inulin, a polysaccharide, to form Algammulin.[45] It is a potent enhancer of the Th1 immune response pathway, boosting seroconversion rates and immunological memory, establishing protective antibody classes, and enhancing cell-mediated immunity.[46] Inulin, which is a natural constituent of many edible plants, increases minerals, such as calcium and magnesium absorption and its effects on Al absorption have not yet been studied.[47] It is a well-known prebiotic that affects human colonic luminal flora. The mutual coexistence of inulin, Al salts, microbiota, and colonic immune system in the human colon have not yet been explored.
4. As mentioned above, alum and alum/LPS immunization induced unregulated ICOS-B7RP-1 expression on antigen-specific T and B cells following Th1 and not Th2 induction.[38] Generation of antigen-committed Th1 or Th2 responses is alum dependent through differential co-stimulation in antigen-specific B cells that may subsequently influence T cell polarization.

Al compound composition affects its immune influence. Al hydroxide is more potent than Al phosphate adjuvant in Th1 immunodeviation toward a multiantigenic formulation.[48] Interestingly, a short-term exposure of a freshwater crayfish with aqueous Al impaired the ability of its hemocytes to recognize and/or remove bacteria from the circulation. Neutral pH aqueous Al impairs invertebrate immunity.[49] Most recently, fine particles that adsorbed LPS via bridging calcium cations induced marked proinflammatory signaling in primary human mononuclear phagocytes.[50] Specifically, caspase 1-dependent IL-1β and apoptosis were induced. The consequence of luminal Al salts

cohabitation with the human intestinal immune system and luminal microbiota is yet an enigma.

Granuloma Formation

Aluminum granuloma is a well-described phenomenon, noticed after intradermal vaccination and hyposensitization.[51–53] It may be formed intradermaly, in buccal cavity, muscle, breast, liver, brain, meninges, and lymph nodes. Pulmonary granulomatosis can be induced by Al.[54]

ALUMINUM AND THE HUMAN TERMINAL ILEUM

The first to describe exogenous pigment in human Peyer's patches were Shepherd *et al*. in 1987.[55] All normal and diseased samples of the small bowel of individuals above the age of 6 years and none of the younger ones were positive. On analysis, the pigmented Peyer's patches' macrophages contained Al and silicon, diffusely spread throughout the cytoplasm and around dilated submucosal lymphatics and in mesenteric lymph nodes. Two years later, Urbanski *et al*. documented black pigment within macrophages in the lamina propria and submucosa of the human Peyer's patches.[56] Most of the particles were predominantly Al and magnesium-rich silicates and considered of exogenous origin. Powell *et al*. extended our knowledge on the physicochemical structure of the pigments.[57] Laser scanning and electron microscopy showed macrophage phagolysosomes in the human gut-associated lymphoid tissue, loaded with three types of microparticles, one of them being aluminosilicates of less than 100–400 nm in length. They suggested this cellular pigment to derive from the environment, to be inert inorganic microparticles that in susceptible individuals cause chronic latent granulomatous inflammation.

ALUMINUM AND THE ANIMAL INTESTINAL INFLAMMATION

In animal experiments, dogs fed on a daily ration of finally divided sand or talcum powder developed intestinal inflammation with pronounced lymphedema and pathological features of regional enteritis.[58] A cluster of six lethal equine granulomatous enteritis cases linked to Al have been described by Fogarty *et al*.[59] Tissue Al concentrations in all horses were elevated in the affected intestine that presented many histological similarities to human CD. Chemical analysis demonstrated concentrated Al within intestinal wall microorganism suggesting microorganism–Al interaction associated with the equine condition.[15] Recently, we studied the effect of dietary Al in specific pathogen-free microbiota-induced colitis in IL-10 knockout mice model.[60] Increased Al-lactate concentration up to 200 μM in their drinking water stimulated T cell

proliferation and INF secretion by splenocytes. Al drinking worsened colitis documented by significantly increased colonic histological scores accompanying higher Al intake. Colonic strips IL-12 secretion increased with higher Al intake. Of note, higher dietary Al induced pink *E. coli* colonies as cultured on MacConkey agar plates suggesting Al to influence intestinal bacterial ecologic composition. This represents the first causal relationship between environmental Al stimulating intestinal and systemic immune responses *in vitro*, and enhancing colitis *in vivo*, in animal.

ALUMINUM AND CROHN'S DISEASE

A major contribution to the microparticles–CD association hypothesis has been reported by the Powell group in the United Kingdom[16,57,61,62] and Perl *et al*. forwarded the bacterial–Al interaction hypothesis in the etiology of CD.[15]

In the Western diet more than 10^{12} ultrafine particles are ingested per person every day[62] and those microparticles adsorb luminal constituents and are taken up by human intestinal lymphoid tissue. Based on the above information, Powell *et al*. studied the effects of microparticle (TiO(2)) on colonic biopsy specimens and PBMCs from IBD patients. Only when LPS adsorbed to Tio(2), and not each alone, was incubated with the two organs, a significant increase of IL-1 secretion occurred in the IBD patients.[63] Comparably, Al was shown to induce IL-1 secretion from human peripheral blood monocytes.[64] It can be concluded that ultrafine dietary particles are not immunogenically inert but may present an important adjunct in overcoming normal gut tolerance to endogenous luminal molecules. When studied on IBD lamina propria macrophages, the conjugate of LPS, calcium, and titanium dioxide induced IL-1β release and macrophage apoptosis above the controls.[65] Thus, endogenous or exogenous microparticles can aggravate the ongoing inflammation of IBD. Despite the fact that Al was not studied in the last two studies on IBD tissues, Al is known to induce IL-1 secretion from human peripheral blood monocytes and is an inducer of apoptosis.[64,66] Inorganic microparticles intake assessment in patients with CD showed no difference compared to controls in the United Kingdom.[62] If exposure to microparticles is associated with CD intestinal inflammation, then the excess intake as a problem was ruled out. After identification of low microparticle-containing food, the same group assessed the impact of a low-microparticle diet in CD. In a preliminary study, CD activity index improved significantly.[67] However, 4 years later the same group accomplished an adequately powered and carefully conducted dietary trial in active CD patients. There was no evidence that reducing microparticles intake led to remission in those patients.[68] Whether dietary microparticles may be involved in the initial triggering or, recurrence of CD in genetically susceptible subjects is a challenge for future investigations.

DISCUSSION

Despite the excitement about the genomics of CD, the major part played by environmental factors is now well recognized.[69] The chief suspects are microbiota and dietary constituents.[70,71] Among the potential dietary agents, none has yet emerged as a favorite. In the present review, we have summarized the literature on the microparticles' component of the diet, focusing on Al as a potential environmental factor in CD induction. This metal is widely distributed in the environment and the main exposure is by water and food entering directly to the gastrointestinal tract. Interestingly, urban areas are more Al contaminated and CD is more prevalent in the cities. CD incidence and Al exposure are increasing as a result of westernization of lifestyle, such as changes in diet and variations in exposure to pollution and industrial chemicals. As recently shown, CD patients do not consume more microparticles than the normal population, at least in the United Kingdom,[62] but Al compound's intestinal handling in CD has not yet been studied.

Concerning human absorption, Al is poorly absorbed but many luminal compounds influence bioavailability determined by its solubility and diffusibility. One such factor is intestinal mucin, which is altered in CD patients.[27,72] Al is absorbed along the gastrointestinal tract, which is the target organ for CD. In fact, once absorbed, it is transported by transferrin at the sites left vacant by iron.[73] Moreover, Al uptake is TfC2 genetically determined and increased Al uptake was observed in rich transferrin receptor cells.[74–76] Parallely, in CD, iron intake and iron stores are low and transferrin levels are high, potentially favoring Al absorption and cellular and systemic transport.[77–79]

From the genetic aspects, intestinal permeability of Al is genetically influenced and CD is genetically predetermined including genetically increased intestinal permeability.[74,75,80–83] In both, DNA damage occurs. In CD there is an increased DNA damage, and Al is a well-known metal that induces DNA helical transition and damage.[84–86]

The etiology for CD is unknown, but recent studies strongly suggest that an inappropriate or exaggerated immune response to normal constituents of the gut bacterial flora exists in CD.[69–71] Perl *et al*. extensively reviewed the data on Al–bacterial interaction.[15] An extended hypothesis elaborating on the immunological aspects shared between CD and Al immune effects is presented (TABLE 1). In CD, inflammatory signals are amplified and maintained as a result of an active cross-talk between immune and nonimmune cells. Endless numbers of such inflammatory molecules were described in CD.[87] Al alone, however, and Al-adsorbed biomolecules, inhabitants of the human intestinal lumen, induces many of them. The main immune phenomena occurring in CD are activation of mucosal $CD4^+$ T lymphocytes, dysregulated apoptosis, Th1 cell-derived cytokines; and IFN-γ, TNF-α, IL-6, IL-1β, and IL-2 secretion, orchestrated multiple immunoactive molecule that drive and maintain Th1 polarization, such as IL-12, IL-18, and osteopontin. In addition,

TABLE 1. Shared aspects between aluminum and Crohn's disease

Aluminum	Crohn's disease
Epidemiology	
Increased exposure in industrial societies	Increased prevalence in industrial areas
Genetic influence	
Genetic influence on Al intestinal permeability	Genetically increased intestinal permeability
Al induced pathology is genetically determined	CD is genetically determined
Induces DNA helical transition and damage	Increased DNA damage
Immunological aspects	
IL-12 overcomes the Al TH2 polarization	IL-12 induces TH_1 differentiation
Alum + IL-12 induce TH_1 response	A TH_1 class disease
Alum + cytokines improve TH_1 effectiveness	Increased TH_1 cytokine profile
Induces macrophage differentiation	Increased mature dendritic cells
Macrophage cytotoxicity is Al particle size dependent	Decreased macrophage function
Promote humeral immune response	Expanded B-cell population
Inflammatory profile	
Proinflammatory genes expression	Classical inflammatory state
Pro-oxidant activity	Increased oxidative stress and pro-oxidants
Proapoptotic	Dysregulated apoptosis
Induces stress-related gene expression	Increased HSP70, cox-2
Induces TNF-α release	TNF drives inflammation
Induces IL-6 release	Increased IL-6, IL-2r, MIP1-α
Activate NF-KB, HIF-1	Dysregulated NF-KB, activated HIF-1
Iron and transferring relationship	
Al compete with Fe on transferrin receptors	Decreased iron intake and body store
Increased Al uptake in rich transferrin receptors cells	Increased free transferring receptors
Tissue Al uptake is TfC_2 genetically determined	

in CD, increased maturation of dendritic cells, decreased macrophage function, and expanded B-cell population have been described.[87–92] On the same line, Al, which is a classical Th2 cytokine profile inducer, in the presence of IL-12, CpG, bacterial DNA or LPS, and other bacterially or dietary originated bioactive constituents, switches Th lymphocyte polarization toward Th1 phenotype.[38,40–45] Importantly enough, the human intestinal lumen is inundated with bacterial constituents and prebiotics, such as inulin. Moreover, CD mucosal inflammation is a major source for key cytokines, such as IL-12, IL-18, etc. that drive Th1 responses. Once adsorbed to Al, enhanced immune stimulation and more selective Th1 polarization is expected.

Immunologic, proinflammatory, apoptotic, and oxidative activities Al suite those aspects description in CD. In both, macrophage differentiation and maturations promoted humeral immune response and B-cell expansion, stress-related molecule induction, increased levels of TNF, IL-6, IL-1β, IL-2, and hypoxia-inducible factor 1 (HIF-1), NF-κB activation, increased oxidative stress, and pro-oxidants presence occurs. In fact, Al is a definite promoter of oxidative stress[93] and increased oxidative stress was described in CD.[94]

Intestinal mucins genotype and phenotype are aberrant in CD.[95] One wonders if Al precipitation of mucin, changing its rheological properties or the luminal mucins regulation of Al hydroxypolymerization, affecting its bioavailability,[27,96] have a role in Al–CD interplay.

In summary, numerous aspects of Al metabolism, starting from its human exposure, absorption, and gastrointestinal and cellular distribution, going through its immune effects on macrophage activation and antigen presentation, humoral and cellular immunity, granuloma formation, its presence in the human terminal ileum and its role in intestinal inflammation induction, the Al-induced proinflammatory cytokine secretion in human tissues, its Th1 phenotype swift when adsorbed to bacterial, dietary, luminal, and intestinal bioactive constituents, the cross-talk with intestinal mucins, and effects on bacterial flora, the proinflammatory and oxidative properties, induction of DNA damage and apoptosis regulator, vacant transferring receptor affinity in the face of iron depletion, all have parallel and shared domains in human CD. Combination of the hypothesis of Al–bacterial interaction,[15] the dietary microparticle association with CD,[16,61] the most recent observations on colitis induction,[60] and the present review on multiple immunopathogenic and harmful inflammatory aspects of Al, put Al as a potential prime environmental factor candidate for CD induction and maintenance.

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