

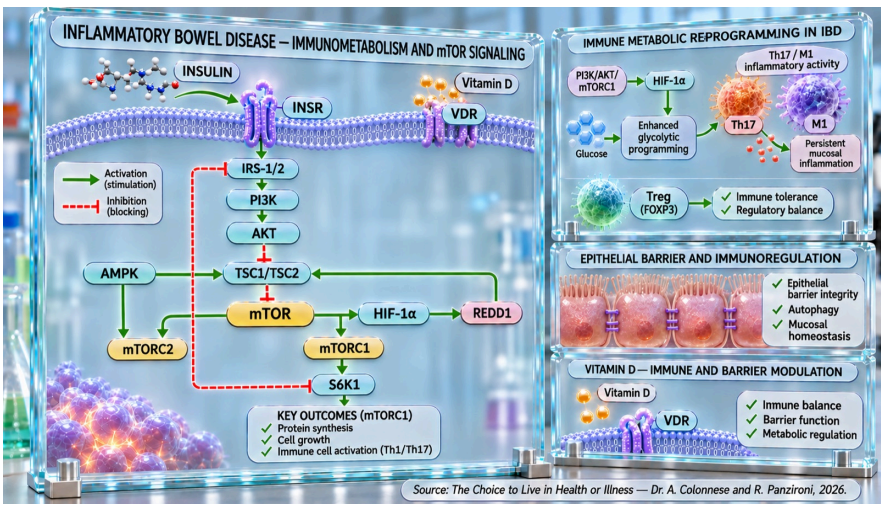
The Choice to Live in Health or Illness

From glycemic variability to insulin resistance
The vicious cycle of modern degenerative diseases

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Chapter 10 – IBD



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10.1 – Epidemiology of IBD

Inflammatory Bowel Diseases, known by the acronym IBD, represent a group of conditions characterized by persistent inflammation of the gastrointestinal tract. Within this group, two main forms are distinguished: Crohn's disease and ulcerative colitis. While they share several clinical and immuno-

pathogenetic aspects (the way the immune system participates in the development of a disease), the two conditions differ in the location of the lesions and the depth of the inflammation: ulcerative colitis exclusively affects the mucosa of the colon and rectum (the terminal segments of the intestine), while Crohn's disease can involve any segment of the digestive tract, from the mouth to the anus, with inflammation that can extend through the entire thickness of the intestinal wall.

In the European landscape, IBD affects approximately 0.2% of the population, amounting to over 2.5–3 million individuals: these are therefore chronic conditions with a growing health impact, also in terms of social costs and quality of life.

The onset occurs most frequently in young adulthood, with a peak between 15 and 40 years of age, a period in which metabolism and the immune system are in full activity. However, epidemiological studies report a second, rarer peak of incidence around the age of 60, suggesting that environmental and immune factors may contribute differently to the onset based on age.

Regarding gender, the differences are not marked, but some international data highlight slight variations: Crohn's disease shows a modest female prevalence, while ulcerative colitis appears to be distributed more evenly between men and women.

IBD, therefore, are configured as chronic diseases with a relapsing course, meaning they alternate periods of well-being with moments in which the pathological process reactivates; they mainly affect young individuals in the prime of their pro-

ductive and family lives, with a significant impact not only on a clinical level but also on a psychological and social one. Understanding their etiology, the underlying inflammatory mechanisms, and the factors that modulate their course represents the first step toward addressing them with a modern, integrated approach based on the physiology of the human body.

10.2 – T-cell imbalance

Inflammatory Bowel Diseases (IBD) represent a condition in which the intestine progressively loses the ability to maintain a stable immune balance. At a microscopic level, the intestinal mucosa becomes the stage for a constant conflict between immune system cells that should cooperate to preserve tissue integrity. Among the key players in this dynamic are T helper 17 cells (Th17, a class of effector T cells) and regulatory T cells (Treg), two populations derived from $CD4^+$ T cells with profoundly opposite yet complementary functions: the former promote inflammation, while the latter promote the suppression and control of the immune response.

Under physiological conditions, these two forces maintain a dynamic balance that ensures tolerance toward the gut microbiota and prevents autoimmune responses. In IBD, however, this balance is broken: Th17 cells increase excessively, and Treg cells, while retaining their ability to regulate inflammation, prove numerically and locally insufficient to counteract it **(Yan et al., 2020)**[1].

The inflamed intestinal mucosa shows an increase in $CD4^+$ CD25 $FOXP3^+$ T helper cells, but this expansion proves inadequate relative to the intensity of the inflammatory response. It is as if a fire brigade, while functional, were too small in number to extinguish a fire that is already out of control. Histological studies have shown that during active phases of the disease, Treg cells decrease in peripheral blood, suggesting their recruitment to sites of intestinal inflammation, where, however, they fail to restore effective homeostasis **(Maul et al., 2005)**[2].

Beyond intracellular mechanisms, metabolism and diet also profoundly influence this balance. Excessive caloric intake, for example, stimulates the mTOR pathway and the differentiation of Th17 cells, while caloric restriction or the activation of the AMPK pathway (an energy-sensing enzyme present in our cells and fundamental for energy metabolism) promotes the formation of Treg cells without compromising their function. This suggests that targeted nutritional interventions could complement pharmacological therapies in restoring immune tolerance and reducing intestinal inflammation **(Zhang et al., 2024)**[3].

In summary, IBD can be understood as the result of a broken immune balance, in which the inflammatory drive of Th17 cells and the regulatory response of Treg cells lose their harmony; the therapeutic goal is not only to suppress inflammation but to reconcile these two forces, restoring to the intes-

tine its natural ability to distinguish what it must tolerate from what it must fight.

10.3 – Metabolic alterations: insulin pathway and insulin resistance

Inflammatory Bowel Diseases (IBD), however, are not limited to affecting the digestive system: they represent a systemic condition capable of profoundly altering the metabolism and functioning of the entire organism. The chronic inflammation that characterizes these pathologies, such as ulcerative colitis and Crohn's disease, does not remain confined to the intestinal mucosa but propagates as a constant signal that involves the vascular endothelium (the inner lining of blood vessels), the autonomic nervous system, and even glucose and lipid metabolism. In recent years, numerous studies have highlighted an increasingly close link between IBD and insulin resistance, opening new perspectives on how chronic inflammation can interfere with the body's energy regulation.

In a clinical study conducted on patients with Crohn's disease, it was observed that, even in the absence of diabetes, these subjects exhibit significantly higher plasma insulin levels compared to healthy controls. This hyperinsulinemia, accompanied by an increase in the HOMA-IR index (an index used to estimate insulin resistance and pancreatic β-cell function) and the insulin resistance index, is a phenomenon that forces pancreatic β-cells into more intense compensatory ac-

tivity to maintain normal glucose tolerance **(Bregenzer et al., 2006)**[6].

This state of metabolic stress is not limited to the endocrine level but also involves vascular function. Patients with IBD, in fact, show an increase in pulse wave velocity (PWV), a reliable index of arterial stiffness and an early marker of endothelial dysfunction (altered functioning of the inner lining of blood vessels). Even in the absence of traditional cardiovascular risk factors, such as hypertension or dyslipidemia, arterial stiffness is increased and correlates positively with disease duration and plasma insulin and HOMA-IR levels. This suggests that chronic inflammation and insulin resistance cooperate in compromising vascular elasticity, predisposing patients to premature cardiovascular risk **(Korkmaz et al., 2014)**[7].

Other studies have highlighted that the metabolic impact of IBD is also reflected in cardiac physiology: in patients with ulcerative colitis and Crohn's disease, a longer corrected QT interval dispersion (QTcd) has been found compared to healthy subjects. In short, this is an anomaly of the electrical processes occurring in biological cells and tissues, particularly in the heart, which increases the risk of ventricular arrhythmias. This prolongation of the QTcd is associated with higher insulin and HOMA-IR values, indicating that insulin resistance may also contribute to modulating the heart's electrical function through alterations in systemic inflammatory processes **(Yorulmaz et al., 2013)**[8].

At an epidemiological level, the relationship between insulin dysfunction and the risk of developing IBD has been further confirmed by a recent prospective study conducted on the UK Biobank, which involved over 327,000 participants: the triglyceride-glucose (TyG) index, a surrogate biomarker for insulin resistance, was significantly associated with an increased risk of ulcerative colitis and Crohn's disease; for every unit increase in the TyG index, the risk of developing IBD grew by 14.3% and 13.8%, respectively. Individuals with the highest TyG values had a risk of disease up to 28% higher than subjects with normal values **(Zhang et al., 2025)**[9]. This association persisted even after adjusting the data for genetic and lifestyle factors, suggesting that metabolic alterations may independently contribute to the etiology of IBD.

Understanding these studies means moving beyond the traditional view of IBD as exclusively gastrointestinal diseases. It means recognizing that, behind abdominal pain and diarrhea, there lies a complex network of inflammatory, hormonal, and metabolic signals that involves the entire organism. And perhaps, intervening in this network by acting on the metabolic factors that determine an alteration of the insulin pathway could represent one of the most promising keys to restoring the lost balance.

10.4 – mTOR as a central node

It is precisely within this network of metabolic and inflammatory signals that one of the main points of convergence be-

tween alterations in the insulin pathway and the immune dysregulation characteristic of IBD emerges: mTOR. Located downstream of the PI3K/AKT pathway, mTOR is not merely an effector of insulin signaling, but a true metabolic sensor capable of integrating nutrient availability, growth signals, cytokines, and stress conditions. Its activity can therefore translate a metabolic alteration into a different cellular and immune response, creating a direct link between the insulin resistance profile described above and the mechanisms that sustain intestinal inflammation.

In 2024, some researchers described mTOR as an important metabolic regulator capable of orienting the behavior of immune cells based on the nutrients and cytokines present in the microenvironment. Its activity contributes in particular to determining the fate of T lymphocytes, influencing the balance between effector and regulatory populations. In IBD, an alteration of this control can therefore favor a more pro-inflammatory response, supporting the differentiation and activity of Th17 cells at the expense of the regulatory mechanisms necessary to contain inflammation of the intestinal mucosa **(Zhang et al., 2024)**[3].

This relationship becomes particularly important considering that Th17 cells produce cytokines such as IL-17, IL-21, and IL-22, which are capable of profoundly modifying the intestinal inflammatory microenvironment. When mTOR activity favors metabolic programs associated with the effector response, naïve T cells (T lymphocytes not yet activated by their

specific antigen) can be more oriented toward pro-inflammatory phenotypes; conversely, the reduction of mTOR signaling can favor the development of Treg cells, which are responsible for controlling the immune response and maintaining tolerance.

An experimental demonstration of this balance emerges from the work of some researchers, in which the use of the mTOR inhibitor INK128 in animal models of colitis resulted in a significant attenuation of intestinal inflammation. The treatment was associated with a decrease in Th1 and Th17 populations and, simultaneously, an increase in the Treg component. The treated animals also showed better colon integrity and less weight loss, indicating how intervention in mTOR signaling can translate into concrete changes in both the immune response and intestinal damage **(Shi et al., 2019)**[4].

Consistent results were also reported in 2016, evaluating the effects of mTOR inhibition using AZD8055 (a substance that directly inhibits mTOR) in experimental models of colitis. In this case as well, the treatment reduced inflammation and the presence of Th1 and Th17 populations, while simultaneously favoring the expansion of Tregs and the increase of IL-10, an important anti-inflammatory cytokine associated with the regulatory response. mTOR inhibition therefore shifted the immune balance from a predominantly effector and pro-inflammatory condition toward a more regulatory profile **(Hu et al., 2016)**[5].

The contribution of mTOR does not end with adaptive immunity: the epithelium (the tissue that lines and protects the body's surfaces) of the colon, far from being a passive barrier, "talks" to the immune system by modulating the cytokine profile of the tissue based on its differentiation state, a process that depends precisely on mTOR signaling. When this circuit is altered, the epithelium promotes hyperplasia and pro-inflammatory recruitment, fueling colitis from within the tissue itself **(Lyons et al., 2018)[13].**

This same metabolic "control unit" governs the language choice of T cells: when mTOR is active, naive T cells take the effector pathways (Th1/Th2/Th17); when the signal is dampened, the regulatory pathway prevails and Tregs and $Foxp3^{+}$ cells appear, which are better suited to restoring tolerance. It is an immunological switch that transforms a dissonant choir into more orderly music **(Delgoffe et al., 2009)[11]**.

In another study from 2013, mTOR was defined as a metabolic sensor that integrates nutrients, cytokines, and stress and decides the fate of intestinal and immune system cells. When its natural brake, PTEN (a protein that slows down the PI3K/AKT pathway), is lowered, the PI3K/AKT/mTOR insulin pathway becomes hyperactivated in T cells and mucosal lymphocytes in Crohn's disease, supporting proliferation, survival, and inflammatory mediators as if one were keeping their foot on the accelerator on a road already crowded with inflammation **(Long et al., 2013)[10]**.

It is no coincidence that, under controlled ex vivo conditions, rapamycin (a drug that primarily inhibits mTOR activity) allows for the expansion of human Tregs while maintaining their phenotype and suppressive function, a practical clue as to how modulating mTOR can rebalance the regulatory arm in contexts of chronic hyper-activation **(Battaglia et al., 2012)**[12].

It is therefore not surprising that pharmacological strategies against mTOR are emerging, as we will see in the next paragraph, as concrete avenues in IBD: preclinical data show reductions in cytokines, restoration of the barrier, and rebalancing of Th17/Treg, while clinical practice still requires larger studies to define long-term efficacy and safety **(Lashgari et al., 2021)**[14]; **(Afzal et al., 2022)**[15].

Overall, the evidence analyzed outlines a close interaction in IBD between metabolic alterations, the insulin pathway, and immune dysregulation. In this scenario, mTOR emerges as a central node capable of integrating signals from the PI3K/AKT pathway with the metabolic programs that regulate T lymphocyte activity. Its excessive activation can favor proliferation, pro-inflammatory responses, and effector polarization, contributing to the Th17/Treg imbalance and the persistence of intestinal inflammation. Conversely, proper modulation of mTOR can support autophagy, the regulatory function of Tregs, and epithelial homeostasis, highlighting the importance of the balance of this network in the pathophysiology of IBD.

10.5 – mTOR inhibitors

The inhibition of mTOR currently represents one of the most promising avenues in therapeutic research for inflammatory bowel disease (IBD). While in the early stages the study of mTOR was limited to its role as a regulator of cell growth, we now know that this metabolic sensor is a true “immune switch”: it controls T-cell differentiation, cytokine production, and the autophagy processes that maintain the health of the intestinal mucosa. Modulating mTOR does not mean suppressing the immune system, but rather restoring its balance, bringing it back from a state of pathological hyperactivation to a physiological equilibrium.

One of the first drugs evaluated in this context was everolimus (a drug derived from rapamycin), a second-generation selective mTORC1 inhibitor. In a mouse model of chronic IL-10$^{-/-}$ colitis, which reproduces the immunopathological characteristics of human Crohn's disease, oral administration of everolimus significantly reduced the severity of colitis. The treatment resulted in a decrease in CD4^{+} T cells in the lamina propria (the layer of tissue beneath the mucosa) and reduced production of interferon-γ (a protein naturally produced by cells to stimulate the immune response), attenuating the aberrant Th1 response typical of the disease **(Matsuda et al., 2007)**[16].

Its structural analog, sirolimus (rapamycin), has also shown extraordinary results in experimental models and early human clinical cases: in a mouse study of TNBS-induced colitis (a

chemical compound used in the laboratory as a reagent), sirolimus reduced the levels of TNF-α, IL-6, and IL-17 (pro-inflammatory molecules for immune system communication) and simultaneously increased TGF-β (a signaling molecule that regulates the immune response) and regulatory T cells, thereby correcting the Th17/Treg imbalance that characterizes the inflamed mucosa **(Yin et al., 2013)**[17].

The efficacy of sirolimus has also been confirmed in pediatric populations: in a cohort of children suffering from refractory IBD—that is, those who do not respond to conventional medical therapies—nearly half of the patients with ulcerative colitis and all those with Crohn's achieved clinical remission or mucosal healing, with a reduction in the use of corticosteroids and biologics and without serious adverse events **(Mutalib et al., 2014)**[18]. These results, while preliminary, indicate that sirolimus can act as a rescue therapy in resistant forms, selectively modulating lymphocyte proliferation and promoting protective autophagy.

Regarding natural molecules, several plant-derived substances show the ability to inhibit the PI3K/AKT/mTOR pathway, restoring immune homeostasis and epithelial integrity. Rhein, an organic compound extracted from *Rheum palmatum* (a medicinal plant known as Chinese rhubarb), reduces the pro-inflammatory cytokines TNF-α, IL-6, and IL-1β and suppresses the activation of PI3K, AKT, and mTOR, while simultaneously modulating the gut microbiota and promoting the expansion of beneficial bacteria **(Dong et al., 2022)**[19]. A similar

effect has been observed for glaucocalyxin A, a compound derived from *Isodon japonicus* (an Asian plant of the Lamiaceae family), which attenuates ulcerative colitis by inhibiting AKT and mTOR, with a reduction in inflammatory mediators and histological improvement **(Zhou et al., 2025)**[20].

Another compound of interest is moringine, an organic compound extracted from *Moringa oleifera* (a plant used as food and in herbal tradition), capable of acting simultaneously on multiple pathways: it activates antioxidant factors, suppresses the PI3K/AKT/mTOR insulin pathway, and protects the mucosal barrier from oxidative inflammation **(Zhang et al., 2024)**[21]. Triptolide, a compound derived from *Tripterygium wilfordii* (a medicinal plant native to East Asia), also acts on the mTOR pathway by promoting the repolarization of macrophages from the pro-inflammatory M1 phenotype to the reparative M2 phenotype, thereby reducing the production of TNF-α and IL-6 and promoting IL-10 **(Zhu et al., 2022)**[22].

All these approaches, both pharmacological and natural, converge on a key concept: mTOR is the meeting point between metabolism, immunity, and tissue regeneration. Its targeted inhibition does not act as a suppression, but as a form of cellular "re-education." By restoring autophagy, reducing effector polarization, and supporting the epithelial barrier, mTOR inhibitors offer an integrated therapeutic perspective capable of extinguishing chronic inflammation at the root, rather than merely containing the symptoms. In this sense, mTOR becomes not only a pharmacological target but the sym-

bol of a paradigm shift in the treatment of IBD: from damage control to the reconstruction of balance.

10.6 – mTOR, HIF-1α, and metabolic reprogramming of immune system cells

In inflammatory bowel diseases, and particularly in ulcerative colitis, mTOR activation can support HIF-1α expression, profoundly transforming the metabolism of immune cells. mTOR functions as a sensor of energy and nutritional availability and, when it remains persistently active, it favors metabolic programs oriented toward glycolysis. HIF-1α represents one of the central effectors of this response: by increasing the expression of glycolytic transporters and enzymes, it allows activated immune cells to rapidly produce the energy and metabolic intermediates necessary for the inflammatory response. In the intestinal context, this axis can promote the polarization of macrophages toward the M1 phenotype and modify the balance between Th17 and Treg lymphocytes, contributing to the maintenance of mucosal inflammation.

This view is part of a broader framework of immunometabolism:

Effector Th cells and inflammatory innate cells thrive on high glycolysis (a fundamental metabolic process that breaks down glucose to produce energy) and mTORC1/HIF-1α; Treg cells, on the other hand, prefer lipid oxidation and metabolic conditions that reduce the cell's ability to activate growth processes, orienting it toward a state of conservation. Intervening

on these metabolic nodes, primarily mTOR, allows for the precise remodeling of the response, going beyond the immunosuppression that broadly affects all components of the immune response, both innate and adaptive, and moving toward therapies targeted at cellular metabolism **(Bittencourt et al., 2021)**[23].

A particularly direct demonstration was provided by some researchers in 2024: using a co-culture consisting of HT-29 intestinal epithelial cells and human $CD4^+$ T lymphocytes exposed to TNF-α, the authors directly manipulated mTOR expression. The increase in mTOR led to an increase in HIF-1α, glycolysis, and the proportion of Th17 cells, accompanied by a reduction in Treg cells and an increase in pro-inflammatory mediators. Conversely, silencing mTOR reduced HIF-1α, glycolysis, and Th17 differentiation, rebalancing the response toward a more regulatory phenotype. The study therefore directly demonstrates the sequence mTOR → HIF-1α → glycolysis → Th17/Treg imbalance → inflammation in ulcerative colitis **(Wang et al., 2024)**[24].

A second particularly significant contribution was provided in 2021, studying macrophage polarization in DSS-induced colitis (a substance used experimentally to induce colitis). Treatment with dioscin (a natural compound belonging to steroidal saponins) inhibited the mTORC1/HIF-1α axis, reducing aerobic glycolysis and the polarization of macrophages toward the pro-inflammatory M1 phenotype; simultaneously, the oxidative metabolism associated with M2 macrophages

was favored. The causal importance of mTORC1 was confirmed using leucine, an mTORC1 agonist, which attenuated the effects of dioscin and reduced its benefit on colitis. This work therefore identifies the mTORC1 → HIF-1α → glycolysis → M1 axis as an important immunometabolic mechanism of intestinal disease **(Wu et al., 2021)**[25].

Further evidence was obtained in 2025 by studying the metabolism of regulatory T cells in a mouse model of DSS-induced ulcerative colitis. In mice with colitis, both glycolytic metabolism and the distribution of Treg populations were altered. Treatment with Astragalus polysaccharides (a medicinal plant of the Fabaceae family) reduced the activation of the mTOR/HIF-1α pathway, decreased glycolysis, and favored the recovery of regulatory T cells, accompanied by a reduction in pro-inflammatory cytokines. The work therefore suggests that the persistent activation of this pathway can compromise Treg homeostasis through pathological glycolytic reprogramming **(Liu et al., 2025)**[26].

Even more recent confirmation comes from a study published in 2026, which analyzed the role of artesunate (a drug derived from artemisinin used primarily against malaria) in DSS-induced colitis. The authors demonstrated that the drug reduces M1 macrophage polarization and macrophage infiltration through the inhibition of mTORC1/HIF-1α signaling. The use of leucine as an mTORC1 agonist allowed for the functional confirmation of the pathway's involvement. Furthermore, target identification experiments indicated INSR as an up-

stream component: artesunate modulated INSR and consequently reduced mTORC1, HIF-1α, and the glycolysis associated with the M1 phenotype. The sequence INSR → mTORC1 → HIF-1α → glycolysis → M1 macrophage → intestinal inflammation is thus outlined **(Huang et al., 2026)**[27].

Finally, another 2026 study further strengthened this model using an in vivo and in vitro approach (two different ways of conducting scientific research): in the colon of mice with DSS-induced colitis, PI3K, AKT, mTOR, and HIF-1α were increased; the same profile was observed in RAW264.7 macrophages (mouse macrophage-like cells used as a model) stimulated with LPS (a component of Gram-negative bacteria capable of activating an inflammatory response). The experimental treatment progressively reduced the activation of the PI3K/AKT/mTOR pathway and, in parallel, the expression of HIF-1α, decreasing M1 macrophage markers and increasing M2 markers. The authors therefore identified HIF-1α as a downstream target of the PI3K–AKT–mTOR cascade, linking the activation of this pathway to the pro-inflammatory polarization of macrophages in ulcerative colitis **(Li et al., 2026)**[28].

Taken together, these findings outline a coherent model in which persistent mTOR activation supports HIF-1α and glycolysis, modifying the behavior of the main immune populations involved in IBD. In macrophages, the mTOR–HIF-1α axis favors M1 polarization and the production of pro-inflammatory mediators; in T lymphocytes, however, it can shift the balance toward Th17 cells at the expense of Tregs. In this way, an origi-

nally metabolic signal is converted into an immune program capable of maintaining intestinal inflammation. The overall sequence can therefore be summarized as PI3K/AKT/mTORC1 activation → increase in HIF-1α → increase in glycolysis → M1 polarization → production of pro-inflammatory cytokines → Th17 and relative reduction of Tregs → persistence of intestinal mucosal inflammation.

10.7 – Vitamin D as an immuno-metabolic modulator

In IBD, vitamin D acts like a silent "orchestra conductor": it makes no noise, but when it is missing, the entire immune symphony becomes discordant. Low levels of this vitamin are more frequently associated with active disease and flare-ups: in a large review of over eight thousand patients, those with vitamin D deficiency had a higher probability of clinical activity, mucosal inflammation, and relapses, as well as a poorer quality of life. In simple terms: when the tank is empty, the intestine loses part of its ability to "tolerate" and becomes inflamed more easily **(Gubatan et al., 2019)**[29].

This link is not theoretical: in real-world clinical cohorts, deficiency is very common and correlates with activity indices and inflammatory markers: in a hospital case series, a cut-off of approximately 27.5 ng/mL (threshold value) better discriminated patients in remission from those in the active phase, suggesting a pragmatic threshold level for clinical monitoring; those who were supplemented showed significantly higher

serum values and a more favorable clinical course **(Hausmann et al., 2019)**[30].

In parallel, a prospective cohort of Crohn's patients followed for three years showed an inverse association between vitamin D and C-reactive protein (a protein produced by the liver in response to inflammatory processes): the lower the vitamin D, the higher the systemic inflammation and the greater the probability of clinically active disease **(Alrefai et al., 2017)**[31].

Meta-analyses confirm the picture: in patients with Crohn's, vitamin D levels are on average lower than in healthy individuals, more than half present with vitamin D deficiency, and as clinical severity increases, values drop further: it is like watching the reserve fuel drop just when the engine—the intestine—is under the most strain **(Sadeghian et al., 2016)**[32].

A meta-analysis conducted on 18 randomized clinical trials, comprising a total of 908 patients with IBD, evaluated the efficacy of vitamin D supplementation: the treatment significantly increased circulating levels of 25(OH)D3 and resulted in a reduction of the relapse rate compared to controls, without significantly increasing adverse events. The authors concluded that vitamin D can represent a useful adjunctive treatment in IBD, especially to correct vitamin deficiency and contribute to the control of relapses **(Li et al., 2018)**[33].

The mechanisms are consistent with what has been observed clinically: through its receptor (VDR), vitamin D reduces IL-6/IL-17/TNF-α, promotes IL-10, supports Tregs, and

strengthens the "hinges" of tight junctions (connections between intestinal cells that regulate the passage of substances and protect the intestinal barrier), such as the protein occludin, limiting bacterial translocation and inflammatory reactivation. In other words, it improves both the "border control" of the barrier and the education of immune cells, with repercussions on the gut microbiota and the response to therapies **(Wu et al., 2022)**[34].

On a practical level, small interventional studies suggest a tangible clinical benefit: in a pilot study on mild-to-moderate Crohn's, supplementing vitamin D up to 5,000 IU/day for 24 weeks brought its values from ~16 to ~45 ng/mL and reduced the CDAI (Crohn's Disease Activity Index) by over one hundred points, with a perceived improvement in quality of life; in everyday terms, refilling the tank coincided with a "quieter" intestine **(Yang et al., 2013)**[35].

Consistently, in a Chinese cross-sectional study, vitamin D levels dropped progressively from remission to severe forms in both ulcerative colitis and Crohn's disease, reinforcing the rationale for measuring and correcting it throughout the course of care **(Zhao et al., 2019)**[36].

Vitamin D, therefore, in simple words, helps the intestine to "recognize friends," keeps the barrier firm, and dampens the excesses of the immune system. Monitoring it and correcting its deficiency does not replace underlying therapies, but it can make the environment less favorable to flare-ups and more receptive to treatments.

In conclusion, this vitamin acts as a universal mediator of immune and metabolic balance; in fact, as we saw in chapter 6 dedicated to the immune system, through the modulation of mTOR, it reduces the production of inflammatory mediators and limits the abnormal proliferation of effector T cells and stimulates the production of regulatory T cells, processes central to the pathogenesis of the disease. This regulatory effect promotes better control of the immune response, preventing autoimmune aggression against tissues.

10.8 – Conclusions

Taken together, the scientific evidence analyzed outlines Inflammatory Bowel Diseases (IBD) as conditions in which inflammation, metabolism, and immune regulation are deeply interconnected. Crohn's disease and ulcerative colitis, while differing in the location and extent of lesions, share a chronic and relapsing inflammatory condition that does not remain confined to the intestine but can involve the entire organism.

The first step concerns the loss of immune balance in the intestinal mucosa. Research documents an imbalance between Th17 cells, which promote inflammation, and Treg cells, which are responsible for immunological tolerance. In IBD, the expansion of Th17 cells is not adequately compensated by Treg cells, which are insufficient relative to the intensity of the inflammatory response. This balance is also closely linked to the cellular metabolic state: conditions that stimulate mTOR favor effector programs, while the activation of AMPK and condi-

tions of lower energy availability can support the regulatory compartment.

Associated with this picture are alterations in insulin metabolism: particularly significant is the prospective data showing that higher values of the TyG index are associated with a greater future risk of both ulcerative colitis and Crohn's disease, reinforcing the hypothesis that metabolic dysfunction may precede and contribute to the pathological terrain of IBD.

It is at this point that mTOR, located downstream of PI3K/AKT, emerges as a convergence node between insulin metabolism and immunity. Its excessive activation can favor Th1 and Th17 cells, cell proliferation, and proinflammatory signals, while its reduction favors Treg cells, FOXP3, autophagy, and epithelial homeostasis. Consistently, experimental inhibition of mTOR using AZD8055 and INK128 has reduced intestinal inflammation and rebalanced the ratio between effector and regulatory cells.

Studies on other mTOR inhibitors also reinforce this model: everolimus and sirolimus have reduced inflammatory mediators and favored Treg cells, with preliminary results also seen in refractory pediatric IBD. Natural compounds such as Rhein, glaucocalyxin A, moringin, and triptolide have also experimentally shown the ability to interfere with PI3K/AKT/mTOR, modulating inflammation, macrophages, and the intestinal barrier.

The next step involves HIF-1α. The evidence reconstructs a sequence in which the persistent activation of PI3K/AKT/mTOR

supports HIF-1α and glycolysis, favoring the M1 phenotype in macrophages and Th17 expansion in lymphocytes at the expense of Treg cells. Experimental studies have directly demonstrated that reducing mTOR/HIF-1α attenuates these metabolic and inflammatory programs, thus outlining the axis PI3K/AKT/mTORC1 → HIF-1α → glycolysis → M1/Th17 → relative reduction of Treg cells → persistence of intestinal inflammation.

Finally, vitamin D emerges as a modulator of the immunometabolic balance and the intestinal barrier. Its deficiency is associated with greater activity, inflammation, and risk of relapse, while supplementation has shown benefits on vitamin status and, in some studies, on the clinical course. Overall, IBD therefore emerges as a group of diseases in which metabolic dysfunction, insulin pathways, mTOR, HIF-1α, and immune cell reprogramming converge in the maintenance of inflammation, identifying immunometabolism as a central interpretive key to the disease.

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