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REVIEW

The Role of AMPK Signaling in Ulcerative Colitis

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Abstract: Ulcerative colitis (UC) is a chronic non-specific inflammatory bowel disease characterized by inflammation and ulcer formation of the intestinal mucosa. Due to its high recurrence rate, prolonged course, limited curative options, and significant impact on patients' quality of life, along with a notable potential for malignant transformation, UC is designated as a refractory global health challenge by the World Health Organization (WHO). The elucidation of the pathogenesis and therapeutic strategies for UC requires further in-depth investigation. AMP-activated protein kinase (AMPK) serves as a central regulator of cellular energy metabolic homeostasis. Emerging evidence indicates that interventions involving traditional Chinese medicine (TCM) components, as well as other pharmacological measures, exert beneficial effects on the intestinal mucosal inflammation and epithelial barrier dysfunction in UC by modulating AMPK signaling, thereby influencing biological processes such as cellular autophagy, apoptosis, inflammatory responses, macrophage polarization, and NLRP3 inflammasome-mediated pyroptosis. The role of AMPK in UC is of significant importance. This manuscript provides a comprehensive overview of the mechanisms through which AMPK is involved in UC, as well as a compilation of pharmacological agents capable of activating the AMPK signaling pathway within the context of UC. The primary objective is to facilitate a deeper comprehension of the pivotal role of AMPK in UC among researchers and clinical practitioners, thereby advancing the identification of novel therapeutic targets for interventions in UC.

Keywords: ulcerative colitis, AMPK, colitis-associated biological processes, traditional Chinese medicine monomers

Introduction

Ulcerative colitis (UC) is a chronic non-specific inflammatory bowel disease (IBD) characterized by chronic inflammation and ulcer formation of the intestinal mucosa. It presents clinically with symptoms such as abdominal pain, diarrhea, and mucous bloody stools. The disease course typically exhibits a chronic, persistent, and recurrent nature.[1] With changes in lifestyle and dietary patterns, the incidence of UC among Asian populations has been steadily increasing.[2] It is generally believed that its pathogenesis is associated with genetic predisposition, environmental factors, luminal factors, and mucosal immune dysregulation.[3] The therapeutic drugs for UC mainly include aminosalicylates, corticosteroids, biologics (such as infliximab), JAK inhibitors, and calcineurin inhibitors. Surgical intervention may be considered for refractory cases of the disease.[4] Nevertheless, the clinical efficacy of these treatments is currently unsatisfactory, with potential long-term side effects, and a propensity for relapse upon discontinuation. Therefore, in-depth research into the pathogenesis, therapeutic methods, and novel treatment drugs and strategies for UC from an integrative perspective of traditional Chinese and Western medicine is highly necessary.

Adenosine monophosphate-activated protein kinase, AMPK, is a pivotal energy sensor and regulator within cells. It functions to perceive alterations in cellular energy status and elicits responses to maintain a balance between energy generation and expenditure by regulating various metabolic and immune-related activities. Its substrates encompass multiple key enzymes and transcriptional regulatory factors involved in cellular growth, proliferation, metabolism, and immune modulation processes.[5] Evidence suggests that aberrant expression of AMPK plays a crucial role in the occurrence and progression of UC. For instance, the modulation of AMPK has the potential to influence cellular

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autophagy, thereby ameliorating intestinal mucosal immunity, inflammation, oxidative stress, and microbiota homeostasis. This modulation contributes to the preservation of the normal function of the intestinal mucosal barrier, thus emerging as a pivotal approach for effectively preventing and treating UC.[6] This process is regulated by a variety of proteins and signaling pathways. When the organism is stimulated by factors such as infection, inflammation, and endoplasmic reticulum stress, AMPK is activated and mammalian target of rapamycin complex 1 (mTORC1) is inhibited, facilitating the initiation of autophagy through the activation of the Unc-51-like kinase (ULK) complex.[7] Studies have indicated that Huangqin decoction improves ulcerative colitis in mice by regulating fatty acid metabolism through AMPK, thereby mediating macrophage polarization.[8] Fermented Platycodon grandiflorum root extract modulates M1/M2 macrophage polarization through the AMPK/NFκB/NLRP3 pathway, enhancing the mRNA expression of intestinal epithelial cell tight junction proteins, and mitigating inflammation in a murine model of IBD.[9] Research indicates that Schisandrin B regulates cell pyroptosis and reduces intestinal epithelial damage in colitis by modulating the AMPK/NRF2/NLRP3 inflammasome pathway.[10] In a study by Su et al,[11] it was found that berberine can enhance the expression levels of LC3II and LC3I proteins in colonic tissues of UC model mice, upregulate the colonic tissue cell P-AMPK/AMPK protein ratio, downregulate intestinal inflammatory responses, restore gut microbiota equilibrium, and mitigate intestinal mucosal barrier damage.[12] Decades of research have demonstrated that dysfunctional autophagy results in disrupted intestinal epithelial function, dysbiosis of the gut microbiota, impaired Paneth cell antimicrobial peptide secretion, endoplasmic reticulum stress response, and aberrant immune responses to pathogens in ulcerative colitis UC;[13] The dysregulated balance of macrophage polarization constitutes a significant factor in the pathogenesis of UC and serves as a therapeutic target;[14,15] Cell pyroptosis can induce potent inflammatory responses to protect the host against microbial infections; however, excessive pyroptosis can lead to autoimmune diseases such as UC. Schisandrin B can mitigate intestinal epithelial cell damage in colitis by modulating cell pyroptosis through the AMPK/Nrf2/NLRP3 inflammasome pathway.[10] AMPK plays a significant role in various biological mechanisms implicated in the pathogenesis of UC. Consequently, the activation of AMPK carries noteworthy therapeutic implications for UC treatment and merits in-depth exploration. This review aims to delve into the correlation between AMPK and regulatory mechanisms, including programmed cell death, mucosal immunity, and intestinal epithelial barrier function in UC. Furthermore, we will investigate the potential of specific Chinese herbal monomers or drugs to modulate these mechanisms through AMPK activation, thereby contributing to the advancement of UC treatment strategies.

The Concept of AMPK Activity Regulation Mechanisms

Introduction to AMPK Molecule

The history of AMPK (Figure 1A) can be traced back to 1973 when two different laboratories discovered the existence of an enzyme in the rat liver that could phosphorylate and inactivate acetyl-CoA carboxylase (ACC)[16] and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR),[17] These two enzymes are key enzymes involved in fatty acid and cholesterol synthesis. In 1980, Yeh et al demonstrated that "ACC kinase" can be activated through 5'-AMP isomerization and proposed a pioneering hypothesis: this mechanism could serve to inhibit fatty acid synthesis (ATP consumption) in situations of compromised cellular energy status.[18] In 1987, Carling et al confirmed that the activities of ACC and HMGR kinases are functions of the same protein kinase. This kinase can be activated both by AMP and through phosphorylation.[19] In 1988, this kinase was renamed AMPK, reflecting the realization that AMPK has a minimum of two downstream targets (a review article listed no fewer than 60 targets).[20] Subsequently, the critical phosphorylation activation site was identified as Thr172, located within the catalytic subunit of rat AMPK.[21] The primary kinase responsible for phosphorylating Thr172 was eventually discovered in 2003 and definitively identified as the tumor suppressor LKB1.[22]

AMPK is a serine/threonine kinase that is ubiquitously present in the form of a heterotrimeric complex composed of a catalytic α subunit and regulatory β and γ subunits. The α subunit encompasses the catalytic domain of the serine/threonine protein kinase and a pivotal residue, Thr172, which can be phosphorylated by upstream kinases. The β subunit includes a carbohydrate-binding module allowing AMPK to interact with glycogen, while the C-terminal domain of the β subunit stabilizes the interaction between the α and γ subunits. The γ subunit comprises four consecutive cystathionine-β-synthase

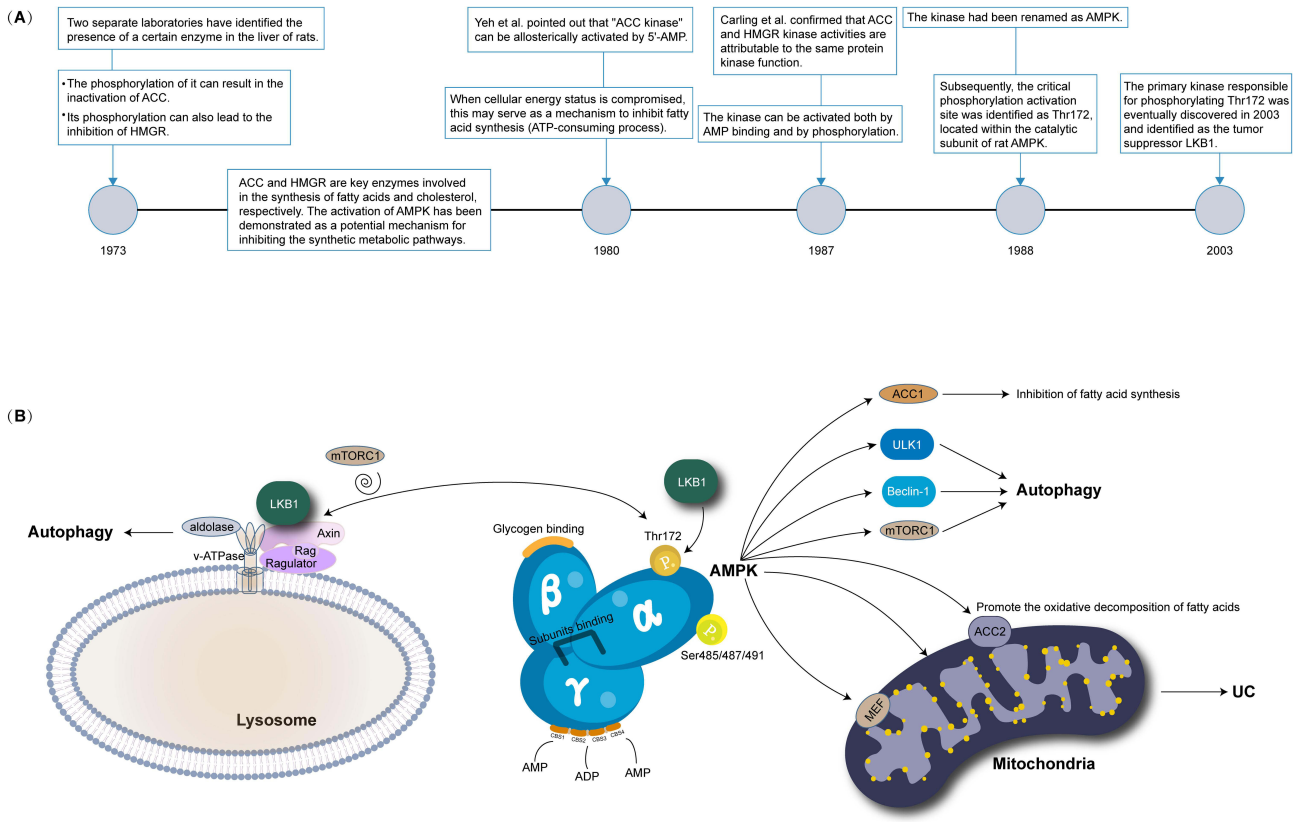

Figure 1 (**A**) A brief history of AMPK; (**B**) The AMPK molecule and its upstream and downstream mechanism.

(CBS) domains, binding adenine nucleotides, thereby ensuring the monitoring and regulation of ATP/AMP levels by AMPK.[23] The γ subunit of AMPK binds to AMP or, to a lesser extent, ADP, thereby stimulating the activity of AMPK[24] (as shown in Figure 1B). Genes encoding these subunits are found in the genomes of essentially all eukaryotic organisms, indicating that AMPK heterotrimeric complexes emerged early in the evolution of eukaryotes.[25] A significant clue to the evolution of eukaryotic cells is the engulfment of aerobic bacteria, which eventually gave rise to mitochondria. Following this engulfment event, the host and mitochondria gradually developed the ability to exchange ADP and ATP. It can be anticipated that the host would require a regulatory mechanism to monitor and control this process.[26] Given its capacity to monitor intracellular adenine nucleotide levels and its engagement in contemporary processes like mitochondrial biogenesis, mitosis, and mitochondrial fission, it is reasonable to conjecture that the functional role of AMPK may have emerged through this mechanism during evolution. Remarkably, mitochondrial impairment is recognized as a hallmark of pathological injury in ulcerative colitis,[13] the pivotal significance of AMPK activation in addressing mitochondrial damage within UC intestinal epithelial cells is conspicuous. AMPK activation leads to a reduction in anabolic metabolism, consequently decreasing ATP consumption, while simultaneously bolstering catabolic metabolism to enhance ATP production, thereby upholding energy equilibrium. As a paramount controller of energy metabolism, AMPK's functionality is intrinsically linked to cellular energy levels, particularly the concentrations of adenine nucleotides (AMP, ADP, and ATP).[27] The interconversion between ATP and ADP constitutes a fundamental mechanism of energy cycling within most cells. Catabolic metabolism transforms ADP into ATP, generating a substantial reserve of easily accessible energy for cellular utilization. Conversely, the conversion of ATP to ADP liberates a noteworthy quantity of energy to drive diverse cellular processes.[28]

Upstream Activation Pathways of AMPK

The classical theory proposes that AMP plays a pivotal role as a signal for AMPK activation. It activates AMPK through three complementary mechanisms, all of which are countered by ATP: (1) promoting the phosphorylation of Thr172; (2)

inhibiting the dephosphorylation of Thr172; and (3) inducing allosteric activation. These mechanisms confer onto mammalian AMPK a high sensitivity to alterations in the intracellular AMP/ATP ratio.[29] Mammalian cells house a range of AMPK subtypes, comprising two α subunits, two β subunits, and three γ subunits, which can come together to generate up to 12 diverse heterotrimeric complexes. While the precise functions of these distinct isoform combinations in vivo remain partially elucidated, substantial evidence indicates potential discrepancies in tissue distribution, subcellular localization, and functionality. Notably, the γ2 and γ3 subunits, characterized by unique variable-length N-terminal regions, have been associated with the subcellular localization of AMPK.[30] The most prominent upstream kinase of AMPK is the tumor suppressor protein LKB1 (also referred to as Stk11). Investigations involving mice with a knocked-out LKB1 gene have unveiled LKB1's role in triggering AMPK activation during energy stress. Research performed on cells devoid of LKB1 has further demonstrated its role in mediating AMPK activation in response to mitochondrial damage and low-energy conditions.[31,32]

In relation to the latest advancements in the field of AMPK research, a non-classical pathway of AMPK activation has come to light, termed the lysosomal pathway. Recent studies have revealed that neither an elevation in AMP levels nor glucose deprivation is observable under glucose-free cell culture conditions or in animals experiencing low blood sugar due to starvation. This compellingly suggests the existence of an unexplored pathway within the body, capable of independently sensing glucose levels apart from AMP. This pathway, coined the "Lin pathway", was unveiled by a research team led by Academician Lin Shengcai. Initially, Professor Lin's research group embarked on investigating the novel physiological roles of Axin, initially recognized as a constituent of the Wnt signaling pathway, and its deficiency's association with developmental irregularities. As their research progressed, the ensuing experimental outcomes yielded even more astonishing insights. Building upon prior experiments demonstrating the essentiality of N-myristoylation modification on the β1 and β2 subunits of AMPK for its activation through glucose deprivation, Lin Shengcai's team formulated a hypothesis that AMPK might necessitate pre-association with lipid-containing membrane constituents under physiological conditions, thereby priming it for activation upon AMP engagement. In subsequent experiments, the research team employed yeast two-hybrid technology, ultimately discovering an interacting protein named p18/LAMTOR1, which interacts with the AXIN protein on the lysosomal membrane. This breakthrough adds a new layer of understanding to AMPK activation and its intricate regulatory mechanisms, unveiling the previously unexplored lysosomal pathway as an essential contributor to glucose-sensing mechanisms in the body.[25] These findings establish a significant link between AMPK activation and the lysosome, unveiling the pivotal regulatory factor within this pathway: the crucial glycolytic enzyme, aldolase. As glucose becomes scarce, the substrate of aldolase, fructose-1,6-bisphosphate (FBP), experiences a rapid reduction. During this phase, aldolase becomes unbound from its substrate, facilitating dynamic interactions among aldolase, v-ATPase, Ragulator, and the AMPK-AXIN-LKB1 complex. Consequently, this cascade triggers the activation of the AMPK pathway, thereby contributing to the intricate regulation of cellular metabolism.[25,33,34] The "anchor" of AMPK within lysosomes constitutes a protein complex that orchestrates both catabolic and anabolic metabolic processes, thereby illuminating the mechanisms governing the transition between catabolic and anabolic metabolism.[33]

The two pathways of AMPK activation mentioned above are mutually complementary (Figure 1B), functioning independently yet synergistically reinforcing each other. Together, they play a collaborative role in the intricate regulation of AMPK activity.

Downstream Pathways of AMPK

The downstream substrate proteins within the AMPK pathway exhibit significant diversity (Figure 1B), with almost 60 recognized substrates governed by AMPK. AMPK has the capability to phosphorylate and activate cytoplasmic acetyl-CoA carboxylase (ACC1), thus impeding fatty acid synthesis. Concurrently, AMPK governs ACC2 within mitochondria to enhance the oxidative degradation of fatty acids.[35,36] AMPK directly activates ULK1 and Beclin-1 proteins, responsible for autophagy initiation,[37,38] and by regulating the activity of upstream key proteins on the mTORC1 pathway, it activates the autophagy pathway.[39] Furthermore, AMPK reacts to declining glucose levels by assembling a supercomplex on the lysosomal membrane, facilitating the separation of mTORC1, Ragulator, and v-ATPase, leading to the activation of the autophagy pathway. AMPK also directly modulates the mitochondrial fission protein MFF,

promoting mitochondrial autophagy.[40] Both cellular autophagy and mitochondrial autophagy are crucial aspects in the context of ulcerative colitis. Additionally, it has been observed that AMPK localizes within the nucleus and establishes direct interactions with TET2.[41]

AMPK-Related Technologies

UC is characterized by disruptions in glucose, energy, and amino acid metabolism. The functions of AMPK, such as inhibiting fatty acid synthesis and promoting fatty acid breakdown, hold the potential to restore the metabolic equilibrium in ulcerative colitis.On October 10, 2022, Academician Lin Shengcai from Xiamen University's School of Life Sciences, in collaboration with Professor Deng Xianming, published a research paper titled "The aldolase inhibitor aldometanib mimics glucose starvation to activate lysosomal AMPK" in the journal Nature Metabolism. This study integrates fasting, calorie restriction, and other physiological conditions based on a novel AMPK activation pathway developed by Academician Lin Shengcai's research team in recent years. Their work led to the creation of an AMPK activator named "Aldometanib", which diverges from the conventional approaches pursued by many pharmaceutical companies. In Chinese, Aldometanib is translated as "Bìgǔjīng", signifying "Fasting Essence".[42] By formulating AMPK activators based on the "Lin pathway", a prevalent mode of AMPK activation during glucose-deprived circumstances, the potential arises to replicate physiological conditions where AMPK is mobilized, eliciting an array of advantageous effects. This innovative approach tackles challenges that conventional methods fail to address. In essence, the "Fasting Essence" operates as a mediator, targeting aldolase within the Lin pathway, which functions as a glucose sensor. As a result, the undesirable effects commonly linked to traditional AMPK activation are circumvented. This approach engenders AMPK activation in a manner that aligns with nature's principles, mimicking a "natural" process that upholds the organism's health and longevity.

AMPK Gets Involved in UC

Programmed Cell Death

Autophagy

Human clinical studies as well as in vitro and in vivo models have consistently underscored the pivotal role of autophagy in upholding intestinal homeostasis, governing gut microbiota, coordinating precise intestinal immune reactions, and furnishing antimicrobial defense. The derangement of autophagy can culminate in the disturbance of intestinal epithelial function, imbalanced gut microbiota, compromised secretion of antimicrobial peptides by Paneth cells, endoplasmic reticulum stress responses, and atypical immune reactions to pathogenic bacteria.[7] The interplay between autophagy and endoplasmic reticulum (ER) stress is broadly acknowledged as a plausible mechanism contributing to the compromise of the epithelial barrier in IBD. Intestinal epithelial cells afflicted with autophagy impairments exhibit heightened vulnerability to damage.[43,44] Autophagy deficiency emerges as a potential pivotal factor driving cellular paracellular permeability in intestinal disorders.[45] Research on AMPK regulation of autophagy for treating UC has become highly advanced. One classic example is the "yin-yang" relationship with downstream mTOR, such as the use of resveratrol A1 to alleviate DSS-induced ulcerative colitis by modulating autophagy mediated by the AMPK/mTOR/p70S6K pathway.[46] Berberine promotes autophagy by regulating the AMPK-mTOR signaling pathway, thereby reducing intestinal damage caused by UC.[11] Foerster et al found that AMPK positively regulates autophagy initiation by activating the ULK1 complex and inhibiting mTORC1. This leads to increased availability of nutrients through the catabolic breakdown activity of autophagy.[13] Sup et al uncovered that estrogen-related receptor alpha (ESRRA) exhibits significant expression in intestinal tissue and plays a pivotal role in maintaining intestinal homeostasis. The absence of ESRRA results in compromised AMPK phosphorylation, diminished transcription factor EB (TFEB) expression, escalated inflammation, compromised mitochondrial function within intestinal epithelial cells, and notably, anomalies in genes associated with autophagy.[47] Studies have found that heat shock protein 90 (HSP90) and NLRP3 inflammasome are both associated with AMPK-mediated autophagy. Additionally, HSP90 and NLRP3 are inflammatory markers in UC, indicating the therapeutic potential of AMPK.[48] SIRT1 deacetylates proteins, a reaction that requires NAD+ as a cofactor. Activation of AMPK increases cellular NAD+ levels, thereby enhancing sirtuin activity. SIRT1 increases

p-AMPK levels through the deacetylation of LKB-1. Both SIRT1 and p-AMPK negatively regulate mTOR signaling to induce autophagy, thereby alleviating colitis.[49] Metrnl, also recognized as Cometin or Subfatin, emerges as a recently identified secreted protein with abundant expression in the intestinal epithelium. Investigations have unveiled that Metrnl deficiency intensifies ulcerative colitis, at least in part, by impeding autophagy via the AMPK-mTOR-p70S6K pathway.[50] Triggering AMPK-ULK1-mediated autophagy could potentially enhance the management of DSS-induced colitis by facilitating P62-mediated mitophagy to suppress the formation of the NLRP3 inflammasome.[51] Subsequent investigations have suggested that the Alpha7 nicotinic acetylcholine receptor mitigates inflammatory bowel disease by inducing autophagy through the AMPK-mTOR-p70S6K pathway.[52] AMPK and mTOR are canonical pathways implicated in autophagy. Research has revealed that the activation of the AMPK/mTOR pathway can mitigate Th17/Treg imbalance, subsequently ameliorating DSS-induced colitis—a characteristic immune dysregulation often observed in UC.[53,54] It is evident that the role of AMPK in UC extends beyond its impact on cellular autophagy for improving colitis. AMPK is implicated in various other mechanisms as well. However, further research is needed to elucidate the precise mechanisms underlying the beneficial effects of AMPK activation on autophagy and UC.

Pyroptosis

Cellular pyroptosis is a type of cell death characterized by cellular swelling and the formation of prominent bubbles on the cell membrane.[55] Research has demonstrated that mitigating cellular pyroptosis can attenuate experimental colitis. Schisandrin B, a compound derived from Schisandra chinensis, mitigates epithelial cell damage in colitis by modulating the AMPK/Nrf2/NLRP3 inflammasome-mediated cellular pyroptosis pathway.[10] Deng et al revealed that the Gly-Pro-Ala (GPA) peptide can mitigate cellular pyroptosis and improve DSS-induced colitis in mice. This effect is achieved by inhibiting the assembly of the NLRP3 inflammasome and cleavage of GSDMD through the AMPK pathway.[56] Evidence suggests that resveratrol has the capacity to reduce the expression of inflammation-induced miR-155, a key regulator of innate immune responses in macrophages, dendritic cells, and epithelial cells. In the context of UC, miR-155 holds prominence due to its heightened expression. Consequently, the mitigation of UC through resveratrol's downregulation of miR-155 becomes evident. Recent research highlights that the disruption of the AMPK and Sirt1 positive feedback loop effectively counteracts the inhibitory impact of resveratrol on miR-155 expression. This disruption leads to heightened miR-155 expression and instigates cellular pyroptosis, driven by NLRP3 inflammasome activation.[57] Therefore, it can be inferred that activation of AMPK-related pathways can alleviate cellular pyroptosis and ameliorate UC.[58]

Inflammatory Response

UC initiates a cascade of inflammatory responses, characterized by the overexpression of pro-inflammatory cytokines including TNF-α, IFN-γ, and IL-1β. These cytokines contribute to a sequential escalation of inflammation, culminating in intestinal tissue damage and the formation of ulcerative lesions.[59] Increasing evidence suggests that AMPK plays a crucial role in UC pathogenesis. AMPK can regulate the signaling pathways of NF-κB and MAPK, as well as the expression of inflammatory genes, thereby exerting anti-inflammatory effects.[60] NLRP3 facilitates the intricate assembly of the inflammasome complex in response to microbial ligands, triggering the activation of caspase-1 and subsequent secretion of IL-1β and IL-18. Both IL-1β and IL-18 play pivotal roles in the pathogenesis of IBD.[61] AMPK has the ability to enhance the expression of SIRT1 by mitigating the inhibitory impact of DBC1 on SIRT1 activity. Consequently, SIRT1 works to diminish the activity of transcription factors through deacetylating NF-κB, AP-1, and histones. This process helps reinstate a condensed chromatin structure, ultimately restraining the transcription of genes related to inflammation.[62] Studies have revealed that activation of the AMPK/SIRT1 pathway can inhibit the formation of NLRP3 inflammasomes in macrophages, thereby alleviating inflammatory responses in colitis.[63] Activation of AMPK exhibits the capacity to impede the activation of the IKK/NF-κB pathway provoked by TNF-α, as well as the JAK/STAT3 pathway prompted by IL-6. Furthermore, it can suppress NADPH oxidase activity, thus mitigating intestinal inflammatory responses.[63] Hydroxycinnamic acid fosters the expression of PPARγ-responsive genes CD36 and LPL, triggers the translocation of PPARγ from the cytoplasm to the nucleus, and facilitates the association of PPARγ with reporter genes. This activation of PPARγ consequently induces the AMPK/ACC1-mediated shift from Th17 to Treg cells, thereby restoring the balance between Th17 and Treg cells and effectively mitigating intestinal inflammatory responses in cases

of colitis.[64] The knockout of P2Y1R, as one of the G protein-coupled receptors, can inhibit Th17 differentiation and alleviate intestinal inflammation through an AMPK-dependent mechanism.[65] Activation of AMPK diminishes the activation of p38 MAPK, subsequently curtailing the expression of IL-6 and effectively mitigating pathological inflammation in the intestinal region.[66] Based on the above information, it is evident that AMPK plays a crucial role in suppressing inflammatory responses in intestinal tissues.

Intestinal Epithelial Barrier

A reduction in the phosphorylation of AMPKαThr172 has been noted in the intestines of individuals with IBD, evident in both the epithelial and lamina propria compartments. This observation underscores the plausible correlation between AMPK and the functionality of the intestinal barrier.[66] The caudal type homeobox 2 (CDX2) serves as a pivotal transcription factor responsible for committing cells to the intestinal epithelial lineage. Deficiency of CDX2 negates the intestinal differentiation facilitated by AMPK activation. In vivo studies reveal that epithelial AMPK knockout results in diminished CDX2 expression, thereby compromising the integrity of the intestinal barrier, including tight junction integrity and ultrastructure. This situation further contributes to epithelial cell migration, intensifies intestinal proliferation, and worsens colitis induced by dextran sulfate sodium.[67] Metformin increases the expression of tight junction proteins ZO-1, Claudin-1, and Occludin in the intestinal epithelium of mice treated with DSS by activating AMPK.[68] Astragaloside IV restores intestinal mucosal barrier by promoting AMPK activation and driving the expression of Muc-2.[69] The compromised integrity of the intestinal barrier results in heightened intestinal permeability, manifesting as increased serum recovery of FD-4 and elevated expression of MLCK protein. Geniposide intervenes by reducing the expression of MLCK protein, thus mitigating LPS-induced in vitro barrier dysfunction through the activation of AMPK phosphorylation.[70] Sinensetin facilitates epithelial autophagy through the activation of the AMPK/ULK1 pathway. Notably, the promotion of epithelial autophagy has been shown to counteract epithelial cell apoptosis while enhancing the degradation of Claudin-2. Given that Claudin-2 expression correlates with epithelial permeability, the notion that AMPK safeguards intestinal epithelial barrier integrity by facilitating Claudin-2 degradation is substantiated.[71] Based on this information, it can be concluded that the activation of AMPK is essential for the proper functioning of the intestinal epithelial barrier.

Macrophage Polarization

The AMPK signaling pathway is one of the classical pathways involved in macrophage polarization.[72] In typical conditions, intestinal macrophages are crucial for preserving intestinal integrity and averting inflammation. Nonetheless, genetic and environmental factors can disrupt the equilibrium between M1 and M2 macrophage polarization within the intestines. This disruption can convert regular inflammatory responses into pathological intestinal harm. In the case of ulcerative colitis (UC) patients, the disturbance of intestinal inflammation is intricately connected to an uneven distribution of M1 and M2 macrophage polarization. Consequently, rectifying the M1/M2 macrophage polarization balance could hold substantial therapeutic potential for addressing UC.[14] Evidence suggests that the traditional Chinese medicine formula "Xianhecao-Changyan Fang" effectively diminishes the expression of M1 macrophage markers (CD11c, IL-6, and IL-1β) and enhances the expression of M2 macrophage markers (CD206) in colitis-afflicted mice. This observation implies that the formula might modulate macrophage polarization, possibly by means of AMPK-mediated metabolic reprogramming. Consequently, this could enhance the anti-inflammatory activity of macrophages.[73] Natural flavonoids have demonstrated a substantial capacity to ameliorate symptoms and pathological alterations in colitis-affected mice. Remarkably, when mice were treated with compound C, a pharmacological inhibitor of AMPK, the therapeutic efficacy of Eup was noticeably diminished. Furthermore, Eup exhibited a noteworthy ability to effectively restrain the inflammatory response induced by LPS in macrophages.[74] These findings suggest that AMPK is involved in the inflammatory response of macrophages in UC. Quercetin, a significant constituent within traditional Chinese medicine formulations aimed at addressing ulcerative colitis (UC), holds noteworthy implications. Studies indicate that quercetin possesses anti-inflammatory properties by suppressing M1 macrophage polarization while concurrently bolstering M2 macrophage polarization and endogenous antioxidant expression within both macrophages and microglial cells. This elevation of M2 markers and inherent antioxidants is attributed to the activation of AMP-activated protein kinase (AMPK) and Akt signaling pathways, orchestrated by quercetin.[75] As per reports, the activation of AMPK through phosphorylation can facilitate the expression and translocation

of Nrf2 into the nucleus. Consequently, this prompts the upregulation of downstream gene HO-1. This intricate mechanism contributes to the modulation of M1 to M2 macrophage polarization in cases of colitis.[76] Numerous studies have demonstrated that AMPK mediates macrophage polarization through the regulation of the NF-κB pathway.[77] Transgenic mice overexpressing SIRT1 in macrophages exhibit enhanced polarization towards M2 macrophages. Activated SIRT1 suppresses LPS-induced NF-κB activity by inhibiting p65 acetylation and the release of M1-related cytokines. SIRT1 also forms a positive feedback regulation with AMPK, further promoting the shift from M1 to M2 polarization.[8,78] XHCF, a traditional Chinese medicine formula documented in the Chinese Pharmacopoeia (2015 edition), has been shown to inhibit M1 macrophage polarization and promote M2 macrophage polarization to ameliorate DSS-induced colitis in mice. This process is likely mediated by the activation of AMPK phosphorylation.[73] Activation of AMPK diminishes the degradation of IκB, enhances Akt activation, and suppresses the NF-κB pathway. These effects contribute to the transition of M1 macrophages to the M2 phenotype, consequently alleviating colitis.[79] Thus, it can be inferred that both macrophage polarization and macrophage inflammatory status in UC can be modulated by AMPK.

The aforementioned involvement of AMPK in various pathophysiological mechanisms of UC is reviewed in Figure 2.

Potential Drugs Targeting AMPK-Regulated Pathway in UC

Potential Drug Inclusion Methods

There are three criteria for potential drugs to be selected: (1) The potential pharmaceutical agent demonstrates a conspicuous therapeutic impact on UC, ameliorating associated phenotypes. (2) A substantial volume of in vivo or in vitro experimentation substantiates that the potential pharmaceutical agent can directly modulate AMPK molecules.

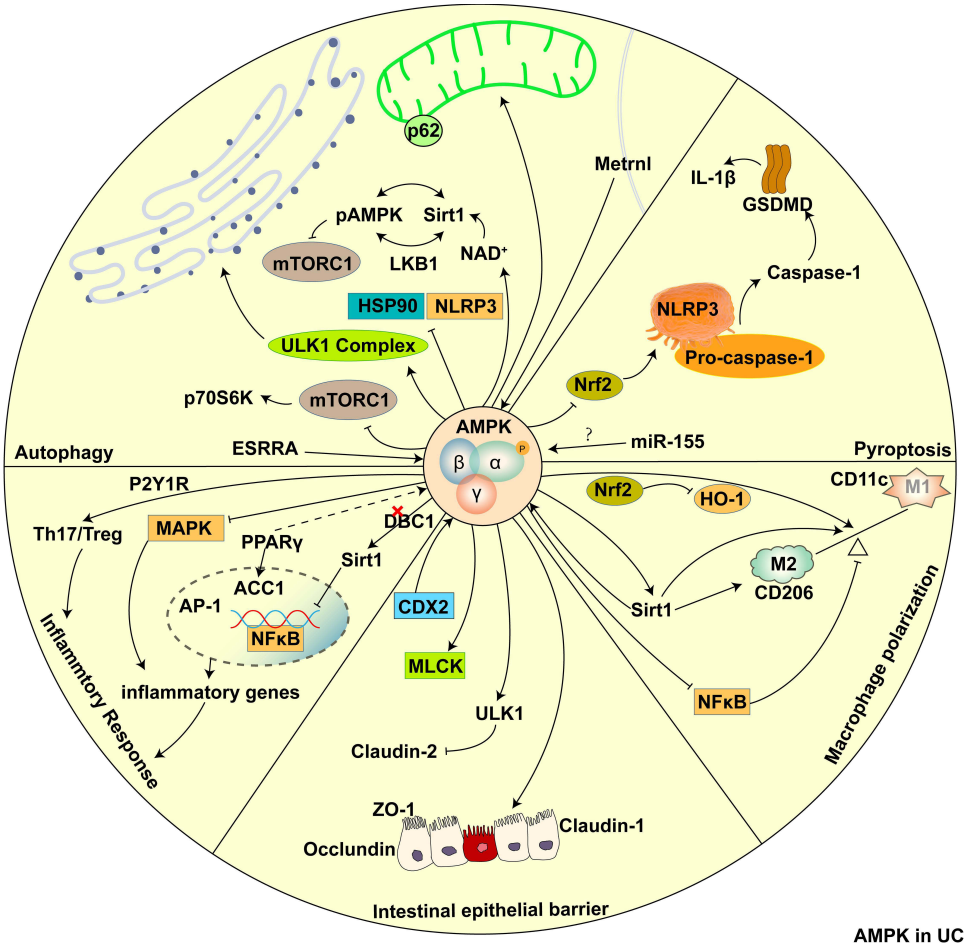

Figure 2 Possible Biological Mechanisms of AMPK in Ulcerative Colitis.

(3) The regulatory influence of this potential pharmaceutical agent on AMPK can elicit alterations in downstream pathways or biological processes. (4) The implicated AMPK-related pathways and biological processes are closely associated with UC.

TCM Monomer

Monomers of traditional Chinese medicine refer to purified substances extracted and isolated from herbal medicines, which are purer compared to compound herbal medicines. This high purity facilitates the accurate determination of their chemical constituents and pharmacological effects, making it conducive to the study of their therapeutic efficacy and safety. The following several monomers of traditional Chinese medicine exert a protective effect in colitis by activating AMPK and promoting its phosphorylation, ultimately repairing the intestinal epithelial barrier function. Mogrol, an aglycone of mogrosides, which protects intestinal epithelial cells by promoting AMPK activation and inhibiting the formation of NLRP3 inflammasome.[12] Phellodendrine, a component of phellodendrone, potentially exerts a protective effect on the intestinal epithelial cells in ulcerative colitis (UC) by activating the AMPK-mTOR signaling pathway to promote autophagy.[11] Schisandrin B, ingredient in Schisandra chinensis, regulates pyroptosis through the AMPK/Nrf2/NLRP3 inflammasome pathway, alleviating epithelial cell damage in colitis.[10] Kai Zhou et al found that Eupatilin significantly suppressed NFκB activation and ROS production in activated macrophages, and fortified epithelial tight junctions (TJs) via an AMPK-dependent mechanism.[74] Andrographolide (Andro) is a naturally occurring compound isolated from Andrographis paniculata (Burm. f.) Nees, which has a long history of traditional use in China, India, and other parts of Asia for managing inflammation-related ailments. In various studies, Andro has demonstrated its ability to suppress inflammatory responses in lipopolysaccharide (LPS)-stimulated macrophages and alleviate murine acute colitis by activating AMPK.[80] Heterophyllin B exhibited significant protection against DSS-damaged intestinal epithelium physical barrier to limit access of enteric microbes through promoting AMPK activation.[69] Wedelolactone treatment effectively alleviated DSS-induced mouse colitis by inhibiting NLRP3-mediated inflammatory responses and restoring epithelial barrier function via AMPK activation.[81] Sinensetin acts by enhancing AMPK phosphorylation to promote autophagy in epithelial cells, thereby further inhibiting cellular apoptosis, facilitating the degradation of claudin-2, and significantly alleviating intestinal barrier dysfunction in patients with colitis.[71] Picroside III can improve DSS-induced colitis in mice by promoting intestinal mucosal wound healing and restoration of epithelial barrier function through activation of AMPK.[82] There are also several monomers that can alleviate UC by modulating intestinal mucosal immunity and mucosal inflammation through activation of the AMPK pathway. Atractylenolide III prevents mitochondrial dysfunction and improves the development of colitis by activating the AMPK/SIRT1/PGC-1α signaling pathway.[83] Cinnamtannin D1 prevents Th17/Treg imbalance and improves DSS-induced colitis by activating the AMPK/mTOR pathway.[53] Geniposide inhibits NLRP3 inflammasome in macrophages through AMPK/SIRT1-dependent signaling, leading to improvement of inflammation response in colitis.[63] Additionally, studies have shown that Geniposide can reduce inflammation and regulate the disrupted epithelial barrier function by activating the AMPK signaling pathway, thereby ameliorating TNBS-induced experimental colitis in rats.[70] Forskolin inhibits the inflammatory response in LPS-stimulated macrophages and acute colitis in mice by activating AMPKα2.[80] Ginsenoside Rd inhibits sodium dextran sulfate-induced experimental colitis in mice by promoting AMPK-ULK1-p62 axis-driven mitophagy-mediated inactivation of NLRP3 inflammasomes, resulting in reduced secretion of IL-1β in macrophages.[51] Madecassic acid restores Th1/Treg balance via the PPARγ/AMPK/ACC17 pathway, exerting anti-colitis effects.[64] Dipotassium glycyrrhizate via HMGB1 or AMPK signaling suppresses oxidative stress during intestinal inflammation.[84] Platycodin D activates AMPK, which in turn activates the PI3K/Akt pathway and inhibits the NF-κB pathway, thereby participating in macrophage polarization and suppressing intestinal inflammation associated with colitis.[79] Xiaofan Xu et al found that BBR (berberine) can promote autophagy through the AMPK/MTOR pathway, leading to the inhibition of lysozyme expression and secretion. In contrast to the Unc-51-like kinase 1 (ULK1) pathway, BBR promotes lysosome maturation and expression. Therefore, BBR has the potential to be a candidate drug for the treatment of UC (ulcerative colitis) patients in the future.[85] The aforementioned studies indicate that the activation of AMPK is indispensable for the efficacy of monotherapy with traditional Chinese medicine monomer in the treatment of UC.

Traditional Chinese Prescription

Traditional Chinese prescription, composed of multiple Chinese medicinal herbs, is a primary application in clinical practice. Numerous studies have shown through experimental research that Chinese herbal formulations have a multi-target comprehensive effect in treating UC (ulcerative colitis), and many of them have been successfully applied in clinical settings with favorable outcomes. Traditional Chinese medicine prescriptions function by suppressing the release of inflammatory factors and regulating intestinal immune response.[86] Baitouweng decoction (BD), consisting of four traditional Chinese medicines - Pulsatilla chinensis (Bunge) Regel (Bai Tou Weng), Phellodendron chinense C.K. Schneid. (Huang Bo), Coptis chinensis Franch. (Huang Lian), and Cortex Fraxini (Qin pi), has a long-standing history in the treatment of intestinal diseases, including UC. The research findings indicate that BD promotes autophagy and facilitates the restoration of the intestinal epithelial barrier in dextran sulfate sodium (DSS)-induced colitis mice by activating AMPK phosphorylation and suppressing mTOR expression. Enrichment analysis results provide evidence that BD can modulate the autophagy, AMPK, and mTOR signaling pathways.[87] The Xian-He-Cao-Chang-Yan formula (XHCF) consists of six crude drugs: Agrimoniae Herba (AH, the aerial part of Agrimonia pilosa Ledeb.), Coptidis Rhizoma (CR, the rhizome of Coptis chinensis Franch.), Aucklandiae Radix (AR, the root of Aucklandia lappa Decne.), Cicadae Periostracum (CP, the exuviae of Cryptotympana pustulata Fabricius.), Acori Tatarinowii Rhizoma (ATR, the rhizome of Acorus tatarinowii Schott.), and Platycodonis Radix (PR, the root of Platycodon grandiflorum (Jacq) A.DC.). These ingredients are combined in a ratio of 5:1.5:1.5:1.5:1.5:1. XHCF has the potential to enhance the activation of AMPK, which consequently regulates macrophage polarization. The therapeutic benefits of XHCF on UC may be attributed to the synergistic actions of its multiple ingredients.[73] Huangqin decoction (HQD) is a traditional Chinese medicine (TCM) formula derived from Shang Han Lun. It consists of a combination of four herbs: the root of Scutellaria baicalensis Georgi. (skullcap), Glycyrrhiza uralensis Fisch. (liquorice), Paeonia lactiflora Pall. (peony), and the fruit of Ziziphus jujuba Mill. (jujube). HQD ameliorated UC by regulating fatty acid metabolism to mediate macrophage polarization via activating FFAR4-AMPK-PPARα pathway.[8] Sishen Pill (SSP) is composed of Euodia rutaecarpa (Juss.) Benth., Schisandra chinensis (Turcz.) Baill, Psoralea corylifolia L., Myristica fragrans Houtt., Ziziphus jujuba Mill. and Zingiber officinale Rosc, which has been treating chronic enteritis in China for thousands of years. The research findings indicate that SSP effectively regulates peripheral blood effector memory T cells, thereby alleviating DSS-induced experimental colitis. This phenomenon may be associated with the inhibition of the PI3K/Akt signaling pathway and the activation of AMPK.[88]

Traditional Chinese prescriptions exhibit a multi-target comprehensive effect in the treatment of UC, and most of them have been clinically utilized with favorable outcomes. However, the specific active components of these prescriptions are intricate, necessitating a more scientific theoretical framework to elucidate their therapeutic principles.[86]

Diet

Dietary factors can be directly associated with the pathogenesis or progression of UC through their impact on the host or indirectly through the modulation of the composition or function of the gut microbiota.[89] The administration of nanoparticles derived from human-consumed broccoli exhibits a suppressive effect on murine colitis through the activation of AMPK in dendritic cells.[90] The activity of AMPK is notably augmented in mice treated with DSS and supplemented with dietary red raspberries, leading to a subsequent decrease in intestinal mucosal and epithelial damage.[91] The potential application of chitosan oligosaccharide as a dietary supplement or nutritional health product has been investigated. It activates AMPK in intestinal epithelial cells to improve gastrointestinal disorders.[92] Creatine levels are maintained through dietary intake and endogenous synthesis of arginine and glycine. The preservation of creatine maintains intestinal homeostasis and helps prevent colitis, partially relying on the AMPK pathway. However, further research is needed to elucidate the precise connection between creatine and AMPK signaling in the context of colitis.[93] Plant-based foods rich in anthocyanins and anthocyanin formulations play a crucial role in the prevention of IBD and its associated colorectal cancer (CRC). The AMPK cascade serves as the primary pathway through which anthocyanins exert their protective effects against colitis.[94] Le Carbone, a dietary supplement (a charcoal supplement), regulates DSS-induced acute colitis in mice by activating AMPKα and downregulating the STAT3 and cystathionine

gamma-lyase-dependent apoptotic pathways.[95] Due to its high nutritional value, jujube fruit is highly regarded. Research has found that polysaccharides extracted from wild jujube enhance intestinal barrier function through the AMPK pathway, thereby preventing experimental inflammatory bowel disease.[96]

These findings will contribute to the formulation of increasingly health-conscious dietary recommendations, specifically targeting the prevention of colitis, while simultaneously mitigating potential negative reactions that may arise from the influence of AMPK on metabolic energy.

Compounds Found in Plants

The chemical constituents extracted from numerous plants exhibit therapeutic effects on UC. Proanthocyanidins are phenolic compounds extracted from various plants. Proanthocyanidin A1 (PCA1) is a type of proanthocyanidin. Studies have revealed that PCA1 alleviates colitis damage by inhibiting the mTOR and p70S6K signaling pathways through the activation of AMPK in DSS-induced UC mice.[46] Alginate is an acidic polysaccharide extracted from marine brown algae. Alginate can be degraded into alginate oligosaccharides (AOS) with lower molecular weight, lower viscosity, improved solubility, and enhanced bioavailability. AOS inhibits LPS-mediated inflammatory responses and alleviates DSS-induced colitis through the activation of AMPK signaling and suppression of NF-κB activation.[97] Dioscin, which is a form of plant steroidal saponin abundant in some medical plants, alleviates DSS-induced colitis by inhibiting the mTOR pathway through the promotion of AMPK phosphorylation.[98] As the precursor of the phytochemical sulforaphane (SFN), glucoraphanin (GRP) is highly concentrated in cruciferous vegetables such as bok choy, broccoli, and cabbage. GRP exhibits its therapeutic effects by activating the AMPK/PGC1α/NRF2 pathway, thus ameliorating dextran-sulphate-sodium (DSS)-induced colitis in mice.[99] Resveratrol (RES), a natural polyphenol, is found in several plants and fruits such as grapes, blueberries, and peanuts. Its microbial metabolite, 4HPP, is involved in the potential mechanism of maintaining intestinal barrier function. This mechanism includes the regulation of TJ expression through AMPK-activated CDX2 expression and the inhibition of pro-inflammatory cytokines through the AMPK-mediated SIRT1/NF-κB pathway.[100] Platycodon grandiflorum (PG), a perennial herb of the Campanulaceae family, exerts anti-inflammatory effects in a murine IBD model through the AMPK/NF-κB/NLRP3 pathway upon administration of PG root fermentation broth (PGRFB).[9]

Anti-Diabetic Compounds

AMPK, being a pivotal molecule in energy metabolism, plays a critical role as a target for anti-diabetic medications. Research findings have demonstrated that specific anti-diabetic drugs possess the ability to partially ameliorate UC. To date, metformin has been demonstrated to possess multiple effects beyond its anti-diabetic properties. It can promote tight junction expression, enhance mucosal integrity, and regulate mucosal immunity to alleviate inflammatory responses through both AMPK-dependent and AMPK-independent mechanisms. Importantly, metformin exhibits greater efficacy in alleviating DSS-induced colitis compared to mesalazine, rendering it more appealing for the treatment of UC.[66,68,101–105] Dapagliflozin has emerged as a promising selective SGLT2 inhibitor for the treatment of type 2 diabetes, offering a reduced risk of hypoglycemia. It exerts its effects by targeting key pathways including AMPK/mTOR, HMGB1/RAGE, and Nrf2/HO-1, which activate autophagy and inhibit apoptosis. This mechanism of action has shown potential in alleviating symptoms associated with experimental IBD in rats.[106] Linagliptin, which is a potent inhibitor of dipeptidyl peptidase-IV (D-IV) and used for the treatment of type 2 diabetes mellitus (T2DM), has been found to improve acetic acid-induced colitis in rats by modulating the AMPK/SIRT1/PGC-1α and JAK2/STAT3 signaling pathways.[107]

AMPK Activator

Several studies have demonstrated the therapeutic effects of various AMPK activators in colitis, as they directly activate AMPK to exert their functions. In a study conducted by Suhrid Banskota et al, it was discovered that the administration of VAS2870, a pan-Nox inhibitor, effectively alleviated colitis induced by dextran sodium sulfate (DSS) in mice with macrophage-specific AMPKβ1 deficiency ($AMPK\beta1^{LysM}$).[108] 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), which is an intermediate in the production of monophosphoryl adenosine, acts as an activator of AMPK. By modulating intestinal mucosal immunity, it can exert a protective effect on the intestinal mucosa of experimental

colitis mice.[109,110] Studies have demonstrated that the small molecule GL-V9 (5-hydroxy-8-methoxy-2-phenyl-7-(4-(pyrrolidin-1-yl)butoxy)4 H-chromen-4-one), an AMPK activator, exhibits a protective effect against DSS-induced colitis by attenuating oxidative stress. This effect is achieved through the up-regulation of (Thioredoxin-1) Trx-1 via the activation of the AMPK/FOXO3 pathway. Moreover, additional investigations have revealed that GL-V9 induces autophagy in macrophages by activating AMPK and also leads to the degradation of NLRP3 inflammasome through autophagosome activation.[111] The research conducted by Luca Antonioli et al indicates that the novel AMPK activator FA5 can serve as an innovative pharmaceutical agent for clinical treatment of intestinal inflammation.[112]

Others

Certain specific drugs, such as bioactive substances, can also exert their effects in UC by activating AMPK. GPA peptides isolated from fish skin collagen hydrolysate can improve DSS-induced colitis by specifically inhibiting NLRP3 inflammasome-mediated pyroptosis. Additionally, GPA peptides can increase AMPK phosphorylation to suppress ROS production and impede NLRP3 mitochondrial localization, thereby inhibiting NLRP3 inflammasome activation.[56] BJ-3105, a 6-alkoxy-pyridin-3-ol derivative, has previously been shown to inhibit T cell differentiation and autoimmune encephalomyelitis by blocking cytokine-induced JAK phosphorylation.[113] Pallavi Gurung et al discovered that BJ-3105 improves DSS-induced colitis and azoxymethane/DSS-induced colitis-associated tumorigenesis in mice through the AMPK-NOX axis.[114] The P2Y1 receptor, a G protein-coupled receptor, plays a crucial role in the immune response of inflammatory bowel disease. Studies have shown that the absence of P2Y1R can inhibit Th17 cell differentiation in an AMPK-dependent manner, leading to improvements in colitis. Therefore, P2Y1R can serve as an important modulator of Th17 cell differentiation to control intestinal inflammation.[65] Coenzyme Q10 (CoQ10), also known as ubiquinone, is a lipophilic antioxidant. CoQ10 treatment has been shown to increase the expression of p-AMPK and FOXP3 while inhibiting the expression of p-STAT3 and IL-17, thereby reducing the severity of colitis. These findings suggest that CoQ10 holds potential as a targeted therapeutic approach for treating UC.[115] A novel bioactive mitochondrial-derived peptide encoded in mitochondrial 12S rRNA, referred to as MOTS-c, has been shown to alleviate inflammatory responses, enhance anti-apoptotic capacity, upregulate p-AMPK expression, and inhibit the activation of the ERK/JNK signaling pathway, thereby exerting anti-colitis effects.[116] Cannabinoid receptor 2 (CB2R) belongs to the G-protein-coupled receptor (GPCR) family and possesses 7 transmembrane α-helices, a glycosylated extracellular N-terminus, and an intracellular carboxyl terminus. Activation of CB2R has been demonstrated to ameliorate DSS-induced colitis by inhibiting the NLRP3 inflammasome in macrophages.[117]

The detailed information for the aforementioned drugs involved in the activation of AMPK for the treatment of UC can be found in Table 1.

Discussion

AMPK is responsible for maintaining the equilibrium between energy production and expenditure through the regulation of a multitude of metabolic activities. Among its targets are pivotal enzymes and transcriptional regulatory factors that play roles in cell growth, proliferation, and metabolic pathways. Consequently, disruptions in AMPK function are intricately linked to metabolic disorders, including diabetes, obesity, and the onset of cancer. Nonetheless, UC does not conform to the conventional framework of metabolic disorders, which might introduce certain biases when exploring AMPK as a mechanism and potential therapeutic target for UC. Nevertheless, I hold the belief that organisms are the remarkable outcomes of evolution, endowed with intricate mechanisms that surpass our imagination in tackling diverse challenges. Moreover, a multitude of studies have underscored the dysregulation of AMPK in UC, and the activation of AMPK through diverse pharmaceutical agents or biological processes has demonstrated substantial mitigation of colitis. However, further research is imperative to delve into the intricate biological underpinnings associated with the pathogenesis and treatment of UC.[119]

The intricate integration of diverse upstream and downstream pathways at the cellular level by AMPK remains an enigma within the realm of AMPK research. AMPK is found across various intracellular locales, including the lysosomal membrane, cytosol, mitochondria, and the cell nucleus. The manner in which AMPK orchestrates and governs these distinct compartments, as well as the potential existence of distinct downstream regulatory genes,

Table 1 AMPK-Targeting Drugs for UC Treatment

Drugs	Type	Brief Function Mechanism	Biological Process	Treatment Outcome	References
Huangqin Decoction	A traditional Chinese prescription	FFAR4-AMPK-PPARα	Macrophage polarization, fatty acid metabolism	Promoted the balance of gut microbiota and metabolites	[8]
Platycodon grandiflorum root fermentation broth	A perennial herb of the Campanulaceae family	Activate AMPK	Macrophage polarization	Restored the intestinal barrier	[9]
Schisandrin B	Ingredient in Schisandra chinensis	AMPK/Nrf2/ NLRP3 inflammasome	Pyroptosis	Reduced epithelial cells damage	[10]
Phellodendrine	A component of phellodendrone	Activate the p-AMPK /mTOR pathway	Autophagy	Protected intestinal epithelial cells	[11]
Mogrol	An aglycone of mogrosides	Activate AMPK	NLRP3 inflammasome	Protected against dysfunction of intestinal epithelial barrier	[12]
Procyanidin A1	Phenolic compounds extracted from a variety of plants	AMPK/mTOR/ p70S6K	Autophagy	Alleviated the inflammation	[46]
Ginsenoside Rd	The most important components of Ginseng	AMPK-ULK1-p62	Mitophagy-mediated NLRP3 inflammasome	Inhibition of the NLRP3 inflammasome	[51]
Cinnamtannin D1	Extracted from Cinnamomum tamala	AMPK/mTOR	Th17/Treg	Alleviated inflammatory response	[53]
GPA peptide	Isolated from fish skin gelatin hydrolysate	AMPK/NLRP3 inflammasome	Pyroptosis	Suppressed ROS production	[56]
Geniposide	The main active ingredients of Gardenia jasminoides	AMPK/Sirt1	NLRP3 inflammasome in Macrophage	Ameliorated inflammatory responses	[63]
Metformin	Anti-diabetic compound	Activate AMPK	Regulating mucosal immunity	Suppressing inflammation of the intestinal mucosa	[66,102–105]
Madecassic acid	The main ingredient of C. asiatica	PPARγ/AMPK/ ACC1	Th17/Treg	Restore the Th17/Treg balance	[64]

(*Continued*)

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Table 1 (Continued).

Drugs	Type	Brief Function Mechanism	Biological Process	Treatment Outcome	References
P2Y1R	A G-protein-coupled receptor	AMPK signaling	Th17 cell differentiation	P2Y1R deficiency suppressing Th17 cell differentiation is dependent on AMPK activation	[65]
Heterophyllin B	The active compounds extracted from the ethyl acetate extract of Pseudostellaria heterophylla	Activate AMPK	Enhance the expression of intestinal epithelial tight junction protein	Enhanced intestinal epithelial barrier	[69]
Geniposide	An iridoid glycosides purified from the fruit of Gardenia jasminoides Ellis	Activate AMPK	Intestinal barrier function, inflammation	Alleviating intestinal inflammatory disorders	[70]
Sinensetin	The polymethoxyflavones isolated from orange peel	Increased phosphorylation of AMPK	Autophagy	Restored impaired epithelial TJ barrier function	[71]
Xian-He-Cao-Chang-Yan formula	A traditional Chinese prescription	Activate AMPK	Macrophage polarization	Inhibited M1 macrophage polarization	[73]
Eupatilin	The major flavone compounds in the leaves of Artemisia argyi H. Lév. et Vaniot	Activate AMPK	Inflammation	Maintaining the integrity of the intestinal epithelial barrier	[74]
Platycodin D	A saponin found in Platycodon grandiflorum	Activate AMPK	Macrophage polarization	Inhibition of inflammation and the conversion of M1-type macrophages to M2-type macrophages	[79]
Andrographolide	A natural compound isolated from Andrographis	Activate AMPK	Macrophages inflammation	Inhibited inflammatory responses	[80]
Wedelolactone	The ethanol extract of Wedelia chinensis	Activate AMPK	NLRP3 inflammasome	Restoring epithelial barrier function	[81]
Picroside III	An Active Ingredient of Picrorhiza scrophulariiflora	Activate AMPK	Intestinal mucosal barrier	Promoting intestinal mucosal wound healing and epithelial barrier function recovery	[82]
Atractylenolide III	Bioactive compounds from the root extracts of Atractylodes macrocephala Koidz	Activate AMPK/ SIRT1/PGC-1α	Mitochondrial function	Protected against mitochondrial dysfunction	[83]
Dipotassium glycyrrhizate	A major active constituent of Glycyrrhiza glabra root	Activate AMPK	Inflammation in oxidative stress-associated diseases	Reduced inflammation	[84]

Berberine	An isoquinoline alkaloid found in many types of medicinal plant	AMPK/MTOR/ ULK1	Autophagy	Regulating the process of intestinal inflammation	[85]
Sishen Pill	A classic prescription of traditional Chinese medicine	Activate AMPK	Mucosal immunity	Regulated glucolipid metabolism of memory T cells	[88]
Broccoli-Derived Nanoparticle	Nanoparticles derived from food	Activate AMPK	Targeting dendritic cells	Maintaining intestinal immune homeostasis	[90]
Dietary red raspberries	A whole fruit contains substantial amount of health beneficial components	Activate AMPK	Inflammation	Reducing the intestinal mucosal and epithelial damages in the colon	[91]
Chitosan oligosaccharide	Dietary supplements or nutraceuticals	Activate AMPK	Facilitation of tight junction assembly	Promotes tight junction assembly	[92]
Creatine	Maintained by diet and endogenous synthesis from arginine and glycine	Phospho-AMPK	The maintenance of the mucosal barrier	Intestinal homeostasis	[93]
Anthocyanins	Belong to the subclass of dietary flavonoids	AMPK cascade	Autophagy	Regulating the process of intestinal inflammation	[94]
Le Carbone	A charcoal supplement which contains a large amount of dietary fibers	Activate AMPK	Apoptosis	Reduced the apoptotic signaling	[95]
Wild jujube polysaccharides	Dietary polysaccharides	Activate AMPK	Intestinal barrier function	Enhanced intestinal barrier function	[96]
Alginate	An acidic polysaccharide extracted from marine brown algae	AMPK/NF-κB	Improving intestinal microbiota	Inhibited inflammation response	[97]
Dioscin	A form of plant steroidal saponin	AMPK/mTOR	Autophagy	Protected against oxidative stress in intestinal epithelial cells	[98]
Broccoli-Derived Glucoraphanin	The precursor of phytochemical sulforaphane	AMPK / PGC1α / NRF2	Mitochondrial homeostasis	Alleviated oxidative stress	[99]
Resveratrol	A natural polyphenol present in several plants and fruits	Activate AMPK	The intestinal barrier	Restoration of the integrity of TJs	[100]
Dapagliflozin	A selective SGLT2 inhibitor for the management of type-2 diabetes mellitus	AMPK/mTOR	Autophagy, apoptosis	Reduced intestinal mucosal injury	[106]

(*Continued*)

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Table 1 (Continued).

Drugs	Type	Brief Function Mechanism	Biological Process	Treatment Outcome	References
Linagliptin	A potent dipeptidyl peptidase-IV (DPP-IV) inhibitor used in the treatment of type 2 diabetes mellitus	AMPK/SIRT1/PGC-1α	Inflammation	Alleviated intestinal inflammation	[107]
Small molecule GL-V9	A small-molecule AMPK activator	AMPK/FOXO3	Inflammation, autophagy	Degraded NLRP3 inflammasome	[111]
FA5	A pharmacological activator of AMPK	Activate AMPK	Inflammation	Curbing intestinal inflammation	[112]
BJ-3105, a 6-Alkoxypyridin-3-ol Derivative	Biologic agent	Activate AMPK, inhibit NOX	Inflammation	Restored intestinal epithelial barrier function and reduce inflammation	[114]
Coenzyme Q10	A lipid-soluble antioxidant	Activate AMPK	Inflammation	Attenuated inflammation	[115]
MOTS-c	A 16-amino acid mitochondrial deri-vative peptide	Activate AMPK	Apoptosis	Inhibited apoptosis	[116]
Cannabinoid Receptor 2	G-protein-coupled receptor	Activate AMPK	Autophagy	Inhibited NLRP3 inflammasome activation in macrophages	[117]
Baitouweng decoction	A traditional Chinese prescription	AMPK/mTOR	Promote autophagy, enhance the expression of intestinal epithelial tight junction proteins	Repaired the intestinal epithelial barrier and alleviates DSS-induced colitis in mice	[87]
Salicylate	A direct AMPKβ1 activator	Activate AMPK	Autophagy	Inhibited macrophage inflammation	[118]
Metformin	Anti-diabetic compound	Independent of intestinal epithelial cells AMPK	Enhance the expression of intestinal epithelial tight junction protein	Epithelial repair	[68,101]
5-aminoimidazole-4-carboxamide ribonucleoside	AMPK agonist	AMPK signaling	Mucosal immunity	Reducing proinflammatory cytokines production	[109,110]

Abbreviations: NLRP3, NOD-like receptor thermal protein domain associated protein 3; Nrf2, Nuclear factor erythroid-2 related factor 2; SIRT1, Silent Information Regulator 1; PGC-1α, Peroxisome proliferator-activated receptor-γ coactivator; mTOR, mammalian target of rapamycin; FFAR4, Free fatty acid receptor 4; PPARα, Peroxisome proliferator-activated receptor α; PPARγ, Peroxisome proliferator-activated receptor gamma; ACC1, Acetyl Co A Carboxylase 1; NOX, NADPH Oxidases; FOXO3, Forkhead box O3; ULK1, unc-51 like kinase 1.

remains shrouded in uncertainty. The predominant focus of AMPK research in the context of UC pertains to its involvement in cellular autophagy. While grasping the significance of AMPK in regulating autophagy offers insights into its mechanism, present conclusions are circumscribed. There exists a dearth of studies that bridge the crucial role of AMPK in autophagy regulation with clinical applications to benefit UC patients. The translation of foundational research into tangible clinical interventions stands as a pressing matter that requires urgent attention.

Recent research has unveiled the advantageous therapeutic outcomes associated with AMPK activators across a range of conditions, including autosomal dominant polycystic kidney disease, inflammatory bowel disease, muscular atrophy, neuronal loss, and X-linked adrenoleukodystrophy. Notably, compounds known for their anti-aging properties, such as dasatinib and quercetin, which extend the lifespan of mice, also function as AMPK activators. It is paramount to recognize, however, that prolonged AMPK activation could potentially entail detrimental consequences, including the risk of cardiac and renal hypertrophy, along with the potential association with Alzheimer's disease.[120] Hence, a targeted and transient approach to AMPK activation, akin to the effects of regular exercise, could prove pivotal in the management of ulcerative colitis and other closely linked disorders.

Conclusion and Perspectives

Disruption of intestinal mucosal barrier function, heightened mucosal permeability, immune-inflammatory infiltration within the mucosa, imbalanced Th17/Treg ratio, skewed macrophage polarization, inflammatory conditions, mitochondrial impairment, mitophagy, cellular apoptosis, autophagy, and necrosis collectively contribute to the progression, recurrence, chronicity, and potential carcinogenesis of ulcerative colitis. Taking into account the aforementioned examination, AMPK is implicated to varying extents in these pathological pathways, assuming a significant yet enigmatic role. Research on the involvement of AMPK in macrophage polarization and cell necrosis in ulcerative colitis remains relatively sparse. In my view, forthcoming investigations should allocate greater attention to exploring these two dimensions. The foundational principles underpinning the majority of these mechanisms continue to center on safeguarding the adenine nucleotide reservoir and, in a broader context, upholding energy equilibrium. Considering drug development, the diverse nature of AMPK has given rise to concerns regarding potential unintended outcomes when targeting it. While potent pan-β activators have been linked to cardiac hypertrophy in non-human primates,[121] clinical investigations centered on type 2 diabetes and/or cardiovascular disease have indicated that judicious use of AMPK activators proves both safe and efficacious.

Undoubtedly, in the future, we need to examine and study the complex and profound relationship between energy, substance metabolism, and the coordinated, interactive, and regulatory aspects of biological stress responses with a broader perspective and comprehensive knowledge.

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Yuyi Yuan, Fang Wang and Xingxing Liu have contributed equally to this work and share the first authorship.

Author Contributions

All authors have made substantial contributions to the work presented in the report, whether in conceptualization, research design, execution, data acquisition, analysis and interpretation, or in all of these domains. They participated in drafting, revising, or critically reviewing the manuscript, ultimately approving the final published version. Consensus was reached on the submission of the manuscript to the journal, and all authors have agreed to take responsibility for various aspects of the work.

Disclosure

The authors declare no conflict of interest.

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