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REVIEW

Apolipoprotein A-I: Potential Protection Against Intestinal Injury Induced by Dietary Lipid

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Abstract: The intestinal barrier system protects the human body from harmful factors, by continuously renewing the intestinal epithelium, tight junctions and enteric microbes. However, dietary fat can harm the intestinal epithelial barrier enhancing gut permeability. In recent years, Apolipoprotein A-I has attracted much attention because of its anti-inflammatory properties. Numerous studies have demonstrated that Apolipoprotein A-I can regulate mucosal immune cells, inhibit the progression of inflammation, promote epithelial proliferation and repair, and maintain physical barrier function; it can also regulate angiogenesis, thereby improving local circulation. This article is intended to elucidate the mechanism by which Apolipoprotein A-I improves intestinal barrier damage caused by dietary fat and to review the role of Apolipoprotein A-I in maintaining intestinal homeostasis.

Keywords: intestinal barrier, apolipoprotein A-I, dietary fat, gut microorganism, angiogenesis

Introduction

The gut is the largest boundary between the human body and the outside environment, with a complex barrier system to protect the body from toxins, bacteria and other potentially harmful substances.[1] It includes continuously renewing intestinal epithelial cells (IECs), tight junctions (TJs), and gut microbes. However, irritants such as those from diet, especially the fat, can breakdown the intestinal barrier, exposing the gut's contents to immune cells in the mucosal layers.[2] These changes will lead to mucosal immune disorder, promote an inflammatory response, damage intestinal structure, and make the body susceptible to various intestinal diseases, such as inflammatory bowel disease (IBD) and infectious diarrhea, etc.[3]

Dietary fat has been the focus of studies on intestinal barrier regulation. In a mouse model of IBD, intake of a high-fat diet (HFD) promotes and exacerbates experimental colitis.[4] In humans, a HFD is associated with an increased risk of IBD, possibly due to enhanced mucosal permeability of gut microbes or dietary antigens.[5] Specifically, there is a significant positive correlation between the prevalence of IBD and a country's industrialization status, as the diets of these societies tend to be richer in processed fats and sugars.[6] Therefore, there is a need to understand the molecular mechanisms of dietary fat-mediated intestinal barrier damage. Dietary fat ruins the intestinal barrier in various ways. Most lipolysis products cause permanent damage to the intestinal mucosal barrier by activating the oxidative stress response in intestinal epithelial cells. In addition, it can change the composition of the intestinal mucus layer and regulate the redistribution of tight junction proteins in the luminal surface of the intestinal epithelium. A HFD induces elevated serum levels of lysophosphatidylcholine(LPC).[7] Serum levels of LPC are positively correlated with intestinal barrier damage, which is thought to be associated with changes in intestinal flora. Therefore, unreasonable dietary fat intake can

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affect the intestinal barrier through oxidation, intestinal flora, IECs and other aspects, thus inducing intestinal diseases and dyslipidemia.[5]

Interestingly, intestinal mucosal injury diseases, such as IBD, are often accompanied by differences in the lipid metabolism profile,[8] even in the absence of a long-term high-fat diet. A US study of lipid profiles in 393 IBD patients (152 men and 241 women) found significant reductions in total cholesterol and high-density lipoprotein-C (HDL-C) and significant increases in low-density lipoprotein-C (LDL-C).[9] Studies have also shown that very low-density lipoprotein (VLDL) and HDL synthesis is associated with abnormal lipoprotein and apolipoprotein composition in patients with IBD.[10] The significant decrease in HDL-C is believed to be caused by missing or abnormal assembly components, and the metabolic abnormality of APOA-I is the main cause.[11]

Apolipoprotein A-I(APOA-I) is a multi-effector molecule. APOA-I is the major protein component of HDL.[12] APOA-I is mainly involved in the ABCA1/ABCG1-related signaling pathway, which plays an important role in the regulation of immune cell function, endothelial cell differentiation, epithelial structure integrity and platelet activation.[13] Colonic inflammation in APOA-I-deficient mice was more severe in a model of Dextran Sulfate Sodium Salt (DSS) - induced enteritis, and the use of APOA-I mimics significantly alleviated the progression of intestinal inflammatory injury.[14] Interestingly, a portion of APOA-I synthesized by intestinal epithelial cells does not enter the blood but is secreted and adheres to the luminal side of the intestine.[15] A long-term HFD reduced the expression of APOA-I in the gut and liver of mice, which was associated with the downregulation of peroxisome proliferator-activated receptor γ (PPARγ) and paraoxonase 1 (PON-1).[16] Similarly, biochemical and genetic markers of inflammation and abnormal lipid metabolism, such as increased C-reactive protein (CRP), lipoprotein (A), homocysteine, and decreased APOA-I and HDL expression, were observed in the serum of IBD patients. These studies suggest that APOA-I may be involved in the HFD-induced intestinal barrier damage.

In summary, APOA-I is involved in oxidation, inflammatory response, immune effect and other aspects, which is consistent with the pathway of intestinal damage caused by high-fat diet. Therefore, it is necessary to fully summarize relevant studies in this area to clarify that APOA-I can alleviate dietary fat-induced intestinal damage. In order to help us utilize our current understanding of APOA-I function in future studies, the source and site of action of APOA-I is summarized in Figure 1, and the possible role of APOA-I in the gut is summarized in Figure 2.

APOA-I is Involved in Inflammation and Immune Responses

It has long been known that the integrity of the intestinal barrier is highly sensitive to the inflammatory state of the gut. For example, the increased intestinal permeability observed in Crohn's disease (CD) is the result of abnormal IEC effects induced by proinflammatory mediators such as IL-1b, IL-6, IFN-γ, and TNF-α.[17] The CD-associated Th1 inflammatory response directly leads to pathological changes in the intestinal barrier by transducting cytokine signals to immune cells and IECs.[18] Of course, these cytokines have become major targets for inflammatory therapy.[19] HFD initially induces increased intestinal permeability and transient symbiosis of the gut microbiome, changes that may ultimately increase the risk of gut inflammation or exacerbate preexisting inflammation.[20] In addition to the above contents, dietary free fatty acids are also involved in the inflammatory reaction by directly stimulating inflammatory signals, further enhancing intestinal hyperpermeability.[21] The following aspects explain how APOA-I affects the pathogenesis of HFD through inflammation.

APOA-I Blocks LPS-Related Inflammatory Effects

LPS, a component of gram-negative bacteria, is an important antigen recognized by proinflammatory Toll-like receptor 4 (TLR4) in immune cells and intestinal epithelial cells. Intestinal permeability facilitates the passive translocation of luminal LPS or LPS-containing bacteria into the mucosal layer, increasing the transfer of LPS into the blood.[22] This relationship may partly explain the elevated serum LPS in patients with IBD and other intestinal diseases, such as necrotizing enterocolitis. Stimulation of a TLR4-CD14-dependent proinflammatory response, which directly alters the intestinal barrier, is the best-known effect of LPS. In addition, LPS directly induces rapid IEC shedding without compensating for TJ resealing.[23] It should be noted that dietary fat increased serum LPS levels independently of permeability status.[24]

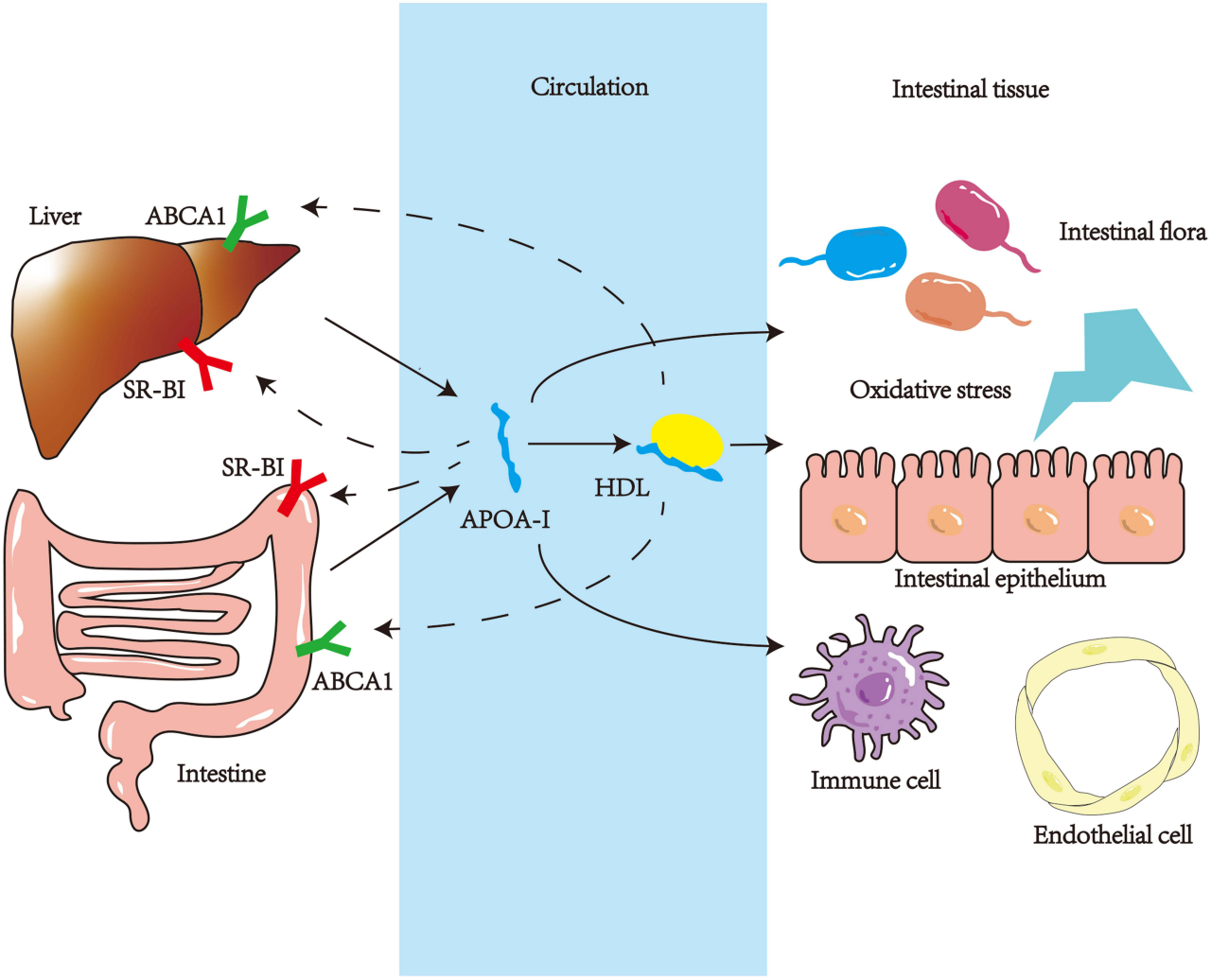

Figure 1 Biogenesis of APOA-I and targets of intestine-related effects. Approximately 75% of APOA-I protein is produced by hepatocytes, with the remaining 25% produced by small intestinal epithelial cells. Studies have shown that some APOA-I is also produced by the proximal end of the mouse colon, which is consistent with the reported expression of APOA-I in the human fetal colon. APOA-I is primarily catabolized in the liver. In the cell membranes of hepatocytes and enterocytes, APOA-I binding to ABCA1 mediates the production of nascent HDL particles and exerts lipid efflux. Also circulating and intestinal APOA-I can directly interact with intestinal epithelial cells, lamina propria immune cells, and vascular endothelial cells.

APOA-I prevents direct contact of LPS with immune cells and intestinal epithelial cells. APOA-I can directly neutralize endotoxins, including lipopolysaccharides (LPS) from gram-negative bacteria and teichoic acid (LTA) from gram-positive bacteria.[25] They constitute a complex that binds to the SR-BI receptor to remove endotoxins. In the absence of endotoxins, the activation of TLR4 is inhibited, and the expression of downstream inflammatory factors such as tumor necrosis factor, interleukin-1β (IL-1β), and interleukin-6 (IL-6) is reduced. The reduction in these proinflammatory factors prevents inflammatory damage to the gut. Thus, APOA-I prevents LPS from activating TLR in excess, thereby ameliorating LPS-related inflammatory damage caused by a HFD.

APOA-I Improves Immune Cell Differentiation and Proliferation

HFD is thought to be associated with low-grade intestinal inflammation,[26] which leads to metabolic disorders and susceptibility to colitis. These changes may be attributed to the effects of fatty acids, which may affect the differentiation and activity of intestinal immune cells. APOA-I seems to change that.

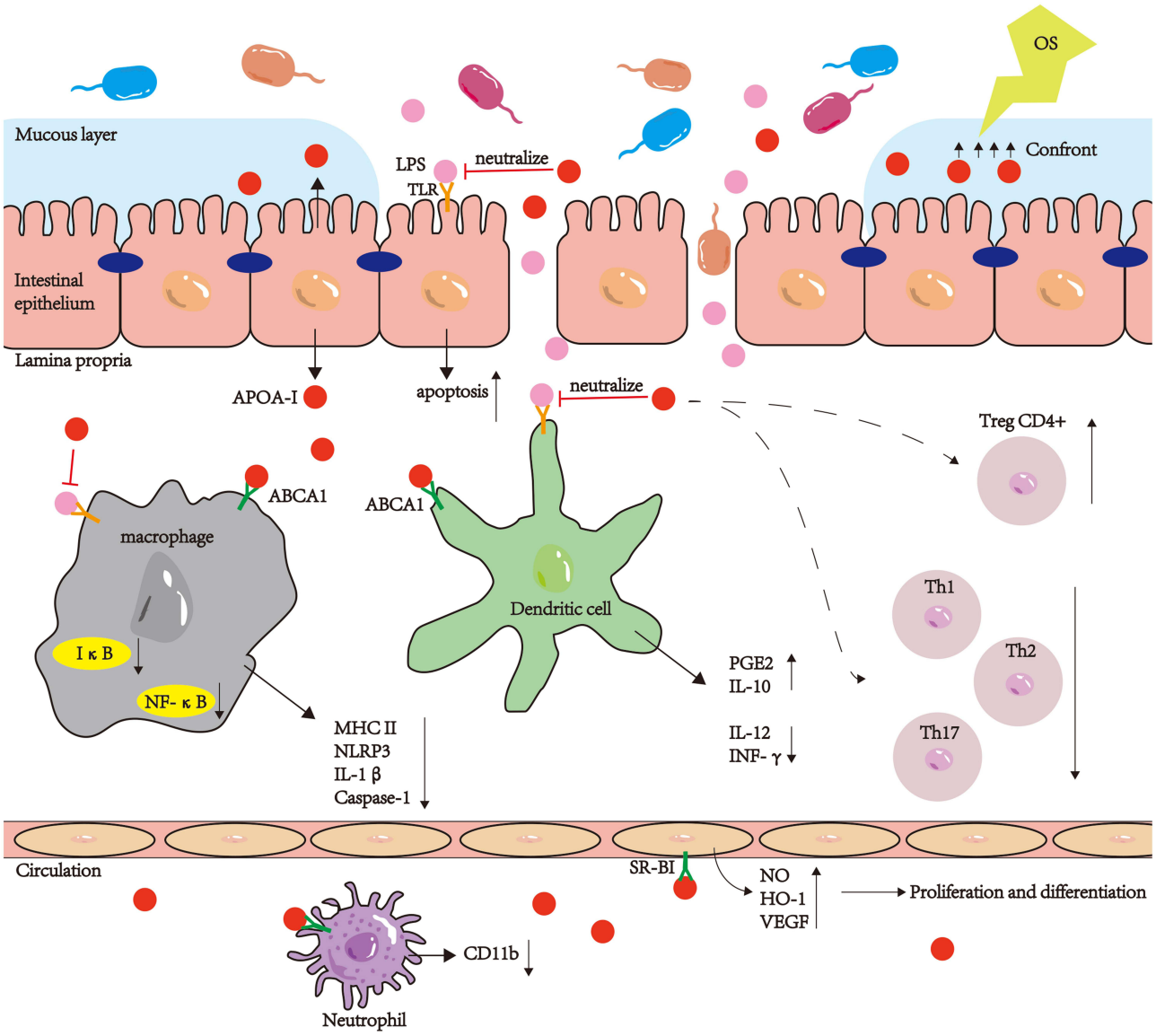

Figure 2 Mechanism by which APOA-I alleviates intestinal damage induced by HFD. APOA-I regulates intestinal immune inflammation, fights oxidative stress and promotes angiogenesis. APOA-I, produced in the intestine and of parenteral origin, acts in the intestinal epithelium, lamina propria and circulation. APOA-I blocks the LPS-induced inflammatory response and inhibits the NF-κB inflammatory pathway of macrophages and dendritic cells in the lamina propria through the ABCA1 receptor, thereby preventing the production of downstream inflammatory factors. Circulating APOA-I also decreases the effector function of neutrophils; APOA-I also regulates T-cell differentiation, causing an increase in Treg cells and a decrease in differentiation to Th1, Th2, and Th17. APOA-I can act directly on intestinal epithelium, promoting epithelial cell differentiation; APOA-I against antioxidant products, which avoids damage to the epithelial barrier. APOA-I can bind to SR-BI of endothelial cells and contribute to vascular neovascularization and vessel wall integrity.

APOA-I and Innate Immunity

In one study, mice deficient in the ATP-binding cassette transporter A1 (ABCA1) /ATP-binding cassette transporter G1 (ABCG1) receptor exhibited signs of the myeloproliferative disease, which could be suppressed by APOA-I transgene expression.[27] Further studies revealed that the immunosuppressive effect of APOA-I was dependent on a cholesterol-rich lipid raft microstructure, which was expressed in macrophages, neutrophils, dendritic cells, B cells, and T cells. There are a large number of docking sites in this microstructure, which trigger a series of signal transduction effects.[28] The binding of APOA-I to ABCA1 on lipid rafts induces cholesterol efflux. It decreases the lipid density on the cell membrane surface, lipid raft area, and CD11b expression and distribution density, which leads to the downregulation of neutrophil activation, migration, and adhesion.[29] Similarly, TLR signaling in macrophages and histocompatibility class II molecule (MHC II) expression in antigen-presenting cells were downregulated.[30] APOA-I also induces dendritic cell maturation

and differentiation, which are associated with increased expression of prostaglandin E2 and IL-10 and decreased expression of IL-12 and IFN-γ.[31] Therefore, APOA-I may regulate the differentiation and maturation of innate immune cells, which may be carried out in conjunction with the regulation of lipid metabolism.

Regardless of the fact that the lipid raft theory explains most of the immunosuppressive effects of APOA-I, there appear to be other pathways for APOA-I.[32] The expression of inflammatory molecules such as NOD-like receptor protein 3 (NLRP3), IL-1β, and Caspase-1 can be inhibited by APOA-I, especially in macrophages. ABCA1/ABCG1 receptor knockout mice showed Caspase-1 activation in monocytes, macrophages, and neutrophils, which induced immune cell apoptosis. Although there is no consensus, the accumulation of cholesterol or lipids in immune cells is a dangerous sign of inflammation, and APOA-I can counteract this effect.[33]

APOA-I and Adaptive Immunity

Eating a HFD has been reported to cause an increase in Th1 cells, CD8+ T cells, and Th17 cells and a decrease in Tregs in the lamina propria of the small intestine and colon. The cytokines produced by these adaptive immune cells also change. For example, the intestines of mice fed a HFD showed significant reductions in IL-17, IL-10, and IL-22.[34] These cytokines can regulate the recruitment of inflammatory cells and maintain the intestinal barrier by stimulating IECs to express TJs or increasing the proliferation of intestinal stem cells.

APOA-I also regulates the activity of adaptive immune cells. APOA-I inhibited inflammation in LDL-receptor null mice, an effect associated with an increase in regulatory T cells and a decrease in effector or memory T cells.[35] While inhibiting dendritic cell maturation, APOA-I also downregulates the responsiveness of Th1 and Th17 cells to reduce the progression of inflammation.[36] This suggests that APOA-I compensates for the excessive depletion of inflammatory T cells and inhibits their sensitivity to proinflammatory stimuli. This in turn counteracts the failure of inflammatory cell recruitment caused by the reduction of inflammatory factors caused by HFD.

The Proinflammatory Effects of NF-κB Were Inhibited by APOA-I

NF-κB plays a critical role in cellular inflammatory and immune responses. Dysfunctions that regulate the balance of NF-κB activation are present in IBD patients.[37] Such changes may result in a decrease in antimicrobial peptides and epithelial barrier disruption, leading to the invasion of pathogenic microorganisms. For example, hyperactivation of NF-κB induces the production of proinflammatory mediators such as cyclooxygenase-2 (COX-2), TNF-α, and IL-6.[38] In a mouse model of enteritis, this agitation is inhibited by the APOA-I mimetic peptide, which seems to be associated with autophagy by IkB kinase.[39] APOA-I excites ABCA1 and subsequently stimulates NF-κB activation. However, this did not demonstrate a significant proinflammatory effect. There appears to be a self-intervention that regulates ABCA1 downstream signaling. In conclusion, APOA-I and its mimicking peptide inhibited the inflammatory cytokine cascade induced by NF-κB overactivation and prevented the progression of intestinal inflammatory injury.

Regulation of Intestinal Epithelial Injury and Proliferation

The integrity of the intestinal epithelium is the most prominent physical part of the intestinal barrier, including the static apical junction complex (AJC) and the dynamic epithelial cell renewal process.[40] Under the guidance of Wnt signaling, IECs are continuously shed and replaced by new intestinal cells.[41] This is controlled by a complex process of superficial intestinal cell apoptosis, rapid AJC resealing, and basal cell upward movement, differentiation, and proliferation. The intestinal epithelium is exposed to digested food all the time, and dietary composition is the most direct factor affecting the intestinal epithelium. Dietary fat can impair intestinal epithelial integrity in both direct and indirect ways, and APOA-I appears to reverse these pathological changes.

APOA-I Improves Epithelial Barrier Function

Changing the integrity of the apical junction complex is part of the mechanism by which dietary fat regulates intestinal permeability.[42] The permeability of IECs can be dynamically altered by the rearrangement of cytoskeletal elements, expression of AJC proteins, or posttranslational modifications. Therefore, disruption of AJC complexes results in increased intestinal permeability. Recent studies have shown that dietary fat directly regulates AJC integrity. For

example, chronic HFD consumption decreases intestinal TJ protein expression in mice.[43] Certain fatty acids enriched in a HFDassist in the redistribution of actin and TJ proteins mediated by protein kinase C (PKC).[44] These results confirm that dietary fat directly alters intestinal epithelial integrity by interacting with intestinal epithelial cells.

APOA-I has been demonstrated to affect the expression and rearrangement of tight junction proteins. Recovery of tight junction proteins ZO-1 and occludin was observed in APOA-I bronchial asthmatic mice, which was associated with increased expression of lipoxin A4 (LXA4).[45] In acute respiratory distress syndrome-sepsis model mice, APOA-I induced proliferation and migration of type II alveolar epithelial cells through the MAPK pathway and enhanced intercellular junctions.[46] Similarly, APOA-I increased renal podocyte density and glomerular synaptic protein expression.[47] An increasing amount of data suggests that APOA-I can increase the integrity of the epithelial barrier. However, the mechanism of interaction between APOA-I and intestinal epithelial cells needs further clarification.

APOA-I Improves Intestinal Oxidation

Dietary fats are rich in polyunsaturated fatty acids, which easily stimulate oxidation (OS).[48] Studies have shown that OS disrupts intestinal barrier function mainly by altering enterocyte shedding-proliferation, disrupting the OCLN-ZO1 pathway, and inducing inflammation, which predisposes the gut to chronic diseases such as IBD. Treatment of Caco2 cells with lipid peroxides not only induced significant oxidative stress, but also inhibited the G0/G1 cell transition and the expression of cyclin D/cycle-dependent kinase 4, and enhanced DNA oxidation in a concentration-dependent manner.[49] Therefore, inhibition of oxidative stress can reverse the damage to the intestinal epithelium caused by dietary fat.

As a cholesterol scavenger, APOA-I promotes oxidative lipid clearance. APOA-I inhibits oxidative stress in several ways. APOA-I mimetic peptide 4F can increase the expression and activity of antioxidant enzymes, including heme oxygenase 1 (HO-1) and superoxide dismutase (SOD), in endothelial and epithelial cells.[50] Indeed, the main effect of APOA-I on oxidative damage may be the change it has on mitochondrial repair.[51] APOA-1 regulates the balance between Th-17 cells and Tregs, improves mitochondrial function, increases mitochondrial electron transport chain (ETC) activity, and stabilizes PON-1 in HDL particles, which maintain PON-1 activity.[52] The latter can prevent immune membrane lipid peroxidation, circulating oxidized lipoproteins, and mitochondrial oxidative damage. Chronically elevated ROS/RNS levels are responsible for the depletion of APOA-1 and PON-1 levels. Meanwhile, chronic oxidative stress induces APOA-1 dysfunction. In this environment, PON-1 also appears dysfunctional, which seems to be mediated by elevated MPO activity. These studies suggest that APOA-I can ameliorate the increased intestinal permeability and risk of intestinal disease associated with intestinal OS.

APOA-I Regulates Energy Metabolism in IECs

Any activity requires an adequate supply of energy, and mitochondria are the main sites for energy metabolism.[53] Mitochondrial function disorders have been observed in IBD patients, suggesting a significant link between the disease and mitochondrial dysfunction. Intestinal cells from patients with IBD have lower energy levels than cells from healthy subjects.[54] Notably, mitochondrial mutations in mice resulted in increased intestinal ATP levels and oxidative phosphorylation activity, thereby protecting mice from experimental colitis.

Improved energy metabolism is regarded as an important component of APOA-I repair of the damaged epithelial barrier in disease states. However, 4F can regulate the glycolysis process and improve energy utilization efficiency.[55] When intestinal mucosal damage stimulates inflammatory injury, the immature vascular network leads to local tissue hypoxia, which further induces OS. At this time, energy metabolism changes from aerobic metabolism to anaerobic digestion. 4F governs the expression of fructose-2 kinase 6-phosphate/fructose-2,6-diphosphatase (PFKFB3), an activator of glycolysis.[56] Therefore, APOA-I enhances glycolytic efficiency, enhances cell proliferation and migration activity, improves cell energy supply, and maintains normal epithelial function under disease conditions. There appear to be fewer SCFA-producing bacteria in the microbiota of IBD patients. Therefore, mice lacking bacteria in their gut have colonic cells that favor glycolysis over mitochondrial respiration, leading to dysfunctional proliferation.[57]

APOA-I Promotes Angiogenesis and Improves Microcirculation

The Microcirculatory Disturbance is a Disease Characteristic of IBD

Microcirculation disorder is deemed to be another important part of the pathogenesis of IBD.[58] Rupture of mucosal capillaries was observed early in the process of DSS-induced enteritis before the appearance of intestinal epithelial injury.[59,60] Confocal microscopy revealed similar microcirculatory disturbances and extensive angiogenesis at sites of intestinal inflammation in IBD patients.[61] However, these capillary networks that are driven by chronic inflammation are relatively immature and hypoperfused. This leads to local hypoxia and energy deficiency, which further cause a large number of inflammatory cells to accumulate and maintain the persistence of inflammation. Dietary fat also harms to intestinal mucosal vascular endothelial cells,[62] which leads to dysplasia of the microvascular network during intestinal mucosal repair, and further promotes the chronic prolongation of the disease course.

Protective Effect of APOA-I on the Vascular Endothelium

Initially, APOA-I-mimicking peptide 4F was considered to promote migration and tubular formation in human umbilical vein endothelial cells (HUVECs) in a dose-dependent manner.[50] Liu et al also showed that 4F ameliorated the impaired proliferation and migration of endothelial cells induced by OX-LDL and further confirmed that 4F upregulated the expression of heme oxygenase-1 (HO-1) through the Akt/MAPK/eNOS pathway.

Endothelial progenitor cells (EPCs) play an important role in the maintenance and repair of the vascular structure and are an important source of vascular endothelial cells.[63] Peptide 4F could significantly enhance EPC proliferation, migration, and adhesion by stimulating NO production. Peptide 4F pretreatment can increase the expression and activation of eNOS and further induce the production of NO, indicating that 4F enhances the biological function of EPCs through the eNOS/NO pathway. Yang et al confirmed that 4F affected eNOS expression through PI3K/AKT.[64] This indicates that APOA-I regulates EPCs in multiple ways. Another APOA-I mimicking peptide, 5F, promotes the differentiation of bone marrow multifunctional adult progenitor cells into endothelial cells by activating ERK1/2 signaling.[65] Thus, APOA-I-mimicking peptides can increase endothelial cell origin and promote endothelial cell proliferation, migration, and tubular formation, which are essential steps in angiogenesis.

APOA-I has been shown to partially reverse the vascular damage of a HFD. In a mouse model of carotid artery injury, 4F promoted reendothelialization of the injured intima.[66,67] Intramuscular injection of 4F into a mouse model of hindlimb ischemia can significantly increase the capillary density and promote blood flow recovery of the ischemic hindlimb muscle and functional recovery of the hindlimb.[68] On the other hand, in hyperlipidemia, inflammatory HDL triggers an impaired VEGF pathway leading to angiogenic dysfunction. Inflammatory HDL is neither reduced in its ability to reverse cholesterol trafficking nor its role in anti-inflammatory and antioxidant stress.[69] 4F can promote the proliferation and reendothelialization of carotid endothelial cells treated with oxidized HDL but not in SR-B1 knockout mice, suggesting that 4F acts through the classical HDL receptor SR-B1.[70] Therefore, 4F may play a protective role in endothelial cells by regulating the quantity and quality of HDL.

APOA-I and Gut Microbiota

There are trillions of microbes in the gut with multiple functions including metabolism, inflammation, and maintenance of intestinal barrier integrity.[71] Changes in diet can directly alter intestinal microbial richness and composition.[72] Numerous studies have investigated changes in gut microbiota species caused by dietary fat.[73] The results of these studies suggest that HFD can temporarily reduce microbes that promote the gut barrier, such as Lactobacillus and Bifidobacterium,[74] while increasing microbes that are involved in lowering barrier integrity, such as Oscillibacter and Desulfovibrio.[75] In one study, APOA-1 expression was positively correlated with the abundance of Proteus and Firmicutes. This may be related to intestinal barrier function, where these microorganisms act on the gut to stimulate the expression of enterocyte genes such as TJ proteins.[76] At present, it is unclear how APOA-I specifically regulates the gut microbiome, and more studies are required to elucidate the mechanisms associated with APOA-I in gut-microbe interactions.

Conclusion

The intestine is the first line of defense against food, toxins and antigens. The intact intestinal barrier includes the mucus layer, AJC, constant renewal of epithelial cells and the mucosal immune system, while the intestinal flora and nutrient supply are also involved in the intestinal defense mechanism. The barrier system can be disrupted by various harmful factors, especially dietary fats. The intake of dietary fat is inevitable in daily life. Therefore, it is necessary to investigate the mechanism of intestinal barrier damage induced by dietary fat and effective intervention methods. The study of the mechanism of dietary fat damage can increase our understanding of the intestinal barrier and requires us to explore new effective therapeutic approaches.

The emergence of APOA-I provides new ideas for future studies on intestinal barrier maintenance. It plays an important role in inflammation, immune response, intestinal flora and blood circulation. APOA-I appears to be involved in, and combats, any aspect of intestinal damage caused by dietary fat. APOA-I is no longer just a simple indicator of lipid metabolism. It is expected to become a new intestinal protective factor under the modern dietary pattern, or as one of the key clues in the study of the mechanism of intestinal injury disease. Increasing APOA-I production or applying APOA-I mimetic peptides seems to be a new alternative therapy to alleviate tissue inflammation and maintain intestinal barrier damage.

Data Sharing Statement

Data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no competing interests.

References

1. Luo J, Liang S, Jin F. Gut microbiota and healthy longevity. *Sci China Life Sci*. 2024. doi:10.1007/s11427-023-2595-5
2. Covello C, Becherucci G, Di Vincenzo F, et al. Parenteral nutrition, inflammatory bowel disease, and gut barrier: an intricate plot. *Nutrients*. 2024;16:2288. doi:10.3390/nu16142288
3. Dhuppar S, Murugaiyan G. miRNA effects on gut homeostasis: therapeutic implications for inflammatory bowel disease. *Trends Immunol*. 2022;43:917–931. doi:10.1016/j.it.2022.09.003
4. Li M, Ding Y, Wei J, et al. Gut microbiota metabolite indole-3-acetic acid maintains intestinal epithelial homeostasis through mucin sulfation. *Gut Microbes*. 2024;16:2377576. doi:10.1080/19490976.2024.2377576
5. Yin L, Azi F, Xia X, et al. Microbiome-metabolomics-based insight into the protective effects of dietary fiber from sweetpotato residues on the high-fat diet-induced intestinal integrity damage. *Int J Biol Macromol*. 2024;275:133620. doi:10.1016/j.ijbiomac.2024.133620
6. Kempinski R, Arabasz D, Neubauer K. Effects of milk and dairy on the risk and course of inflammatory bowel disease versus patients' dietary beliefs and practices: a systematic review. *Nutrients*. 2024;16:2555. doi:10.3390/nu16152555
7. Chen H, Ye C, Wu C, et al. Berberine inhibits high fat diet-associated colorectal cancer through modulation of the gut microbiota-mediated lysophosphatidylcholine. *Int J Biol Sci*. 2023;19:2097–2113. doi:10.7150/ijbs.81824
8. Hung C-T, Ma C, Panda SK, et al. Western diet reduces small intestinal intraepithelial lymphocytes via FXR-Interferon pathway. *Mucosal Immunol*. 2024. doi:10.1016/j.mucimm.2024.07.001
9. Tilg H, Fumery M, Hedin CRH. Does cardiovascular risk matter in IBD patients? *J Intern Med*. 2023;294:708–720. doi:10.1111/joim.13735
10. Chen H, Li W, Hu J, et al. Association of serum lipids with inflammatory bowel disease: a systematic review and meta-analysis. *Front Med Lausanne*. 2023;10:1198988. doi:10.3389/fmed.2023.1198988

11. Tao X, Tao R, Wang K, Wu L. Anti-inflammatory mechanism of Apolipoprotein A-I. *Front Immunol*. 2024;15:1417270. doi:10.3389/fimmu.2024.1417270
12. Giorgi L, Niemelä A, Kumpula E-P, et al. Mechanistic insights into the activation of lecithin-cholesterol acyltransferase in therapeutic nanodiscs composed of apolipoprotein A-I mimetic peptides and phospholipids. *Mol Pharm*. 2022;19:4135–4148. doi:10.1021/acs.molpharmaceut.2c00540
13. Khattib A, Shmet M, Ashkar R, Hayek T, Khatib S. Novel bioactive lipids enhanced HDL-mediated cholesterol efflux from macrophages through the ABCA1 receptor pathway. *Chem Phys Lipids*. 2024;258:105367. doi:10.1016/j.chemphyslip.2023.105367
14. Li WH, Tanimura M, Luo CC, Datta S, Chan L. The apolipoprotein multigene family: biosynthesis, structure, structure-function relationships, and evolution. *J Lipid Res*. 1988;29:245–271. doi:10.1016/S0022-2275(20)38532-1
15. Danielsen EM, Hansen GH, Rasmussen K, Niels-Christiansen -L-L, Frenzel F. Apolipoprotein A-1 (apoA-1) deposition in, and release from, the enterocyte brush border: a possible role in transintestinal cholesterol efflux (TICE)? *Biochim Biophys Acta*. 2012;1818:530–536. doi:10.1016/j.bbamem.2011.11.011
16. Xing L, Liu Y, Wang J, Tian P, Liu P. High-Density Lipoprotein and Heart Failure. *Rev Cardiovasc Med*. 2023;24:321. doi:10.31083/j.rcm2411321
17. Maddipatla SC, Kolachala VL, Venkateswaran S, et al. Assessing cellular and transcriptional diversity of ileal mucosa among treatment-naïve and treated crohn's disease. *Inflamm Bowel Dis*. 2022;2022:1.
18. Che S, Qin B, Wu K, et al. EGCG drives gut microbial remodeling-induced epithelial GPR43 activation to lessen Th1 polarization in colitis. *Redox Biol*. 2024;75:103291. doi:10.1016/j.redox.2024.103291
19. Zuurveld M, Ayechu-Muruzabal V, Folkerts G, Garssen J, Van't Land B, Willemsen LEM. Specific human milk oligosaccharides differentially promote th1 and regulatory responses in a CpG-Activated epithelial/immune cell coculture. *Biomolecules*. 2023;14:13. doi:10.3390/biom14010013
20. Wekema L, Schoenmakers S, Schenkelaars N, et al. Obesity and diet independently affect maternal immunity, maternal gut microbiota and pregnancy outcome in mice. *Front Immunol*. 2024;15:1376583. doi:10.3389/fimmu.2024.1376583
21. Arifuzzaman M, Won TH, Li -T-T, et al. Inulin fibre promotes microbiota-derived bile acids and type 2 inflammation. *Nature*. 2022;611:578–584. doi:10.1038/s41586-022-05380-y
22. Vermeire B, Walsh M, Cox E, Devriendt B. The lipopolysaccharide structure affects the detoxifying ability of intestinal alkaline phosphatases. *BMC Vet Res*. 2024;20:358. doi:10.1186/s12917-024-04208-3
23. Wang Y, Xiao J, Wei S, et al. Protective effect of zinc gluconate on intestinal mucosal barrier injury in antibiotics and LPS-induced mice. *Front Microbiol*. 2024;15:1407091. doi:10.3389/fmicb.2024.1407091
24. Erlanson-Albertsson C, Stenkula KG, Bagnato VS, Romero MP. The importance of food for endotoxemia and an inflammatory response. *Int J Mol Sci*. 2021;23:22. doi:10.3390/ijms23010022
25. Owen AR, Farias A, Levins A-M, et al. Exposure to bacterial PAMPs before RSV infection exacerbates innate inflammation and disease via IL-1α and TNF-α. *Mucosal Immunol*. 2024. doi:10.1016/j.mucimm.2024.08.002
26. Zhang W, Zhu M, Liu X, et al. Edible bird's nest regulates glucose and lipid metabolic disorders via the gut-liver axis in obese mice. *Food Funct*. 2024;15:7577–7591. doi:10.1039/D4FO00563E
27. Teigen M, Ås Ø, Bjune K, Leren TP, Bogsrud MP, Strøm TB. Functional characterization of missense variants affecting the extracellular domains of ABCA1 using a fluorescence-based assay. *J Lipid Res*. 2024;65:100482. doi:10.1016/j.jlr.2023.100482
28. Harsch BA, Borkowski K, Walker RE, Pedersen TL, Newman JW, Shearer GC. ABCA1 and apoA-I dependent 12-hydroxyeicosatetraenoic acid efflux regulates macrophage inflammatory signaling. *bioRxiv*. 2024. doi:10.1101/2024.07.11.603001
29. Richart AL, Reddy M, Khalaji M, et al. Apo AI nanoparticles delivered post myocardial infarction moderate Inflammation. *Circ Res*. 2020;127:1422–1436. doi:10.1161/CIRCRESAHA.120.316848
30. Sana I, Mantione ME, Meloni M, et al. Dimethyl itaconate selectively targets inflammatory and metabolic pathways in chronic lymphocytic leukemia. *Eur J Immunol*. 2023;53:e2350418.
31. Kim KD, Lim HY, Lee HG, et al. Apolipoprotein A-I induces IL-10 and PGE2 production in human monocytes and inhibits dendritic cell differentiation and maturation. *Biochem Biophys Res Commun*. 2005;338:1126–1136. doi:10.1016/j.bbrc.2005.10.065
32. Choi S, Choi S-H, Bastola T, et al. AIBP: a new safeguard against glaucomatous neuroinflammation. *Cells*. 2024;2024:13.
33. Westerterp M, Gautier EL, Ganda A, et al. Cholesterol accumulation in dendritic cells links the inflammasome to acquired immunity. *Cell Metab*. 2017;2017:25.
34. Yoshida M, Funasaka Y, Saeki H, Yamamoto M, Kanda N. Dietary fiber inulin improves murine imiquimod-induced psoriasis-like dermatitis. *Int J Mol Sci*. 2023;25:24. doi:10.3390/ijms25010024
35. Chen W, Wu Y, Lu Q, Wang S, Xing D. Endogenous ApoA-I expression in macrophages: a potential target for protection against atherosclerosis. *Clin Chim Acta*. 2020;505:55–59. doi:10.1016/j.cca.2020.02.025
36. Delk SC, Chattopadhyay A, Escola-Gil JC, Fogelman AM, Reddy ST. Apolipoprotein mimetics in cancer. *Semin Cancer Biol*. 2021;73:158–168. doi:10.1016/j.semcancer.2020.11.002
37. Tsopmejio ISN, Yuan J, Diao Z, et al. Auricularia polytricha and Flammulina velutipes reduce liver injury in DSS-induced Inflammatory Bowel Disease by improving inflammation, oxidative stress, and apoptosis through the regulation of TLR4/NF-κB signaling pathways. *J Nutr Biochem*. 2022;111:109190. doi:10.1016/j.jnutbio.2022.109190
38. Meriwether D, Sulaiman D, Volpe C, et al. Apolipoprotein A-I mimetics mitigate intestinal inflammation in COX2-dependent inflammatory bowel disease model. *J Clin Invest*. 2019;129:3670–3685. doi:10.1172/JCI123700
39. Gerster R, Eloranta JJ, Hausmann M, et al. Anti-inflammatory function of high-density lipoproteins via autophagy of IκB kinase. *Cell Mol Gastroenterol Hepatol*. 2015;1:1.
40. Ma R, Feng L, Wu P, et al. Dietary copper improves intestinal structural integrity in juvenile grass carp (Ctenopharyngodon idella) probably related to its increased intestinal antioxidant capacity and apical junction complex. *Anim Nutr*. 2024;2024:18.
41. Wang K, Liu Y, Li H, et al. Claudin-7 is essential for the maintenance of colonic stem cell homoeostasis via the modulation of Wnt/Notch signalling. *Cell Death Dis*. 2024;15:284. doi:10.1038/s41419-024-06658-x
42. Mashaqi S, Laubitz D, Morales EJD, et al. Interactive effect of combined intermittent and sustained hypoxia and high-fat diet on the colonic mucosal microbiome and host gene expression in mice. *Nat Sci Sleep*. 2022;14:1623–1639. doi:10.2147/NSS.S370957
43. Poritz LS, Garver KI, Green C, Fitzpatrick L, Ruggiero F, Koltun WA. Loss of the tight junction protein ZO-1 in dextran sulfate sodium induced colitis. *J Surg Res*. 2007;140:12–19. doi:10.1016/j.jss.2006.07.050

44. Usami M, Komurasaki T, Hanada A, Kinoshita K, Ohata A. Effect of gamma-linolenic acid or docosahexaenoic acid on tight junction permeability in intestinal monolayer cells and their mechanism by protein kinase C activation and/or eicosanoid formation. *Nutrition*. 2003;19:150–156. doi:10.1016/S0899-9007(02)00927-9
45. Park SW, Lee EH, Lee EJ, et al. Apolipoprotein A1 potentiates lipoxin A4 synthesis and recovery of allergen-induced disrupted tight junctions in the airway epithelium. *Clin Exp Allergy*. 2013;43:914–927. doi:10.1111/cea.12143
46. Yang L, Liu S, Han S, et al. The HDL from septic-ARDS patients with composition changes exacerbates pulmonary endothelial dysfunction and acute lung injury induced by cecal ligation and puncture (CLP) in mice. *Respir Res*. 2020;21:293. doi:10.1186/s12931-020-01553-3
47. Kon V, Yang H-C, Smith LE, Vickers KC, Linton MF. High-density lipoproteins in kidney disease. *Int J Mol Sci*. 2021;23:22.
48. Shen Y, Li X, Bao Y, et al. Lipid metabolic disorders and physiological stress caused by a high-fat diet have lipid source-dependent effects in juvenile black seabream acanthopagrus schlegelii. *Fish Physiol Biochem*. 2022;48:955–971. doi:10.1007/s10695-022-01095-z
49. Gotoh Y, Noda T, Iwakiri R, Fujimoto K, Rhoads CA, Aw TY. Lipid peroxide-induced redox imbalance differentially mediates CaCo-2 cell proliferation and growth arrest. *Cell Prolif*. 2002;35:221–235. doi:10.1046/j.1365-2184.2002.00241.x
50. Xu W, Qian M, Huang C, et al. Comparison of mechanisms of endothelial cell protections between high-density lipoprotein and apolipoprotein A-I mimetic peptide. *Front Pharmacol*. 2019;10:817. doi:10.3389/fphar.2019.00817
51. Duan M, Chen H, Yin L, et al. Mitochondrial apolipoprotein A-I binding protein alleviates atherosclerosis by regulating mitophagy and macrophage polarization. *Cell Commun Signal*. 2022;20:60. doi:10.1186/s12964-022-00858-8
52. Guirgis FW, Black LP, Henson M, et al. A hypolipoprotein sepsis phenotype indicates reduced lipoprotein antioxidant capacity, increased endothelial dysfunction and organ failure, and worse clinical outcomes. *Crit Care*. 2021;25:341. doi:10.1186/s13054-021-03757-5
53. Schavemaker PE, Muñoz-Gómez SA. The role of mitochondrial energetics in the origin and diversification of eukaryotes. *Nat Ecol Evol*. 2022;6:1307–1317. doi:10.1038/s41559-022-01833-9
54. G-T H, Theiss AL. Mitochondria and inflammatory bowel diseases: toward a stratified therapeutic intervention. *Annu Rev Physiol*. 2022;84:435–459. doi:10.1146/annurev-physiol-060821-083306
55. Jiang T, Du Q, Huang C, et al. NMR-based metabolomic analysis on the protective effects of apolipoprotein A-I mimetic peptide against contrast media-induced endothelial dysfunction. *Molecules*. 2021;26:5123. doi:10.3390/molecules26175123
56. De Bock K, Georgiadou M, Schoors S, et al. Role of PFKFB3-driven glycolysis in vessel sprouting. *Cell*. 2013;154:651–663.
57. Trapecar M, Communal C, Velazquez J, et al. Gut-liver physiomimetics reveal paradoxical modulation of IBD-Related inflammation by short-chain fatty acids. *Cell Syst*. 2020;2020:10.
58. Di Y, Li H, Yang J, et al. PPARγ/NF-κB axis contributes to cold-induced resolution of experimental colitis and preservation of intestinal barrier. *Biochim Biophys Acta Mol Basis Dis*. 2024;1870:167326. doi:10.1016/j.bbadis.2024.167326
59. Saijo H, Tatsumi N, Arihiro S, et al. Microangiopathy triggers, and inducible nitric oxide synthase exacerbates dextran sulfate sodium-induced colitis. *Lab Invest*. 2015;95:728–748. doi:10.1038/labinvest.2015.60
60. Zhang C, Chen H, He Q, et al. Fibrinogen/AKT/microfilament axis promotes colitis by enhancing vascular permeability. *Cell Mol Gastroenterol Hepatol*. 2021;11:683–696. doi:10.1016/j.jcmgh.2020.10.007
61. Tian Y, Zheng Y, Teng G, Li J, Wang H. Imbalanced mucosal microcirculation in the remission stage of ulcerative colitis using probe-based confocal laser endomicroscopy. *BMC Gastroenterol*. 2019;19:114. doi:10.1186/s12876-019-1037-6
62. Meng L-B, Chen K, Zhang Y-M, Gong T. Common injuries and repair mechanisms in the endothelial lining. *Chin Med J*. 2018;131:2338–2345. doi:10.4103/0366-6999.241805
63. George AL, Bangalore-Prakash P, Rajoria S, et al. Endothelial progenitor cell biology in disease and tissue regeneration. *J Hematol Oncol*. 2011;4:24. doi:10.1186/1756-8722-4-24
64. Wang J, Zhan H, Wang M, Song H, Sun J, Zhao G. Correction for: sonic hedgehog signaling promotes angiogenesis of endothelial progenitor cells to improve pressure ulcers healing by PI3K/AKT/eNOS signaling. *Aging*. 2023;15:15703–15704. doi:10.18632/aging.205458
65. Zhang J, Cui Y, Li X, et al. 5F peptide promotes endothelial differentiation of bone marrow stem cells through activation of ERK1/2 signaling. *Eur J Pharmacol*. 2020;876:173051. doi:10.1016/j.ejphar.2020.173051
66. Liu D, Ding Z, Wu M, et al. The apolipoprotein A-I mimetic peptide, D-4F, alleviates ox-LDL-induced oxidative stress and promotes endothelial repair through the eNOS/HO-1 pathway. *J Mol Cell Cardiol*. 2017;105:77–88. doi:10.1016/j.yjmcc.2017.01.017
67. He D, Zhao M, Wu C, et al. Apolipoprotein A-1 mimetic peptide 4F promotes endothelial repairing and compromises reendothelialization impaired by oxidized HDL through SR-B1. *Redox Biol*. 2018;15:228–242. doi:10.1016/j.redox.2017.11.027
68. Takata K, Imaizumi S, Kawachi E, et al. The ApoA-I mimetic peptide FAMP promotes recovery from hindlimb ischemia through a nitric oxide (NO)-related pathway. *Int J Cardiol*. 2016;207:317–325. doi:10.1016/j.ijcard.2016.01.012
69. Navab M, Ananthramaiah GM, Reddy ST, et al. The oxidation hypothesis of atherogenesis: the role of oxidized phospholipids and HDL. *J Lipid Res*. 2004;2004:45.
70. Kluck GEG, Qian AS, Sakarya EH, Quach H, Deng YD, Trigatti BL. Apolipoprotein A1 Protects Against necrotic core development in atherosclerotic plaques: PDZK1-dependent high-density lipoprotein suppression of necroptosis in macrophages. *Arterioscler Thromb Vasc Biol*. 2023;43:45–63. doi:10.1161/ATVBAHA.122.318062
71. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007;56:1761–1772. doi:10.2337/db06-1491
72. Gupta VK, Paul S, Geography DC. Ethnicity or subsistence-specific variations in human microbiome composition and diversity. *Front Microbiol*. 2017;8:1162. doi:10.3389/fmicb.2017.01162
73. Wu W, Lv L, Shi D, et al. Protective effect of against immune-mediated liver injury in a mouse model. *Front Microbiol*. 2017;8:1804. doi:10.3389/fmicb.2017.01804
74. Chen L, Jiang Q, Lu H, et al. Effects of tea seed oil extracted by different refining temperatures on the intestinal microbiota of high-fat-diet-induced obese mice. *Foods*. 2024;2024:13.
75. Wang B, Kong Q, Li X, et al. A high-fat diet increases gut microbiota biodiversity and energy expenditure due to nutrient difference. *Nutrients*. 2020;13:12. doi:10.3390/nu13010012
76. Anderson RC, Cookson AL, McNabb WC, et al. Lactobacillus plantarum MB452 enhances the function of the intestinal barrier by increasing the expression levels of genes involved in tight junction formation. *BMC Microbiol*. 2010;10:316. doi:10.1186/1471-2180-10-316