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Research Progress on the Multifunctionality of Dipeptidyl Peptidase 4 and the Mechanism of Action of Related Drug Targets

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Abstract:

Dipeptidyl peptidase 4 (DPP4) is a serine membrane-anchored exopeptidase that plays an important regulatory role in various physiological or pathological processes in the human body. DPP4 not only acts as a transcription factor to regulate the transcription and expression of downstream target genes, but also functions as a regulator independent of transcription, exerting its regulatory effects through protein-protein interactions. In current research, DPP4 is closely related to a variety of diseases, and multiple substances with potential targeting of DPP4 have been discovered. This article mainly reviews the multifunctionality of DPP4 in regulating various aspects such as energy metabolism, inflammation, tissue repair, and carcinogenesis. Simultaneously, based on the pathological development process of chronic liver disease, it also summarizes the screening of DPP4 inhibitors *in vitro* and their research progress in regulating chronic liver disease.

Keywords:

Dipeptidyl peptidase 4
Drug target
Inflammatory response
Tissue repair
Energy metabolism
Chronic liver disease

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1. Introduction

Dipeptidyl peptidase 4 (DPP4) is a serine protease capable of cleaving peptides with specific N-terminal characteristics. It is widely expressed in various cell types, including endothelial cells, fibroblasts, and lymphocytes, and exists in the cell membrane as a dimer. DPP4 is a type II transmembrane protein with a short six-amino acid cytoplasmic tail. It exhibits activity in the form of a dimer, with a monomeric molecular weight of 110 ku, and also exists in a soluble form in bodily fluids. Currently, soluble

DPP4 has been found to mainly originate from myeloid cells, skeletal muscle cells, vascular smooth muscle cells, and adipocytes. Based on comprehensive research findings, DPP4 has multiple substrates, exhibiting pleiotropic functions [1]. DPP4 inhibitors are a class of drugs that prevent the degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) by inhibiting the activity of DPP4. These drugs play a significant role in glucose metabolism and have been widely recognized.

2. Molecular structural characteristics of DPP4

DPP4 is a serine membrane-anchored exopeptidase belonging to the dipeptidyl peptidase family. It is also known as T-cell surface antigen CD26 and is widely present in various tissues and cells in humans, with high expression levels in the kidney and small intestine. DPP4 is a transmembrane glycoprotein composed of 766 amino acids with a relative molecular weight of 110 ku. Its structure includes an extracellular domain, a transmembrane domain, and an intracellular domain. The extracellular domain consists of an N-terminal signal peptide sequence, an N-terminal region of about 720 amino acid residues, and a C-terminal region of about 200 amino acid residues. The N-terminal region contains a conserved enzymatic active site that can hydrolyze various biologically active peptides. The transmembrane domain is composed of a hydrophobic alpha-helix structure, allowing it to be anchored to the cell membrane. The DPP4 protein consists of four domains, including a short cytoplasmic domain (1–6), a transmembrane domain (7–28), a flexible stalk segment (29–39), and an extracellular domain (40–766) [1] (**Figure 1**).

3. Regulatory mechanisms of DPP4

3.1. Transcriptional regulation of DPP4

DPP4 plays an important role in various biological processes. It not only serves as a downstream target gene of transcription factors but also regulates their biological functions through interactions with other proteins. The human DPP4 gene is located on chromosome 2, spans 70 kb, and consists of 26 exons. The transcriptional regulation of DPP4 mainly involves the action of transcription factors and can serve as a downstream target for multiple transcription factors. Transcription factors are key elements that regulate gene transcription, and they can bind to gene promoter regions to promote or inhibit gene transcription. The promoter region of DPP4 contains multiple consensus sites for transcription factors such as nuclear factor kappa B (NF-κB), activating protein-1 (AP-1), specificity protein 1 (Sp1), and hypoxia-inducible factor-1 alpha (HIF-1α). These transcription factors are significant for studying inflammatory responses and cancer markers [2].

3.2. Protein-level regulation of DPP4

DPP4 interacts with various proteins through a cysteine-rich region separated from the catalytic domain, further broadening its activity spectrum and highlighting its multifunctional role in different biological processes. The main proteins that interact with DPP4 include adenosine deaminase (ADA) and extracellular matrix proteins. ADA is closely related to tissue remodeling, inflammatory responses, and glucose and lipid metabolism, playing a crucial role in regulating the development of diabetes and inflammatory diseases. The complex formed by the interaction between ADA and DPP4 can enhance T-cell activation, further exacerbating the inflammatory response caused by obesity. However, when DPP4 undergoes glycosylation, it may interfere with ADA binding. When ADA successfully binds, plasminogen-2 is activated, increasing plasmin levels, and leading to the degradation of matrix proteins and activation of matrix metalloproteinases [3]. There are interactions

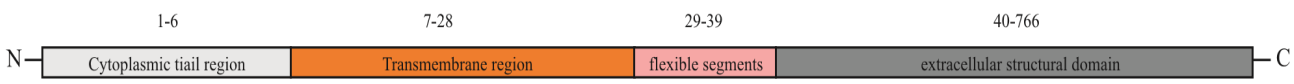

Figure 1. Diagram of the molecular structure domain of DPP4 protein.

between collagen and fibronectin in the extracellular matrix proteins and DPP4. Collagen and fibronectin play important roles in wound healing and bone growth and development. They can promote the transition of inflamed areas into scar stages, while fibronectin can inhibit the reproduction of aerobic bacteria in open wounds, and collagen can promote bone growth and development. The interaction between DPP4 and fibronectin was revealed through the determination of nitrocellulose binding in rat hepatocytes. This interaction leads to local degradation of the extracellular matrix, facilitating the migration and invasion of endothelial cells [4].

4. Biological functions of DPP4

4.1. DPP4 and energy metabolism

Energy metabolism involves the storage and release of energy, and the balance between these two processes is called energy homeostasis, which is crucial for overall health and survival. Imbalances in energy homeostasis can lead to various pathological conditions. Long-term energy intake exceeding output can result in diseases such as diabetes mellitus type 2 (T2DM), obesity, and cancer. Conversely, long-term energy output exceeding intake can lead to decreased metabolism, bone loss, decreased thyroid hormone levels, and reduced physical performance. Therefore, maintaining a balance between energy intake and output is essential.

In glucose metabolism, DPP4 primarily regulates glucose metabolism by degrading GLP-1 and GIP, shortening their half-lives, thereby reducing insulin secretion and increasing blood glucose levels [5]. Insulin is a hormone secreted in response to nutrients that rapidly stimulate insulin secretion from pancreatic beta cells. GLP-1 and GIP are significant in the treatment of metabolic diseases such as diabetes and obesity. GLP-1 is a peptide hormone mainly secreted by intestinal endocrine cells. It is an important insulin sensitizer that promotes insulin secretion, inhibits glucagon secretion, reduces gastrointestinal motility, and suppresses appetite. GIP, also a peptide hormone secreted by the intestine, primarily by the upper small intestine and duodenum, is a vital component of the gut-pancreatic axis and regulates blood glucose levels along with insulin and glucagon. GLP-1 and GIP exert their metabolic effects by activating their respective G-protein coupled receptors, GLP-1R and GIPR, but their biological activity is significantly reduced after degradation by DPP4.

DPP4 plays a potentially important role in lipid metabolism. DPP4 is considered a new adipokine associated with macrophages, influencing insulin sensitivity through autocrine and paracrine mechanisms. Adipose tissue is the primary storage organ for excess energy. Although the role of adipose tissue as a central energy source has been recognized for centuries, in the past decade, adipose tissue has also demonstrated characteristics of an endocrine organ, releasing many adipose tissue-specific factors called adipokines. According to Barchetta *et al*. (2022) [6], DPP4 is highly expressed in human primary adipocytes, and its release is closely related to adipocyte size, suggesting that adipocytes may be a major source of DPP4. Individuals with a high body fat percentage express more DPP4 in subcutaneous and visceral adipose tissue compared to those with a low body fat percentage. Furthermore, DPP4 levels are highest in the visceral adipose tissue of obese individuals, indicating a significant increase in DPP4 release during adipocyte differentiation. Compared to preadipocytes and adipose tissue, macrophages may be the primary source of DPP4 release from intact organs into the circulation.

4.2. DPP4 and inflammation

Inflammation is a defensive response of the body's immune system to external stimuli. A moderate inflammatory response is a normal physiological reaction that helps the body defend against invading pathogens and clear necrotic tissue. However, increased persistent inflammation promotes the release of proinflammatory factors and inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β). This persistent inflammatory response may lead to immune system dysfunction and trigger the development of various diseases.

DPP4 has been found to be associated with the progression of inflammatory responses, and its mechanism involves GLP-1, GIP, NF-κB, mitogen-activated protein kinase (MAPK) pathways, NLRP3 inflammasome activation, and oxidative stress responses. GLP-1 and GIP, substrates of DPP4, have the ability

to inhibit the release and synthesis of inflammatory mediators by inflammatory cells. They also protect cells from inflammatory damage by reducing oxidative stress and apoptosis. Studies have shown that DPP4 enhances the production of advanced glycation end products by reducing the expression of GLP-1 and GIP, thereby suppressing the expression levels of inflammation-related factors such as TNF-α, IL-6, and transforming growth factor-β (TGF-β). Additionally, DPP4 activates the NF-κB pathway, promoting the occurrence of inflammatory responses. NF-κB is a transcription factor that regulates the expression of various inflammation-related genes, including IL-6 and TNF-α. Research indicates that DPP4 can activate the NF-κB pathway, increasing the nuclear translocation of NF-κB and the expression of inflammation-related genes, thereby promoting inflammatory responses [7].

The inflammasome is a cytoplasmic multi-protein complex whose primary function is to mediate the host's immune response to microbial infections and cellular damage. Among its components, the pattern recognition receptor (PRR) plays a crucial role, and within the PRRs, NLRP3 belongs to the NOD-like receptor protein family (NLRs) and contributes to the formation of the inflammasome. The activation of the NLRP3 inflammasome relies mainly on two signals. Firstly, microorganisms or endogenous molecules induce the expression of the NLRP3 inflammasome by activating NF-κB, serving as the initial priming signal. Secondly, substances such as adenosine triphosphate, pore-forming toxins, viral RNA, or particulate matter trigger the second activation signal. The synergistic effect of these two signals enhances the activity of the NLRP3 inflammasome, thereby promoting the occurrence of inflammatory responses. Related to this process is DPP4, a substrate of the NLRP3 inflammasome, whose presence can further augment the activity of the NLRP3 inflammasome and exacerbate inflammatory responses [8]. Consequently, DPP4 plays a significant role in regulating the function of the inflammasome. Additionally, DPP4 promotes inflammatory responses by facilitating the onset of oxidative stress reactions. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the scavenging capacity of the antioxidant system. ROS, including hydrogen peroxide and superoxide radicals, are byproducts of cellular energy metabolism that can severely damage cellular structure and function, potentially leading to somatic cell mutations and tumor transformation. Research indicates that DPP4 can increase ROS production and decrease cellular antioxidant capacity, thus promoting the occurrence of oxidative stress reactions and subsequently intensifying or inducing inflammatory responses [9].

4.3. DPP4 and Tissue Repair

Tissue repair refers to the process of repairing and regenerating damaged tissue. DPP4 plays a crucial role in tissue repair, primarily manifesting in promoting the formation of fibrous connective tissue and cellular senescence. Fibrous connective tissue, rich in collagen and elastic fibers with a tight structure, is primarily synthesized by fibroblasts. This tissue is widely distributed in the human body, serving functions such as supporting and protecting bodily tissues while maintaining tissue morphology and structure. Additionally, fibrous connective tissue participates in various physiological and pathological processes, including wound healing, inflammatory reactions, and immune responses. However, excessive proliferation or abnormal deposition of fibrous connective tissue can lead to fibrosis and organ dysfunction. Research has found that DPP4 can serve as a marker for fibroblast activation, regulating fibroblast activation and collagen release both *in vitro* and *in vivo*. Furthermore, the expression level of DPP4 is positively correlated with increased levels of TGF-β. Therefore, DPP4 holds significant importance in the treatment of liver, lung, and kidney fibrosis [10].

Cell proliferation and differentiation are key processes in tissue repair. However, as age increases, the ability of cells to divide and proliferate gradually decreases, leading to a decline in tissue repair capacity, which is one manifestation of cellular senescence. Cellular senescence refers to the permanent cell cycle arrest induced by factors such as mitochondrial dysfunction, inflammatory reactions, and metabolic abnormalities. Under various known stimuli, senescent cells cannot re-enter the cell cycle, affecting tissue repair capacity. When this senescent phenotype accumulates to a certain extent, it may further lead to organ or even whole-body dysfunction, becoming one of the main hallmarks

of aging. DPP4 plays different roles in different types of cellular senescence. On the one hand, DPP4 can promote the senescence of mesenchymal stem cells and endothelial cells. Mesenchymal stem cells, which maintain the regenerative capacity of human tissues, are affected by various factors, leading to senescence and stem cell depletion, which in turn affects the overall aging process of the body. Studies have found that DPP4 expression levels increase in senescent mesenchymal stem cells. However, the use of DPP4 inhibitors can significantly delay the senescence process of mesenchymal stem cells (MSCs) [11]. Endothelial cell senescence is a major process leading to vascular aging, which further exacerbates atherosclerosis and triggers various diseases.

Research indicates that DPP4 plays an important role in this process. Specifically, DPP4 promotes the occurrence of inflammatory reactions by activating the NLRP3 inflammasome, thereby further promoting the senescence of endothelial cells [8]. On the other hand, DPP4 plays a role in inhibiting fibroblast senescence. Studies have found that DPP4 levels also rise during the senescence of human fibroblasts. However, unlike mesenchymal stem cells, DPP4 is targeted for destruction by natural killer cells in human diploid fibroblasts, serving to eliminate senescent cells [12]. Mitochondrial dysfunction is a crucial factor in cellular senescence, with one aspect being the decrease in mitochondrial membrane potential. Besides, reversing the decline in mitochondrial membrane potential can improve mitochondrial dysfunction, thereby slowing down the rate of cellular senescence. In a study based on T2DM mice, it was found that DPP4 binds to the insulin-like growth factor 2 receptor (IGF2-R) on the surface of regulatory T cells and promotes mitochondrial calcium overload in these cells, thereby facilitating the occurrence of mitochondrial dysfunction [13].

4.4. DPP4 and cancer development

DPP4 is associated with various types of cancer, including thyroid cancer, lung cancer, stomach cancer, and liver cancer. However, the role of DPP4 differs among different cancer types. Several studies have examined the expression of DPP4 in various malignancies to determine its role in tumor progression. Nevertheless, the expression levels and functions of DPP4 vary among different tumor types. Research has revealed that DPP4 promotes the nuclear localization of c-Jun N-terminal kinase (JNK) through mediating integrin signaling activation and interacting with the focal adhesion kinase (FAK)/protein kinase B (PKB) pathway, which is associated with cancer metastasis. This, in turn, induces the transcription of transforming growth factor-β1, promoting epithelial-mesenchymal transition and facilitating the metastasis process of tumors [14].

DPP4 plays a crucial role in thyroid cancer, and its mechanisms include promoting the growth and metastasis of thyroid cancer cells by regulating p62 nuclear translocation related to cell proliferation and increasing the expression of the oxidative signaling molecule nuclear factor erythroid 2-related factor 2 (Nrf2) [15]. Lung cancer is a malignant tumor with high incidence and mortality rates, classified into small-cell lung cancer and non-small cell lung cancer (NSCLC). There is some controversy regarding the expression and role of DPP4 in lung cancer. Compared to normal lung epithelial cells, the mRNA and protein expression levels of DPP4 are generally lower or even absent in human NSCLC cells. However, in experimental mouse subcutaneous tumor models established using mouse-derived lung adenocarcinoma cells and human lung adenocarcinoma cell lines, tumor growth was significantly slowed when DPP4 activity was inhibited [16]. In summary, existing data suggest that DPP4 may be a potential therapeutic target in lung cancer and has important clinical significance. In gastric cancer research, data on DPP4 expression in gastric cancer is still relatively limited. However, studies have indicated that DPP4 may play a hallmark role in gastric cancer with an invasive phenotype. Additionally, cancer-associated fibroblasts (CAFs) play a crucial role in promoting the development of human gastric cancer, and DPP4 is considered a growth factor for CAFs, promoting their proliferation [17]. In hepatocellular carcinoma (HCC) research, DPP4 expression levels show varying degrees of increase and are significantly correlated with increased tumor volume. Ferroptosis is a new type of programmed cell death caused by lipid peroxidation and is iron-dependent. This death mode is characterized by the reduction of glutathione (GSH) and glutathione peroxidase 4 (GPX4). Studies have shown that DPP4 can induce ferroptosis in liver cancer cells, thereby inhibiting the proliferation and metastasis of HCC [18]. This

discovery is significant for inhibiting the development of HCC. In conclusion, DPP4 plays an important role in energy metabolism, inflammatory response, tissue repair, and carcinogenesis through various mechanisms (**Figure 2** and **Figure 3**).

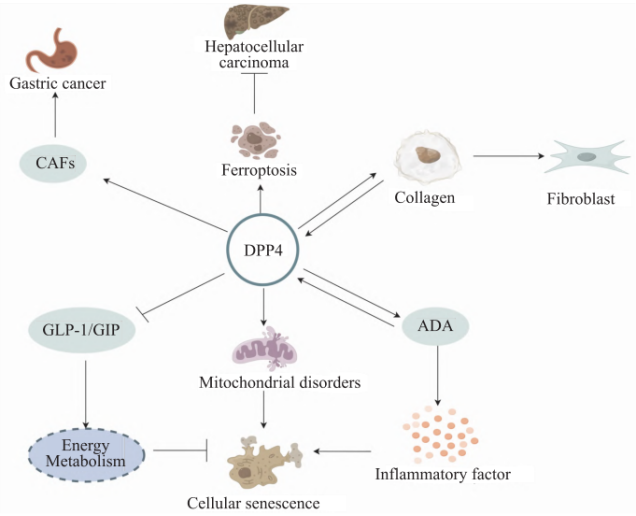

Figure 2. DPP4 regulates multiple physiological/pathological activities through modulation of various mechanisms.

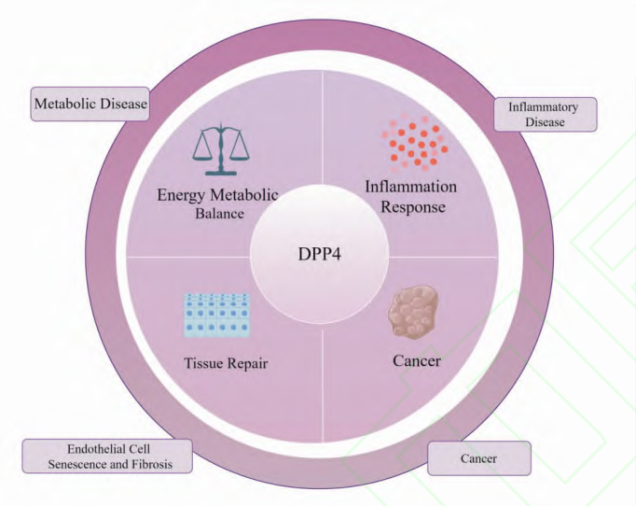

Figure 3. DPP4 regulatory mechanism.

5. DPP4 and chronic liver disease

5.1. DPP4 and nonalcoholic fatty liver disease (NAFLD)

NAFLD refers to a clinicopathological syndrome characterized by excessive fat deposition in hepatocytes, excluding alcohol and other clear liver-damaging factors as the main cause. As mentioned earlier, DPP4 plays an important role in energy metabolism, inflammation, tissue repair, and carcinogenesis. Energy metabolism disorder is the initial cause of NAFLD, liver inflammatory response is the intermediate stage, liver fibrosis is the tissue repair stage, and carcinogenesis is the final stage. Therefore, preventing energy metabolism disorder and halting the further development of NAFLD at various stages is crucial for the treatment of NAFLD. Hence, pharmacological therapy targeting DPP4 is of great significance in the treatment of NAFLD.

Nonalcoholic fatty liver disease occurs when there is a disorder in fat metabolism, leading to the accumulation of lipids in hepatocytes. When lipids accumulate in hepatocytes and cause steatosis, it can trigger a more severe stress response and inflammation. Vildagliptin and Alogliptin are both highly selective DPP4 inhibitors that are significant in reducing liver fat accumulation and steatosis. Studies have found that Vildagliptin can affect postprandial lipid and lipoprotein metabolism by reducing intestinal triglyceride absorption and promoting lipid mobilization and metabolism triggered by the sympathetic nervous system. On the other hand, Alogliptin can inhibit the progression from simple steatosis to nonalcoholic steatohepatitis in mice without affecting systemic glucose and lipid metabolism [19].

Based on the above research results, it was found that the main mechanism hindering the occurrence of NAFLD is related to the inhibition of DPP4 in the liver. However, recent studies have shown that if the overall level of DPP4 in the body decreases, it may promote the occurrence of NAFLD. Therefore, it is important to conduct more comprehensive research to provide a more thorough molecular basis for DPP4-targeted therapy for NAFLD.

5.2. DPP4 and nonalcoholic steatohepatitis (NASH)

DPP4 inhibitors can improve NASH by reducing inflammatory responses. NASH is a disease caused by the accumulation of fat in the liver, which activates oxidative stress responses and inflammatory pathways and molecules, leading to hepatocyte damage and inflammatory reactions. If not treated promptly, the condition may progress to liver fibrosis. Sitagliptin, alogliptin, and saxagliptin are significant in inhibiting liver inflammatory responses. Studies have found that

when sitagliptin is used to inhibit DPP4 activity in hepatocytes, ROS levels decrease, thereby inhibiting the activation of the NF-κB pathway, oxidative stress responses, and apoptosis induced under diabetic conditions [20]. Alogliptin can inhibit the activation of macrophages by increasing the level of GLP-1 in circulation, thereby inhibiting the production of proinflammatory cytokines and reactive oxygen species in cells and further improving liver inflammation [19]. Saxagliptin can reduce TGF-α levels, inhibit inflammatory responses, and improve steatosis, thereby hindering the development of NASH [21]. DPP4 inhibitory peptides can also improve NASH by alleviating endoplasmic reticulum stress (ERS). ERS refers to various stimuli that disrupt the dynamic balance of the endoplasmic reticulum, leading to the accumulation of unfolded and misfolded proteins, which in turn trigger inflammatory responses through multiple inflammatory signaling pathways, resulting in pathological consequences and playing a significant role in the development of liver diseases. VLA, a DPP4 inhibitory peptide isolated from salmon skin, can reduce DPP4 activity without changing DPP4 mRNA expression levels, thereby alleviating ERS responses and playing an important role in improving NAFLD and NASH [22].

5.3. DPP4 and liver fibrosis

Liver fibrosis refers to the accumulation of extracellular matrix (ECM) in liver tissue, leading to the proliferation and deposition of fibrous tissue, which in turn causes abnormal changes in liver structure and function. Under normal circumstances, liver cells undergo repair after being damaged, but if the damage persists or occurs repeatedly, it can trigger inflammatory responses and fibrous tissue proliferation. Long-term hepatitis, alcohol abuse, drug poisoning, and liver diseases can all cause liver fibrosis. As fibrous tissue continues to increase, the elasticity and softness of the liver gradually decrease, which may ultimately lead to the development of liver cirrhosis. Current research mainly focuses on the interventional effects of DPP4 inhibitors on liver fibrosis, while the specific relationship between DPP4 and liver fibrosis still needs further clarification. DPP4 inhibitors can improve liver fibrosis by inhibiting the accumulation of extracellular matrix. Current studies have found that alogliptin can inhibit the transcription of genes related to ECM accumulation in the liver, such as TGF-β and type I collagen, thereby hindering the progression of liver fibrosis [19].

5.4. DPP4 and liver cancer

Hepatocellular carcinoma is the most common primary tumor affecting the liver and the third leading cause of cancer-related deaths in the world. By using DPP4 inhibitors, the proliferation and metastasis of cancer cells can be effectively inhibited, thereby hindering the development of hepatocellular carcinoma. Specifically, alogliptin and vildagliptin can activate natural killer cells and enhance T-cell chemotaxis by blocking the DPP4 truncation of the CXCL10 chemokine, thereby inhibiting the growth of hepatocellular carcinoma in nude mouse xenografts and in situ liver tumors in mice with liver cancer [23]. However, studies have found that DPP4 can also promote ferroptosis in liver cancer cells, thereby inhibiting the proliferation and metastasis of liver cancer cells [18]. This study suggests that there are still questions about the mechanism by which DPP4 inhibitors affect DPP4. In summary, DPP4 can regulate liver energy metabolism, inflammatory responses, tissue repair, and carcinogenesis through multiple mechanisms, which is significant for the treatment of various types of liver diseases (**Figure 4**).

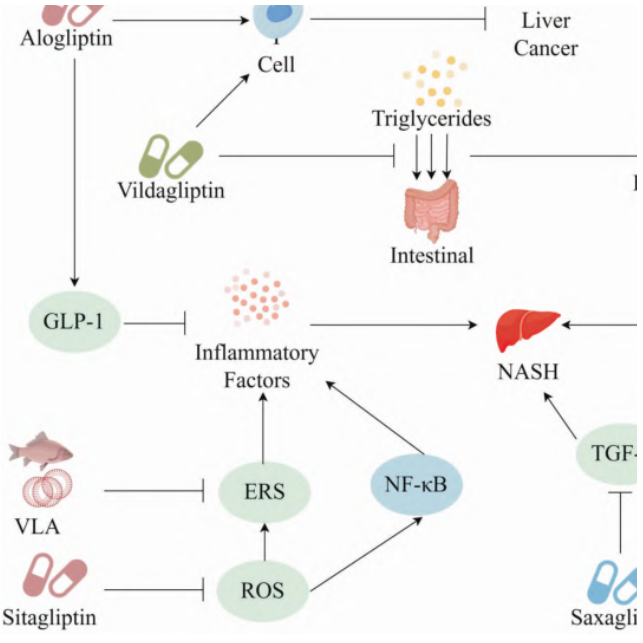

Figure 4. DPP4 inhibitors modulate chronic liver disease through multiple mechanisms.

6. Conclusion

DPP4 as a protein with enzymatic activity, has been found to have regulatory effects on various physiological or pathological phenomena. In recent years, studies have also discovered that DPP4 plays a role in inflammatory responses, carcinogenesis, energy metabolism, and tissue repair in terms of non-enzymatic functions, although many of these regulatory functions remain unclear. In the process of carcinogenesis, DPP4 usually has a negative impact. However, recent studies have found that DPP4 can inhibit the occurrence of liver cancer by promoting ferroptosis in liver cancer cells, indicating that DPP4 may play different roles in different types of cancer or different stages of the same type of cancer, but further research is still needed to confirm this. As a bridge connecting the internal and external environments of the human body, gut microbes have been proven to play a key role in various human metabolic diseases. In the latest research reports, scientists have proposed a new scientific concept of gut microbiota-derived host isoenzymes. In the study, it was found that microbiota-derived DPP4 can be secreted into the host body and decompose GLP-1, thereby inducing abnormal glucose tolerance. Moreover, the DPP4 inhibitor sitagliptin cannot effectively inhibit the activity of microbiota-derived DPP4. This suggests that future researchers can target DPP4 to treat metabolic diseases by studying gut microbiota [24]. Additionally, DPP4 indirectly interferes with human energy metabolism, but studies have found that DPP4 can also directly affect energy metabolism as a novel adipokine. Therefore, searching for plant components that can target DPP4 in natural plants is also an important research direction, which has significant implications for future treatments of various diseases related to DPP4.

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Disclosure statement

The authors declare no conflict of interest.

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