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A review on the relationship between Arachidonic acid 15-Lipoxygenase (ALOX15) and Diabetes Mellitus

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Short Title: A review between ALOX15 and DM

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Number of Tables:1
Number of Figures:3
Number of supplementary Tables:0

Key words： Arachidonic acid 15-Lipoxygenase;Diabetes Mellitus; Diabetic kidney disease; Inflammatory response; Oxidative stress; Ferroptosis.

Abstract

Arachidonic acid 15-lipoxygenase (ALOX15), as one of the lipoxygenase family, is mainly responsible for catalyzing the oxidation of various fatty acids to produce a variety of lipid components, contributing to the pathophysiological processes of various immune and inflammatory diseases. Studies have shown that ALOX15 and its related products are widely distributed in human tissues and related to various diseases such as liver, cardiovascular and cerebrovascular diseases, diabetes mellitus and other diseases. Diabetes mellitus (DM), the disease studied in this paper, is a metabolic disease characterized by a chronic increase in blood glucose level, which is significantly related to inflammation, oxidative stress, ferroptosis and other mechanisms, and has a high incidence in the population, accompanied by a variety of complications. Figuring out how ALOX15 is involved in DM is critical to understanding its role in disease. Therefore, ALOX15 inhibitors or combination therapy containing inhibitors may deliver a novel research direction for the treatment of DM and its complications. This article aims to review the biological effect as well as the possible function of ALOX15 in the pathogenesis of DM.

Introduction

In recent years, diabetes mellitus (DM) is prevalent worldwide, and its incidence is increasing year by year. According to the prediction from International Diabetes Federation, the number of people with DM will reach 700 million until 2045, with the majority of new cases occurring in developing countries such as China and Africa(Teo et al. 2021). Various studies have found that inflammation, oxidative stress and apoptosis participate in the development and progression of insulin resistance and DM. Firstly, the expression of important pro-inflammatory factors such as interleukin-1β (IL-1β), IL-1, IL-6 and tumor necrosis factor-α (TNF-α) is increased in patients with DM(Turkmen 2017).Meanwhile, these pro-inflammatory mediators are interdependent in inducing tissue-specific inflammation , which may be related to the pathogenesis of insulin resistance and DM. In addition, the glycolipid toxicity of DM can lead to elevated levels of oxidative stress, which in turn results in increased production of the aforementioned pro-inflammatory factors(Rendra et al. 2019).Moreover, hyperglycemia can inhibit the release of insulin and increase the apoptosis of pancreatic β cells, and the increase of apoptosis leads to a decrease in the number of cells, and ultimately leads to insufficient insulin secretion and the occurrence and development of DM(Biarnés et al. 2002). Therefore, it is urgent to search for targets that play important roles in inflammation, oxidative stress and apoptosis of DM. Studies have shown that the relative protein molecular weight of arachidonic acid 15-lipoxygenase (ALOX15) is about 75kbp, and the isoforms of Lipoxygenase ~~isoforms~~ are widely distributed in plants, mammals, lower m~~M~~arine organisms and some microorganisms(Kühn & Borchert 2002).~~Studies have shown that Arachidonic acid 15-Lipoxygenase (ALOX15), whose relative protein molecular weight is about 75kbp, is commonly distributed in plants, mammals, lower marine organisms, and some microorganisms.~~ In animals, ~~A~~arachidonic acid 12-lipoxygenase was first identified in human platelets in 1974 (Hamberg & Samuelsson 1974) and named platelet-type 12-LOX (ALOX12). Then, in 1975, Schewe et al. identified a different LOX isoenzyme in the lysate of immature red blood cells that oxidizes membrane lipids and was named reticulocyte type 15-LOX(rabbit alox15 is the rabbit ortholog of human ALOX15).~~rabbit homologue of human ALOX15)~~(Schewe et al. 1975; Sigal et al. 1990). ~~However,~~ ALOX15 is not expressed in normal erythrocytes but is found in the immature red cell precursors, the reticulocytes. ~~ALOX15 was not expressed in normal erythrocytes and reticulocytes.~~ Interestingly, this enzyme is almost undetectable in young reticulocytes, but during in vitro red

blood cell maturation the expression of ALOX15 anti-paralleles the maturational decline of reticulocyte respiration.~~young reticulocytes, but during its maturation in vitro, the expression of ALOX15 is similar to the maturation decline of reticulocyte respiration~~(Höhne et al. 1983; Rapoport et al. 1979), suggesting that ALOX15 is associated with the maturation breakdown of mitochondria in the later stages of erythropoiesis(Schewe et al. 1977). According to studies, ALOX15 and its related products are expressed at higher levels in many pathological human tissues and organs, which in turn causes inflammation, oxidative stress, and ferroptosis, all of which are closely related to the onset of DM and its complications (Singh & Rao 2019). For ALOX15, an important enzyme discovered many years ago, it was necessary to write a review of its association with DM and its complications, but the reviews were inevitably selective and heavily dependent on the authors' opinions. We will do our best to be neutral in this article, but we may miss some important contributions, and we apologize to those outstanding colleagues who have made vital contributions to the field but cannot mention them due to space limitations. Also, in this review, we use normal letters when referring to genes (small letters for mice, capital letters for human genes).

Survey methodology

Publications from 1 January 1985 to 1 January 2023 were retrieved from the Web Of Science, Cochrane Library, PubMed, EMBASE and MEDLINE database, without any language restrictions. We used a mix of MeSH and keywords. With the following terms: Diabetes Mellitus OR (Diabetes) OR (Blood glucose, High) OR (High Blood glucose) OR (DM) AND (AA) OR (Arachidonic acid) ,-Diabetes Mellitus OR (Diabetes) OR (Blood glucose, High) OR (High Blood glucose) OR (DM) AND (ALOX15) OR (12/15-LOX) OR (Arachidonate 12/15-Lipoxygenase) OR (12/15-lipoxygenase) OR (12-LOX) OR (15-LOX). The final reference list was generated on the basis of relevance and originality with regard to the topics covered in this review.

1.Arachidonic acid metabolism and diabetes mellitus

Arachidonic acid (AA) is an omega-6 PUFA found primarily in the form of phospholipids in cell membranes. When the cell is under stress, AA is released from phospholipids by phospholipase A2 (PLA2), or diacylglycerol (DAG) can be converted to AA via DAG lipase activity (Doherty & Walsh 1996; Sperling et al. 1993; van Dorp 1975).~~(van Dorp 1975).~~The decrease of AA concentration in serum is an early event of insulin resistance, and the AA concentration in serum of patients with type 2 diabetes is significantly decreased. In vitro studies have shown that AA can promote the utilization of glucose by muscle cells, promote the uptake of glucose by adipocytes, inhibit the synthesis of resistin by adipocytes, etc. (Haugen et al. 2005; Nugent et al. 2001; Rosenthal et al. 2001; Steppan et al. 2001). In addition, AA can synthesize prostaglandins under the action of a series of enzymes after entering the cell. It has been reported that PGE2 and PGE1–（the main metabolite of COX pathway） can enhance the insulin sensitivity of rat flounder muscle cells, and further affect the metabolism of Zn and enhance the insulin sensitivity of cells(Ezaki 1989; Leighton et al. 1985). Dixon G et al. reported in vitro studies that AA can enhance the ability of islet bechilla to secrete insulin (Dixon et al. 2004). A cohort study of T2DM patients found that circulating AA was negatively associated with UAE and macroalbuminuria(Okamura et al. 2021). AA has been reported to enhance hypoxia-induced vascular endothelial growth factor (VEGF) expression through Notch-1, Wnt-1 and hif-1α pathways(Okamura et al. 2021). Various previous studies have shown that VEGF can improve diabetic nephropathy, normalize glomerular hyperpermeability and restore endosylcalyces in diabetic nephropathy(Falkevall et al. 2017) (Flyvbjerg et al. 2002; Oltean

et al. 2015). Studies have shown that in men, AA is negatively correlated with the risk of diabetes(Wu et al. 2017).In addition, a lower incidence of type 1 diabetes has been reported in people who breastfeed for more than 3 months (human breast milk is rich in various PUFAs, especially AA)(Grzywa & Sobel 1995).

At present, at least three metabolic pathways (COX pathway, CYP450 pathway and LOX pathway) are known to participate in the metabolism of AA. The relationship between the first two metabolic pathways and DM has been studied extensively. The following part summarizes the latest progress of ALOX15 (one of the research hotspots in LOX pathway) between DM and its complications.

~~1~~2. Introduction of ALOX15 in the lipoxygenase family

~~1~~2.1 ALOX15 genotype and structural characteristics

Lipoxygenase (LOX) is a kind of non-heme iron-containing fatty acid dioxygenases, which can catalyze polyunsaturated fatty acids (PUFAs) with cis, cis-1 and 4-pentadiene structures into specific hydroperoxy derivatives ~~hydroperoxides, and then reduce the reaction products to hydroxyl fatty acids and other substances~~. The human genome involves six functional LOX genes that encode six different LOX subtypes (ALOX5, ALOX12, ALOX12B, ALOX15, ALOX15B, ALOXE3). Interestingly, there are two types of ALOX15 homologous genes in mammals. Highly developed primates (humans, chimpanzees, orangutans) express an arachidonic acid 15-lipoxygenating ALOX15, whereas lower primates and other mammals express an arachidonic acid 12-lipoxygenating enzyme. ~~express the arachidonic acid-15-lipoxygenase homolog, while lower primates and other mammals (rhesus monkeys, rats, mice, pigs) express arachidonic acid-12-lipoxygenase.~~ Mouse Alox12, Alox12b, Aloxe3, and Alox5 have a high degree of amino acid conservation with their human congeners and exhibit similar enzymatic properties, while a similar degrees of amino acid conservation was found for the Alox15 orthologues of rats, pigs and cattle (Kuhn et al. 2018) (Kuhn et al. 2015). However, this is not the case with mouse Alox15 and mouse Alox15b. In fact, mouse Alox15 ~~is~~ is an arachidonic acid 12-lipoxygenating enzyme that mainly~~a 12-lipoxygenase that mainly~~ converts ~~arachidonic acid (~~AA~~)~~ to 12S-hydroxy-peroxy-eicosatetraenoic acid (12S-H(p)ETE)(Kühn et al. 1993).In contrast, the human ortholog exhibits an arachidonic acid 15-lipoxygenating activity primarily converting AA to hydroperox eicosatetraenoic acid~~human homologues exhibit 15-lipoxygenase activity, primarily converting AA to 15S-hydroxy-peroxy-eicosatetraenoic acid (15S-H(p)ETE)~~(Chen et al. 1994).

Human ALOX15 is widely existing in eosinophils, macrophages, bronchial epithelial cells and skin, and can convert linoleic acid (LA), arachidonic acid (AA) and other PUFAs into active lipid metabolites, thereby affecting cell structure, metabolism and signal transduction. Human ALOX15 is initially present in the late stage of reticular cell maturation and immature red blood cells, and is highly expressed in eosinophils and bronchoalveolar epithelial cells(Nadel et al. 1991). Human immature red blood cells can express ALOX15, but in different species (human, rabbit, mouse, rat) mature red blood cells do not express ALOX15. The expression of this enzyme is upregulated in immature red blood cells during experimental and natural anemia (Kroschwald et al. 1989; Ludwig et al. 1988; Schewe et al. 1990). In addition, human and mouse peripheral blood mononuclear cells do not express ALOX15 in circulation, but IL-4 and IL-13 induce mRNA and protein expression of ALOX15 in human mononuclear cells and mouse macrophages in vitro (Brinckmann et al. 1996; Conrad et al. 1992; Heydeck et al. 1998). In human umbilical vein endothelial cells, IL-4 induces ALOX15 mRNA expression but does not induce active enzyme expression(Lee et al. 2001) Interestingly, because 10-40% of cells do not express ALOX15, IL4 did not induce ALOX15 expression

in all peripheral monocytes(Kühn & O'Donnell 2006). The reason for this heterogeneity is unclear, but it may be related to the maturation stage of cells and/or their metabolic status(Tsao et al. 2014).

~~1~~2.2. Human ALOX15 substrates and metabolites

~~Arachidonic acid (AA) is an omega-6 PUFA found primarily in the form of phospholipids in cell membranes. When the cell is under stress, AA is released from phospholipids by phospholipase A2 (PLA2) and phospholipase C (PLC) to become free AA, which acts as a precursor to a pro-inflammatory bioactive medium(Doherty & Walsh 1996; Sperling et al. 1993; van Dorp 1975).~~ In DM, AA acts as a strong inducer of insulin secretion, but the contribution of its metabolites to insulin resistance depends on the cells and tissues involved (Luo & Wang 2011).AA can be converted to leukotrienes (LTs) and lipotoxins (LXs) through the lipoxygenase (LOX) pathway (Calder 2015; Rae et al. 1982; Yates et al. 2014), thus widely participating in a variety of physiological and pathological processes(1981; Kopp et al. 2019). AA as one of the main substrates of ALOX15 in vivo, is mainly oxidized to 15-H(p)ETE in human(Kühn et al. 1993; Sigal et al. 1990), while rat(Pekárová et al. 2015; Watanabe & Haeggström 1993) or mouse (Freire-Moar et al. 1995; Sun & Funk 1996) congeners mainly produced 12-H(p)ETE. These data indicate that the structure of the catalytic center of ALOX15 is slightly different between rodent and human. The above differences suggest that experimental data on LOX metabolism should be handled with caution if transferred from one species to another(Funk et al. 2002; Kuhn 2004). Next, under the action of cellular glutathione peroxidase, 15(S)-H(p)ETE and 12(S)-H(p)ETE were further reduced to 15-hydroxy eicosapenoic acid (15(S)-HETE) and 12-hydroxy eicosapenoic acid (12(S)-HETE), respectively. ~~Both~~ 12(S)-H(p)ETE ~~and 12(S)-HETE~~ can be metabolized to hepoxilin, which are further metabolized to trioxilin, the corresponding tri-hydroxyl metabolites. These metabolites have been shown to induce insulin secretion in animal models of DM(Funk 1996). Meanwhile,15(S)-H(p)ETE and 15(S)-HETE could be metabolized into different bioactive lipids, for instance, lipoxins, hepoxillin, and eoxins (Kühn & O'Donnell 2006). The ratio of 12(S)-HETE to 15(S)-HETE catalyzed by Alox15 varies among species: the ratio is about 3:1 in mice, 6:1 in rat brain tissue, and 11:1 in bovine bronchus(Funk et al. 2002) . In addition, using linoleic acid(LA) as substrate, ALOX15 can be dominantly metabolized into 13(S)-hydroperoxyoctadecenoic acid (13(S)-HPODE) , and then the metabolites can be further metabolized into 13(S)-HODE (Kutzner et al. 2017). 13(S)-HODE was found to be involved in neuronal activation, lipid metabolism and monocyte maturation through peroxisome proliferators-activated receptors (PPAR), transient receptor potential cationic channel subfamily V member 1 (TRPV1) and G protein-coupled receptor 132 (GRP132). The main substrates and metabolites of ALOX15 are shown in Figure 1.

Figure 1 Human ALOX15 substrates and metabolites.

~~2~~3.Biological effects of ALOX15

~~2~~3.1 The dual effect of ALOX15 in inflammation

Inflammation is one of the main causes of insulin resistance, and in DM, the expression of many pro-inflammatory factors is increased, such as IL-1 β ,IL-6,IL-8,IL-12,TNF-a and so on. Since the immune regulatory system of the human body has a very clear regulatory mechanism, the enhancement of the pro-inflammatory response will negatively stimulate the activation of the anti-inflammatory response, which also means that the anti-inflammatory factor will be increased, for example IL-4,IL-10,IL-11,IL-13, to inhibit the tissue damage caused by the excessive inflammatory response(Burhans et al. 2018).

Lipoxins (LXs), as one of the downstream products of the oxidation of a series of essential PUFAs

by ALOX15, have significant anti-inflammatory effects when their synthetic levels are elevated(Chan & Moore 2010). Chinthamani et al. found that LXs can play an anti-inflammatory role by inhibiting the adhesion of immune cells to vascular endothelial cells and up-regulating the expression of vascular cell adhesion molecule-1 (VCAM-1) (Chinthamani et al. 2012). Moreover, LXs can protect the expression of IL-4, IL-10, IL-13 through MAPK pathway (ERK, P38, JNK) and PIPP pathway, so as to play a certain anti-inflammatory role. Current studies have shown that when AA is deficient, the formation of LXA4, one of the metabolites of LXs, is reduced, and the production of PGE(prostaglandin E) is increased, ultimately leading to pancreatic β cell dysfunction and the occurrence of DM(Gundala et al. 2018). It also found that plasma phospholipid content of AA(Das 1995) and circulating level of LXA4(Kaviarasan et al. 2015) are lower in patients with T2DM. In addition, in STZ-induced animal models of T2DM, oral intake of AA can inhibit the IL-6 and TNF-α production, and STZ-induced inhibition of LXA4 production returned to normal, thereby completely preventing hyperglycemia and improving insulin sensitivity(Gundala et al. 2018). Sufficient AA can promote the formation of LXA4, a potent anti-inflammatory compound, which can antagonize the pro-inflammatory effect of leukotrienes(Tan et al. 2022). At the same time, AA can inhibit the expression of NF-kB in pancreas and adipose tissue, and enhance the expression levels of ALOX5 and ALOX15, which may be the reason for its anti-diabetic effect. In type 2 diabetes (T2DM), AA brings plasma TNF-α and IL-6 levels back to normal levels, which may be responsible for the return of insulin sensitivity to normal(Gundala et al. 2018). In conclusion, AA and LXA4 have a protective effect on DM(Das 2013; Gundala et al. 2017a; Gundala et al. 2017b; Suresh & Das 2001). Of note, other unsaturated fatty acids: gamma-linolenic acid (GLA, 18:3n-6), eicosapentaenoic acid (EPA, 20:5n-3), and docosahexaenoic acid (DHA, 22: n3) has also shown cytoprotective effects in vitro against pancreatic beta cytotoxicity in alloxan and STZ induced type 1 and type 2 DM in experimental animals, although their beneficial effects are much weaker than AA(Krishna Mohan & Das 2001; Suresh & Das 2001; Suresh & Das 2003a; Suresh & Das 2003b). We hypothesized that EPA and DHA may replace AA in the lipid pool of the cell membrane, thus promoting the production of LXA4.However, recent studies have challenged the biosynthesis and biological relevance of LXs. The study showed that the putative deletion of biosynthetase did not provide evidence consistent with the role of LXs in resolving inflammation(Schebb et al. 2022). Therefore, the evidence for the role of LXs in promoting inflammatory regression through specific receptors is still controversial and incomplete, and needs further study. At the same time, 15-HETE, a metabolite of ALOX15, acts as an endogenous ligand of PPAR-γ . Activated PPAR-γ takes part in inflammatory response by detering the release of TNF-a, iNOS through PI3K/Akt/NFkB and PI3K/p38MAPK/NFkB pathways(Paintlia et al. 2006). To sum up, as one of the endogenous metabolites of ALOX15, LXs is a strong anti-inflammatory factor which is known as the "brake signal" or "stop signal" of inflammatory response.

In addition, studies have shown that ALOX15 also has pro-inflammatory effects. Alox15 catalyzes LA to produce 13-HPODE and induces MCP-1 production in blood vessels through activation of NF-kB, thus promoting inflammation(Dwarakanath et al. 2004). Lindley et al. indicated that the augmented expression level of Alox15 aggravates airway allergic inflammation, and the inflammatory mediators produced after the inflammatory reaction upregulate the level of Alox15 in vivo(Lindley et al. 2010). These above results confirmed that Alox15 promoted the inflammatory response. Moreover, lipopolysaccharide (LPS) induced impaired IL-12 synthesis in Alox15 knockout mice, indicating that it is participated in the secretion of inflammatory factors(Middleton et al.

2009). Recent studies found that Alox15 metabolites can stimulate the expressions of IL-6 and TNF-a in a dose-dependent manner. In Plox-86 cells capable of constant expression of Alox15, the amount of Alox15 metabolites was approximately 3.6-fold higher and the expression of cytokines was 2-7-fold higher than in normal cells. 12S-HETE promotes the production of inflammatory factors mainly by activating mitogen-activated protein kinases (P38, MAPK, JUK), protein kinase C(PKC) as well as other kinases. After blocking the activity of these kinases, the expression of IL-6 and TNF-a were dramatically diminished(Wen et al. 2007). The biological activity of ALOX15 itself may promote inflammation(Uderhardt & Krönke 2012). These researches indicate that ALOX15 can directly stimulate cytokine expression and induce inflammatory cascades. In conclusion, ALOX15 has the dual effect of promoting or inhibiting inflammation. While LOX-mediated AA metabolites (such as 5-HETE and leukotriene B4 (LTB4) from ALOX5-mediated metabolism) help initiate acute inflammation(Funk 2001), other products of LOX-mediated PUFAs metabolism (lipotoxins (from AA)), resolvins (from DHA and EPA, protective proteins (DHA) and fatty acids (DHA)) are essential for the active process of inflammation resolution, the failure of which leads to the development of chronic inflammation(Serhan 2014).

~~2~~3.2 The effect of ALOX15 in oxidative stress

Except its significant role in inflammation, ALOX15 is also related to oxidative stress in human body. During cell metabolism, lipid oxidase ALOX15 interacts with glutathione peroxidase (GSH-Px) to regulate cell redox state and apoptosis pathway. GSH-Px is a main peroxide reducing enzymes, which broadly exists in the human body. It can catalyze the transformation of GSH into GSSG and reduce toxic peroxide into non-toxic hydroxyl compounds, so as to ensure the function and structure of cell membrane are not disturbed and damaged by oxides. In oxidative stress reaction, oxygen molecules generate superoxide anions under the metabolic action of oxidase and mitochondria. Superoxide anions act on cell membranes after transformation to promote the transformation of Fe^{2+} into Fe^{3+} and activate ALOX15, which catalyzes the formation of 12(S)-H(p)ETE from AA on membrane phospholipids, and in the presence of glutathione peroxisase-4 (GPX4), ALOX15 can be isomerized to form hepoxilin or 12(S)-HETE(Schnurr et al. 1999). GPX4 can regulate ALOX15 to prevent the conversion of 12S-H(p)ETE to 12S-HETE and isomerize into hepoxilins. In turn, ALOX15 also regulates GPX4 and promotes the redox process of GSH-dependent membranes, and its decreased activity may have a complementary effect on GPX4. These two enzymes play antagonistic roles in lipid peroxidation metabolism(Kühn & Borchert 2002; Schnurr et al. 1999), and it has been shown that $Alox15^{-/-}$ cells consume GSH through L-Buthionine sulfoximine (BSO) to resist GPX4 inhibition. Therefore, their balanced expression is important for intracellular redox homeostasis. ALOX15 homologues oxidize complex lipids carrying PUFAs to corresponding hydroperoxides, which may initiate secondary oxidation reactions(Ivanov et al. 2015; Singh & Rao 2019). GPX4 homologues reduce this complex hydroxyl lipid to a core responsive hydroxyl derivative at the expense of reducing glutathione, and as a result, the enzyme reduces the cell oxidation potential(Brigelius-Flohé & Maiorino 2013; Schnurr et al. 1996).The apoptotic pathway induced by GPX4 inactivation can be blocked by the application of ALOX15 inhibitors. GSH is a synergistic substrate of GPX4, and ALOX15-deficient cells are greatly immune to oxidative damage caused by GSH deficiency(Seiler et al. 2008). In addition, the expression of ALOX15 augmented the secretion of reactive oxygen species (ROS) and free radical, which increased NADPH oxidase activity, promoted NADPH oxidation decreased cytochrome C activity, and promoted the oxidative stress process(Othman et al. 2013).

~~2~~3.3 The effect of ALOX15 in ferroptosis

Ferroptosis belongs to programmed iron-dependent cell death, which is a new cell death mode proposed by Dixon et al in 2012(Dixon et al. 2012). The main pathophysiological manifestations of ferroptosis include increased iron ions, enhanced lipid peroxidation, smaller mitochondria and increased membrane density, including oxidative stress. The present study showed that ferroptosis involved in the study of the pathogenesis of various diseases, including ischemic tissue damage (such as brain damage(Gou et al. 2020), ischemic heart disease(Del Re et al. 2019), renal failure(Wang et al. 2021) and acute lung injury(Liu et al. 2020), etc.), neurodegenerative diseases (such as alzheimer's disease(Bao et al. 2021), Parkinson's and huntington's disease(Reichert et al. 2020), etc.), tumor diseases (such as breast cancer(Li et al. 2020), colorectal, lung, liver, pancreatic and urologic cancer(Wei et al. 2021; Ye et al. 2021; Zhang et al. 2021; Zhang et al. 2019; Zhao et al. 2021)), autoimmune encephalomyelitis(Li et al. 2022), etc. ALOX15 can catalyze the stereotactic oxygenation of PUFAs such as AA and LA, leading to lipid peroxidation and further causing ferroptosis(Lee et al. 2021). Studies suggested that silencing of ALOX15 significantly reduces ferroptosis induced by erastin or RSL3(Ras-selective lethal small molecule 3), while overexpression of exogenous ALOX15 increased ferroptosis. At the same time, the results of immunofluorescence results demonstrated that ALOX15 was always localized in the cell membrane during the process of ferroptosis. These results suggest that LOX-catalyzed hydrogen peroxide production of cell membrane lipids promotes tumor ferroptosis(Shintoku et al. 2017). Notably, in a large number of cell model systems, ferroptosis occurred even though ALOX15 was not expressed in these cells (such as human mature red blood cells)(Chen et al. 2022b).Therefore, ALOX15 is not a necessary participant in ferroptosis, but only has an important role in the ferroptosis of those cell lines which express ALOX15.

In addition, ALOX15 has been reported to be involved in the occurrence of cell ferroptosis in RSL3-induced acute lymphoblastic leukemia (ALL). They found that RSL3, as a GPX4 inhibitor, leads to increased lipid peroxidation, reactive oxygen species (ROS) production, and cell death in ALL cells. Meanwhile, LOX inhibitors can protect cells from the above effects of RSL3 stimulation. Therefore, these results indicated that ALOX15 can promote the occurrence of ferroptosis in cells(Probst et al. 2017). The esterification and oxidation of PUFAs is vital in promoting ferroptosis, as well as studies have found that ALOX15 is participated in this process, suggesting that it may be a significant regulator in ferroptosis. Studies have shown that phosphatidyl ethanolamine binding protein 1(PEBP1) binds to ALOX15 to form PEBP1/ALOX15 complex, which can change the specificity of PUFA-PE catalyzed by ALOX15 to form HpETE-PEs from free PUFA. Due to insufficient or dysfunctional production of selenoperoxidase GPX4, excess production of HpETE-PEs cannot be eliminated in time, resulting in ferroptosis(Stoyanovsky et al. 2019). Thus, the PEBP1/ALOX15 complex is regarded as a main regulator of ferroptosis in airway epithelial cells from asthma patients, renal epithelial cells from renal failure patients, and cortical and hippocampal neurons from brain trauma patients(Stoyanovsky et al. 2019). The biological effects of ALOX15 in different diseases are shown in Figure 2.

Figure2 The biological effects of ALOX15 in different diseases.

~~3~~4. ALOX15 in the pathogenesis of DM and its associated complications

~~3~~4.1 ALOX15 and islet cell dysfunction

ALOX15 and its metabolites are associated with DM. The main function of islet β cells is to secrete insulin, which can promote the uptake and utilization of glucose, and convert glucose into

protein, fat and glycogen, thereby reducing blood glucose(BG) levels(Leto & Saltiel 2012). As early as 1999, Bleich et al reported that in the established drug-induced DM mice model, C57BL/6J mice suffered islet cell damage similar to T1DM, leading to a significant increase in the incidence of DM in mice. However, in low-dose streptozotocin (STZ) -induced DM models, Alox15 knockout mice showed reduced damage to islet cells and reduced incidence of DM (Bleich et al. 1999; Bosma et al. 2022). A study in 2017 also confirmed that reducing Alox15 expression level is an effective treatment for glycemic exacerbation in T1DM(Hernandez-Perez et al. 2017). In addition, studies of obese rats with insulin resistance have also suggested that the expression level of Alox15 in adipose tissue of obese rats induced by high fat diet (HFD) is higher than that of normal controls, and the use of Alox15 inhibitors could antagonize insulin resistance in obese rats. Similarly, reduced expression of Alox15 significantly improved the occurrence of T1DM in non-obese diabetic (NOD) mice(Green-Mitchell et al. 2013). In conclusion, the expression of ALOX15 can lead to dysfunction of islet cells, which may play a part in the occurrence of DM in obese patients(Dobrian et al. 2011). It is well known that damage to islet β cells can lead to the occurrence of both type 1 and type 2 DM(Cnop et al. 2005). Studies have found that different concentrations of AA had different effects on islet β cells, and gradually showed toxic effects on islet β cells with the increase of its dose(Keane et al. 2011). Nunemaker et al. and Sears et al. identified the function of Alox15 in islets by gene knockdown and targeted protein knockdown, which showed that reducing Alox15 expression could prevent islet function impairment as well as insulin resistance induced by HFD (Nunemaker et al. 2008; Sears et al. 2009). Moreover, Tokuyama et al. found that Alox15 expression levels were elevated in diabetic Zucker rats, and β-cells were the preferred cells for Alox15 expression(Tokuyama et al. 1995). Meanwhile, it has been shown that the expression of Alox15 coexists with α-cells (secrete glucagon) of rat islets, and the increased expression of Alox15 in α-cells can promote the secretion of glucagon, thereby increasing BG level (Kawajiri et al. 2000). Moreover, in human islets, an increase in exogenous 12S-H(p)ETE or 12S-HETE lead to a major decline in islet activity and insulin production (Ma et al. 2010). A recent review by Nadler's group discussed the harmful effects of 12-HETE on the onset of DM (type 1 and type 2) and obesity in Alox15 knockout mice(Kulkarni et al. 2021). Moreover, 12S-HETE can increase the apoptosis of islet-β cells by increasing mitochondrial oxidative stress(Nazarewicz et al. 2007). Although 12S-H(p)ETE is the main product of Alox15 in mice models and not human ALOX15, it plays an important role in DM. The researchers only used physiological concentrations of 12(S)-HETE and did not test its enantiomer (12(R)-HETE) or the specific role of 15-H(p)ETE/15S-HETE, the main product of human ALOX15 in AA, in β-cell apoptosis.

However, it is noteworthy that although AA can stimulate insulin secretion by β-cells in the pancreas, ALOX15 constrains insulin secretion, possibly because of the reduction of free AA(Persaud et al. 2007). It has also recently been suggested that a Alox15 cell-specific deletion in islets improves insulin secretion and protects the body from abnormal BG level associated with HFD. Besides, it has been reported that Alox15 level in islets is significantly increased in a db/db mice model from 10 weeks of age, besides the extent of the growth in Alox15 level is consistent with the extent of the reduction in islet cell number(Dobrian et al. 2018). Notably, the nonobese diabetic (NOD) mice congenic for a targeted deletion of Alox15 are protected from autoimmune DM(McDuffie et al. 2008). These results suggest that Alox15 plays a role in both pathology and mechanism of DM, which may be related to the effect of Alox15 on the function of islet cells and/or macrophages(Green-Mitchell et al. 2013). Although the underlying mechanism is unknown, the

results suggest an interaction between Alox15 expression in adipose tissue and islet inflammation, and inhibition of Alox15 expression in adipose tissue may provide systemic protection against obesity-induced consequences. Moreover, blocking the activity of Alox15 in adipose tissue may constitute a new therapeutic principle for the treatment of T2DM(Cole et al. 2013).

Hepoxilins are bioactive epoxy hydroxyl products metabolized by AA through the 12S-lipoxygenase pathway. After the dioxygenation of AA with 12S-H(p)ETE, a recently discovered enzyme, hepoxilin A3(HXA3) synthetase, readily converts 12S-H(p)ETE into biologically active compounds, 8S/R-hydroxy-11, 12-epoxy-5Z,9E, 14z-trienoic acid (hepoxilin A3), commonly known as HXA3, and the inactive compounds 10S/R-hydroxy-11, 12-epoxy-5Z,8Z, 14z-trienoic acid (HXB3)(Nigam et al. 2007). Hepoxilins (HXs) can participate in various physiological processes, such as the release of inflammatory mediators, insulin secretion, calcium regulation, potassium regulation, etc(Newman et al. 2005). Studies have found that exogenous HXA3 can increase the release of insulin after acting on the Langerhans islets of well-perfused rats (Pace-Asciak & Martin 1984). After injection of the HXA3 isomer (100 ug HXA3 per rat), enhancement of circulating insulin levels was observed within 20 minutes. In this earlier study, researchers found that Langerhans' islets were able to convert 12S-H(p)ETE to HXA3 and HXB3 in addition to 12-HETE, thus demonstrating the activity of hepoxilins synthetase. At a concentration of 2μM, the glucose produced by HXA3 (10 mM) stimulated the release of insulin almost three times as much as the control group(Pace-Asciak 2015). Subsequently, studies have shown that hepoxilins can release insulin in the body after intra-arterial administration in rodents(Pace-Asciak et al. 1999). The effect of HXA3 on insulin release from β cells may be caused by the specific mobilization of calcium as a direct effect on the endoplasmic reticulum(Dho et al. 1990). However, whether hepoxilins are formed in Alox15 knockout mice has not been studied, so it is not possible to determine whether they are responsible for additional anti-diabetic effects.

~~3~~4.2 ALOX15 and Diabetic retinopathy (DR)

Diabetic retinopathy (DR) is a common complication of DM, which can lead to blindness in severe cases(Cheung et al. 2010). Previous studies in human patients and animal models have demonstrated that ALOX15(Alox15) is highly expressed in the retina(Al-Shabrawey et al. 2011). Recent studies on DR have found that Alox15 is involved in vascular hyper-permeability during DR through NADPH oxidation-dependent mechanisms, including inhibition of protein tyrosine phosphatase and activation of VEGF receptor 2 (VEGF-R2) signaling pathway. At the same time, inhibiting the expression of Alox15 decreased the levels of retinal inflammatory cytokines, the production of reactive oxygen species (ROS), and the expression of phosphorylated VEGF-R2 in DM mice(Othman et al. 2013). However, there is no clear cellular origin of the above metabolites, and it is reasonable to assume that they may come from retinal tissues, including retinal vascular endothelial cells, glial cells and pigment epithelial cells, as well as infiltrating inflammatory cells. In addition, Augustin et al. found the expression of the ALOX15 metabolite 15S-HETE was hugely increased in the retinal adventitia of patients with DR in the 1990s (Augustin et al. 1997). Subsequent studies found that 5S-HETE, the main product of ALOX5, was significantly increased in the vitreous body of DM patients, while the level of 15S-HETE was not significantly changed(Ibrahim et al. 2015). In addition, 5S-HETE, 12S-HETE, and 15S-HETE have also been reported to be crucial in diverse phases of DR(Othman et al. 2013). Intravitreal injections of 12-HETE have been studied to produce many of the characteristics of early DR, including pro-inflammatory responses and edema. Secondly, 12- or 15-HETE enhanced several in vitro

endothelial cell activities related to barrier function and angiogenesis, including reduced resistance, adhesion response to Polymorphonuclear neutrophils, migration, and tube formation(Graeber et al. 1990). 15-HETE activates retinal endothelial cells through the NOX system, resulting in increased white blood cell adhesion, high permeability, and ultimately retinal neovascularization, which is a major symptom of DR(Ibrahim et al. 2015).

~~3~~4.3 ALOX15 and diabetic peripheral neuropathy (DPN)

Diabetic peripheral neuropathy (DPN), a common neuropathy caused by DM, has an incidence of about 30% to 90% and is a leading reason of amputation(Boulton et al. 2005). Recent studies have shown that ALOX15 is highly expressed in sciatic nerve, spinal cord and DRG neurons of mice as well as human Schwann cells, and its expression is increased in diabetes and high glucose(Stavniichuk et al. 2010), and the expression level of Alox15 in peripheral nerves and dorsal root ganglia of mice fed HFD is significantly increased(Obrosova et al. 2007). Increased expression of Alox15(ALOX15) in the sciatic nerve of DM-induced mice was associated with enhanced oxidative stress and PARP activation, and compared to untreated wild-type mice with DM, these two phenomena were less present in Alox15$^{-/-}$mice or Alox15-inhibitor-treated DM wild-type mice(Stavniichuk et al. 2010). Therefore, it is very plausible that Alox15 overexpression at least partially explains the enhanced oxidative nitrosation stress and PARP activation of peripheral nerves and DRG neurons in HFD fed mice. Although LOX overexpression and activation play key roles in pain functional changes of large and small fiber as well as axonal atrophy of large myelin fibers in DPN, it has little function in epidermal nerve fiber loss, sympathetic plant ganglion dystrophy and neuronal degeneration. These results indicate the functional changes of ALOX15 in DPN and the important role of ALOX15 in demyelination of DPN, providing a theoretical basis for further use of ALOX15 inhibitors or combination therapy containing ALOX15 inhibitors(Coppey et al. 2021). It has also been reported that PM5011, a substance extracted from Artemisia annae, can reduce the level of Alox15 from STZ-induced DM mice and improve peripheral neuropathy(Watcho et al. 2011). With regard to diabetic cognitive dysfunction, Alox15 can promote inflammation and neuronal apoptosis by activating p38/MAPK and participate in diabetic brain injury. Meanwhile, intervention with Alox15 can improve the above changes(Chen et al. 2022a).

~~3~~4.4 ALOX15 and diabetic kidney disease (DKD)

Diabetic kidney disease (DKD) is one of the most main complications of DM patients. The incidence of DKD in China is also increasing, and it has become the leading reason of end-stage renal disease (ESRD). Studies have shown that lipid mediators and oxidized lipids are involved in the pathological processes of various kidney diseases including DKD, especially the LOX metabolic pathway of AA is involved in the pathological and biological processes of kidney tissue. At present, various reports have shown the significant function of Alox15 in DKD(Dobrian et al. 2011). Immuno-histochemical (IHC) results showed that Alox15 was located in glomerular mesangial cells, podocyte and microvessels, and and its expression level increased with the progression of DKD (Kang et al. 2001). The level of ALOX15 was greatly upregulated in glomerular mesangial cells cultured with high glucose(Xu et al. 2006). Besides, TGF-β or angiotensin II (AngII) stimulation increased the expression of ALOX15 in glomerular mesangial cells, while the inhibition of ALOX15 levels can reduce the corresponding glomerular mesangial cell hypertrophy and matrix production(Kim et al. 2003; Yiu et al. 2003). Simultaneously, silencing the expression of Alox15 by siRNA significantly attenuates renal dysfunction in the mice models of T1DM(Yuan et al. 2008).

The research reported that in a mouse model of T1DM kidney disease, the mRNA and protein levels

of Alox15 are positively correlated with the expression level of fibronectin, and the urinary excretion rate of 12S-HETE is increased. Researches have suggested that ALOX15 and its metabolite 12S-HETE can stimulate the expression level of COX2 and promote the production of prostaglandin E2, which in turn can increase the level of ALOX15 and 12S-HETE. Another study point out that ALOX15 and COX2 work together to aggravate the pathological process of DKD(Xu et al. 2006). In vitro experiments showed that 12S-HETE could directly stimulate the proliferation and proliferation of rat mesangial cells, lead to the expression of fibronectin, the migration and proliferation of VSMC, and regulate the growth of mesangial cells and the production of extracellular matrix. In addition, 12S-HETE stimulated VSMCS in mesangial cells in the same way as AngII, and 12S-HETE regulated them in part through P38/MAPK and its target transcription factor CREB(Reddy et al. 2002). Knockdown of Alox15 reduced the growth, matrix production, oxidative stress response, and activation of MAPK and CREB in rat mesangial cells. In addition, in obese nephropathy, ALOX15 also tends to be highly expressed, and the growth in its expression level is related to the activation of P38/MAPK as well as ERKl/2 pathways(Xu et al. 2005). Figure 3 shows the role of ALOX15 in the pathogenesis of DM and its related complications.

Figure3 ALOX15 in the pathogenesis of DM and its associated complications.

45. Summary of ALOX15 inhibitors in a variety of diseases

45.1 Baicalein

In neurodegenerative disorder diseases, HT22 cells were treated with a dose of baicalin (the selectively ALOX15 inhibitor), which resulted in inhibition of ERK and decreased ROS production (Stanciu et al. 2000). Moreover, studies have indicated that baicalein can significantly reduce the behavioral deficits after embolic stroke in rabbits, suggesting that baicalein or baicalein derivatives can be developed as a new therapy for acute ischemic stroke (AIS) (Lapchak et al. 2007). It has been reported that ischemia-reperfusion injury can induce PPAR-γ expression and translocation, whereas baicalin can reverse the above PPAR-γ changes (Xu et al. 2010). In prostate cancer (PCa), the use of baicalein sensitized prostate cancer cells to radiation, but not normal cells (Lövey et al. 2013) . Besides, researches have reported that baicalein may reduce the level of VEGF in human PC-3 cells, thereby mediating the angiogenesis of prostate cancer(Nie et al. 2006) .

45.2 PD146176

Recent researches indicated that PD146176, another specific inhibitor of ALOX15, can reduce plasma 12-HETE levels, resulting in increased calcium deposition in aortic arch and vascular calcium content(Han et al. 2021). It has also been reported that PD146176 can reduce the epithelial-mesenchymal transition (EMT) in eosinophilic chronic rhinosinusitis (ECRS) with nasal polyps after inhibiting ALOX15 expression(Yan et al. 2019). In addition, in kidney disease, compared with wild-type animals, renal inflammation, fibrosis and macrophage infiltration were significantly reduced after UUO treatment in ALOX15 knockout mice. PD146176 reduced the above levels of inflammation, fibrosis, and macrophage infiltration, and the reduction extent was similar to that in Alox15 knockout mice(Montford et al. 2022).

45.3 BHPP

A ALOX15 inhibitor, N-benzyl-N-hydroxy-5-benzamidine (BHPP), has been shown to reduce 12-HETE in urine as well as significantly improve DKD over 4 months of treatment, Administration of BHPP (3 mg/kg/ day) reduced 12-HETE/ creatinine (cr) in urine by about 30-50% of DM rats after 1 week, and at the same time, the excretion rate increased in the corresponding control group. Because urinary 12-HETE/cr excretion was highly correlated with urinary albumin /cr ($r=0.79$, $P<10^{-}$

[5]), indicating renal ALOX15 expression is related to proteinuria, so the use of ALOX15 inhibitor can alleviate proteinuria in DN(Ma et al. 2005).

45.4 NDGA

Dihydroguaiacic acid north (NDGA), a ALOX15 pathway inhibitor, has been regarded as a positive role in STZ-induced DKD. NDGA is more effective in improving renal function when blood glucose is well controlled. NDGA treatment can reduce the expression of oxidative stress index in DKD(Gad 2012).

45.5 ML351

Quantitative high-throughput screening (qHTS) has identified ML351, a novel chemotype that inhibits ALOX15. Furthermore, kinetic experiments have shown that this class of inhibitors is a tightly bound hybrid inhibitor that does not diminish ferric ions in active site. Lastly, ML351 protected mouse neuronal cells (HT-22) from glutamate oxidative toxicity and mainly diminished cerebellar infarct size in the mice models of ischemic stroke(Rai et al. 2010).

45.6 ML355

It has been reported that ML355 exhibited nM potency about ALOX15, indicating its outstanding selectivity against related LOX and COX. ML355 reduces 12-HETE expression level in mice/human β-cells mainly by inhibiting PAR-4 -induced aggregation and calcium mobilization in the platelets of human, suggesting a potential role for this inhibitor in animal models of DM and anti-platelet therapy(Luci et al. 2010) .

The main functions of these above ALOX15 inhibitors in various diseases are summarized in table 1.

Table 1 Summary of ALOX15 inhibitors in a variety of diseases

56. Limitations and problems in using ALOX inhibitors

56.1. Isomer specificity of ALOX15 inhibitors

First of all, most LOX inhibitors in the table 1 (such as NDGA, CDC, baicalin, PD146176, etc.) have no significant specificity, and most of them can inhibit a variety of Lox-isomers. Therefore, it is impossible to backinfer the biological activity of a certain lox isomers based on the results of inhibitor studies. Secondly, how to determine the specificity of LOX inhibitors is a problem. A recent study overexpressed the 12-lipoxylate rat LOX subtype in HEK cells and then tested a series of LOX inhibitors using cell lysates. The results showed that these lox inhibitors (NDGA, CDC, AA861, baicalin, PD146176) exhibited only a low degree of isomeric specificity. Although some were previously thought to be isomer specific inhibitors(Gregus et al. 2013).

56.2. Homologous specificity of ALOX15 inhibitors

Since the discovery that mammalian ALOX isoforms play an important role in various biological effects, a large number of ALOX inhibitors have been developed. Unfortunately, for most of them, there are neither parallel nor homologous features. Studies have shown that most ALOX inhibitors exhibit a limited degree of parallel specificity under rigorous and comparable experimental conditions. In addition, because of functional differences between mice and human ALOX homologues, inhibition of human ALOX homologues by an inhibitor does not necessarily mean that the corresponding mice homologues are also inhibited. For example, PD146176 was used as a specific inhibitor of ALOX15 in experimental strategies that completely failed to inhibit Alox15 in rats(Gregus et al. 2013). The reason may be related to the different location specificity of the two ALOX15 homologues, but future experiments are needed to support this conclusion. Therefore, inhibitors that effectively interfere with human ALOX15 may not inhibit homologous enzymes in

other species due to species specificity. For example, recent studies have shown that some oxazol-4-carbonitrile-based LOX inhibitors have high inhibition ability on ALOX15 in humans and mice, but can hardly inhibit other mammalian LOX subtypes(Rai et al. 2014). Thus, when interpreting the role of a given ALOX inhibitor in complex biological systems, consideration needs to be given to the lack of homologous specificity and varying degrees of homologous specificity of currently available ALOX inhibitors.

~~5~~6.3. Off-target effects of ALOX15 inhibitors

Some of the ALOX15 inhibitors (NDGA, baicalin) in the above table have antioxidant properties and may directly affect cellular redox homeostasis. The regulation of cellular redox state on gene expression has been discussed in genetic(Brüne et al. 2013) and epigenetic (Goswami 2013; Kim et al. 2013) level, so it is difficult to distinguish between the biological effects we observed due to inhibition of LOX or inhibition of the redox state. In conclusion, the results obtained with some ALOX15 inhibitors need to be interpreted to a certain extent and confirmed by further experiments of alternative function.

Future questions need to be detected

To date, most of the literature on the role of ALOX15 in the occurrence of DM has focused on its expression and mechanism in glomerular mesangial cells, while its expression in other renal cells remains unclear. Therefore, it will be important to address the potential relationship between cell populations in the next step. Secondly, due to the dual role of ALOX15 in inflammation, is ALOX15 mainly an anti-inflammatory molecule or a pro-inflammatory molecule in the pathogenesis of DM? More researches are needed to determine whether the regulatory role of ALOX15 in DM is specific to DM or also applies to other related metabolic diseases. Finally, we have to admit that trying to do something with ALOX15 is bound to create perturbations in other ways that are not considered. In vivo experiments, it can be observed that Alox12 and Alox15 knockout mice are currently viable. Although the epididymal maturity of Alox15 defective sperm is irregular, the animals reproduce well and establish corresponding mouse colonies easily(Walters et al. 2018). On the other hand, the mild phenotype of Alox15, Alox12, and Alox5 knockout mice may be partly related to the fact that these two enzymes are not currently conditionally knocked out. One problem with unconditioned knockout mice is that they are produced to a certain extent selectively (only embryonic stem cells that survive the genetic manipulation are selected for blastocyst injection), and compensation mechanisms during early embryogenesis cannot be ruled out. In order to overcome these problems, induced knockout systems should be established, but such experiments are time-consuming and expensive, and need to be further explored in the future.

Rationale and Perspective

ALOX15 is a vital enzyme involved in catalyzing fatty acid oxidation, which takes part in physiological and pathological procedures of the human body. In addition, ALOX15 can participate in the occurrence of DM and its complications through inflammatory reaction, oxidative stress, ferroptosis and other mechanisms, while the inhibition of ALOX15 expression can reduce the occurrence of DM and its complications. The specific mechanism and treatment plan need to be more studied. In addition, studies have shown that ALOX15 inhibitors, such as baicalin, BHPP, NDGA, etc have positive effects on different diseases in vivo and in vitro models. However, further clinical researches are needed to clarify the efficacy of these inhibitors in diseases. Therefore, in terms of scientific research, this study aims to provide research direction for researchers in diabetes-related

research. In clinical aspect, there is an urgent need to explore new and specific anti-DKD ALOX15 inhibitors in the field of diabetes, so as to provide a new direction for the diagnosis and treatment of DM.

Highlight

1. ALOX15 was initially found to be associated with the maturation of mitochondria in the later stages of erythropoiesis. Subsequent studies indicated that the expression of ALOX15 may also be involved in the occurrence of DM and its related complications.

2.ALOX15 can participate in the occurrence and development of various diseases through pro-inflammation or anti-inflammation, oxidative stress, ferroptosis and other functions.

3.ALOX15 can be used as a biomarker. Inhibition of the expression level of ALOX15 can help protect the kidney tissue and reduce the urinary protein level, which can be used as a new therapeutic target for the treatment of DM and its complications.

4.Baicalin, BHPP, NDGA and other ALOX15 inhibitors have positive effects on both in vivo and in vitro models of different diseases. Further studies are needed to develop and test specific pharmacological inhibitors of each LOX in order to apply them to therapeutic intervention of human diseases.

Funding

This work was supported in by Lanzhou Science and Technology Bureau talent innovation and entrepreneurship (2021-RC-94); National Natural Science Foundation of China (No. 81960142), Youth Science and Technology Fund Program of Gansu Province (No. 21JR1RA157), and Talent Innovation and Entrepreneurship Project of Lanzhou City, Gansu Province (2021-RC-94). Lanzhou University Second Hospital Youth Fund (CY2021-QN-B01). Project of Department of Education of Gansu Province (2022B-050). Meanwhile, our experiments are supported by the Clinical Medical Research Center of Gansu Province (21JR7RA436).

Author contributions

XCZ and JQW contributed to the conceptualization of the research; KYH writing-original draft; HXD visualization of figures and table; JZ literature search; RRD article review and revision.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Ethical Statement

Not applicable.

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