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REVIEW ARTICLE

TNF-α, a potent lipid metabolism regulator

Xiuping Chen[1,2]*, Keli Xun[3], Lidian Chen[2] and Yitao Wang[1]

[1]*Fujian College of Traditional Chinese Medicine, Fuzhou, China*
[2]*Institute of Chinese Medical Sciences, University of Macau, Macau, China*
[3]*Department of Dermatology, People's Hospital of Binzhou, Binzhou, China*

As a multifunctional cytokine, tumor necrosis factor alpha (TNF-α) exerts a series of biological actions in different cells, tissues, organs, and species and has been demonstrated to regulate and interfere with energy metabolism, especially lipid homeostasis. A large body of researches suggested that the effects of TNF-α on lipid metabolism mainly include five aspects: (1) suppresses free fatty acid (FFA) uptake and promotes lipogenesis; (2) induces lipolysis; (3) inhibits lipid-metabolism-related enzymes activity; (4) regulates cholesterol metabolism; (5) regulates other adipocyte-derived adipokines. The molecular mechanisms underlying these actions are complex and several signal transduction pathways might be involved. Regulation of metabolism-related gene expression at transcriptional and protein levels and impact on enzymes activity might be of importance. Identification and verification of these pathways might provide novel potential strategies and drug targets for dyslipidemia therapy. However, the inconsistent and even conflict conclusions on lipid profile drawn from human subjects after infliximab therapy poses the possibility that the effect of TNF-α on lipid metabolism might be more complicated than it appeared to be.

KEY WORDS — tumor necrosis factor alpha; free fatty acid; lipolysis; cholesterol; leptin; adiponectin; infliximab

INTRODUCTION

Lipids have long since been recognized as signaling molecules that have the capacity to trigger profound physiological responses.[1] Changes in lipid metabolism have been the most important biomarkers and risks of cardiovascular diseases. Furthermore, plasma or serum lipids concentration has always been the widely used index to evaluate the validity of clinical interference. Tumor necrosis factor alpha (TNF-α), a 17 kDa polypeptide, was originally discovered as a factor produced by macrophages in endotoxin stimulated rabbits that could cause hemorrhagic necrosis of experimental tumors.[2] Recently, TNF-α was confirmed to be one of the most important cytokines exerting a series of biological effects in different tissues and species and at multiple layers. Although TNF-α has been widely used as a kind of ''tool drug'' for studying cell proliferation, apoptosis, gene expression, inflammation, etc., the functions and mechanisms of itself have not been fully elucidated. Accumulated data revealed that TNF-α could perturb the normal regulation of energy metabolism, especially the lipid metabolism, which might be one of the pathophysiological basis of atherosclerosis, diabetes, coronary heart diseases, etc. Several critical reviews concerning the role of TNF-α in adipocytes, chronic inflammation, and adipocytes biology have been published recently.[3–5] However, most of these reviews were confined to adipocytes, and the biological function of TNF-α on other kinds of cells and/or tissues was rarely mentioned. In this review, the effects of TNF-α on lipid metabolism are summarized and updated and the molecular mechanisms underlying these effects are discussed.

THERE IS A LINK BETWEEN TNF-α AND DYSLIPIDEMIA

Both clinical observations and basic researches put insight that there is a potential link between inflammation and lipid metabolism. It is well known that TNF-α plays an important role in both acute and chronic inflammation. Close relationship between TNF-α and lipid metabolism is supported by multiple facts.

Firstly, in clinical patients with dislipidemia, significant changes of plasma TNF-α level have been documented. Compared with healthy subjects, patients with hyperlipoproteinemia IIb showed higher TNF-α plasma concentration and increased level of total cholesterol (TC), total

* Correspondence to: X. Chen, Av. Padre Tomas Pereira S.J., Taipa, Macau, China. Tel: 86 853 83974873. Fax: 86 853 28841358.
E-mail: chenxiu0725@yeah.net

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triglyceride (TG), and low density lipoprotein (LDL). Furthermore, the decreased levels of TC, TG, and LDL after fenofibrate therapy were correlated with the decreased concentration of TNF-α.[6] In patients with hypercholesterolemia, increased plasma TNF-α level was also accompanied by elevated TC and LDL concentrations.[7] Besides, in hyperlipidemic patients, TNF-α levels positively correlated with very-low-density lipoprotein (VLDL), TG, and TC concentrations but negatively with high density lipoprotein cholesterol (HDL-C) concentration.[8] These results were further supported by laboratory experimental data from rats and mice.[9–11] A very new study suggested that increased TNF-α could be a marker of familial combined hyperlipidemia, a disorder characterized by elevated levels of serum TC, TG, or both.[12]

Secondly, drugs that ameliorate hyperlipidemia could also decrease plasma TNF-α level in the meantime. Administration of rosuvastatin, one of the widely used hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor for hyperlipidemia therapy, decreased TC, LDL-C, triglycerides, and increased HDL-C, which was accompanied by significant reduction of TNF-α in patients with hypertension and dyslipidemia.[13] Simvastatin and atorvastatin, another two HMG-CoA inhibitors, also decreased TNF-α level in hyperlipidemic and hypercholesterolemic subjects.[14,15] Furthermore, HMG-CoA inhibitors and peroxisome proliferator-activated receptor alpha (PPARα) activators could normalize TNF-α levels in type IIa and IIb dyslipidemic patients, who exhibit an abnormal pattern of TNF-α.[16] In addition, atorvastatin treatment significantly reduced high cholesterol diet induced high levels of TNF-α serum concentration and mRNA expression in hypercholesterolemic rabbits.[17] These data suggested that there might be certain relationship between the lipid profile improvement and the decreased serum level of TNF-α.

Thirdly, TNF-α blockade could significantly affect lipid metabolism. Short-term administration of adalimumab, a fully human anti-TNF monoclonal antibody, to patients with active rheumatoid arthritis (RA), significantly increases HDL-C concentrations. In addition, the atherogenic index also decreased.[18] Infliximab, a chimeric anti-TNF monoclonal antibody showed similar results.[19,20]

Fourthly, administration of TNF-α had been demonstrated to directly interfere with the plasma lipid level and metabolic pathways, which provides direct evidence that TNF-α is an important lipid metabolism regulator. In mice, administration of TNF-α resulted in an acute increase of plasma TG and inhibition of TNF decreased LPS-induced TG elevation.[21,22] TNF administration to insulinopenic diabetic rats also increased serum triglycerides.[23,24] While in a phase I pharmacological study, continuously infused rH-TNF (recombinant human tumor necrosis factor) for 24 h was associated with significant decreases in serum cholesterol and HDL levels.[25]

The influence of TNF-α on lipid metabolism is so complicated that the detailed mechanisms underlying these actions are still not very clear. However, documented data have demonstrated that the mechanisms through which TNF-α exerts its effects on lipid metabolism takes place at different levels and different steps, and varied in different cells, tissues, and organs: from increasing free fatty acid (FFA) production to inducing lipolysis, from affecting lipid-metabolism-related gene expression to regulating enzymes activity. In addition, TNF-α could also affect lipid metabolism by altering the expression and secretion of other adipokines such as leptin, adiponectin, etc.

TNF-α REGULATES LIPID METABOLISM

TNF-α increases FFA production

FFA is the basic material for neutral triacylglycerols (TAG), the form of lipid droplets in adipocyte synthesis. Generally, there are three FFA sources: (a) from the circulation, (b) from lipolysis of intracellular TAG, or (c) *de novo* FFA synthesis from glucose.[26] Hence, the availability of relevant substrates and the regulation of several enzymatic pathways might exert on the overall metabolic flux of lipids into TAG.

Grunfeld *et al*.[27] showed that bolus intravenous administration of TNF to normal rats resulted in a rapid stimulation of hepatic FFA *de novo* synthesis and induced an acute increase in the plasma levels of FFA, which was supposed to be through raising hepatic levels of citrate, an allosteric activator of acetyl-CoA carboxylase. Suppression of liver peroxisomal β-oxidation by inhibiting the activity of peroxisomal fatty acyl-CoA oxidase may also contribute to this process.[28] Other possible mechanisms include down-regulation of the expression of FFA transport protein (FATP), translocase (FAT) in adipose tissue and the FA-binding protein (FABP4/aP2), and/or inhibition of the transcript levels and expression of many proteins involved in glyceroneogenesis, *de novo* FFA synthesis and esterification, which also leads to impaired triglyceride storage in adipose tissue.[26] However, it is interesting to note that TNF stimulated plasma FFA production might be diet dependent since TNF increases plasma FFA in chow-fed rats while in rats fed a high sucrose diet no such phenomenon was observed.[29]

Early studies have demonstrated that administration of TNF-α to rats stimulates lipid (plasma TG, cholesterol), sterol synthesis, and incorporation of tritiated water into fatty acids in the liver *in vivo*, which appeared 2 h after TNF-α infusion and lasted for 17 h. However, it does not stimulate lipid synthesis in other tissues, including adipose tissue suggesting that stimulation of hepatic lipogenesis by TNF-α contributes to the hyperlipidemia of infection.[30] The mechanism was not due to the increase of enzymes of triglyceride synthesis (phosphatidate phosphohydrolase, glycerol-phosphate acyltransferase, or diacylglycerol acyltransferase) but resulted from providing increased FFA as substrate.[29] Incorporation of glycerol into triglycerides in the liver induced by TNF might also contribute to this process.[31]

A single injection of human recombinant TNF-α to female NMRI mice induced hypoglycemia within a 2 h period, accompanied by a severe depletion of liver glycogen,

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which might be due to the consumption of glucose by the liver for lipogenesis.[32] While in dogs the decrease in glucose concentrations after TNF-α infusion was due to a stimulation of glucose clearance and TNF-α did not directly affect glucose production. Furthermore, changes in lipid kinetics were not mediated by changes in insulin or glucagon and might have reflected direct effects of TNF-α.[33] This divergence might be due to the differences of animal species (female NMRI mice vs. dogs) and the administration regimen (a single injection of 7.5×10^7 U kg^{-1} vs. constant infusion (prime, 2.5 μg kg^{-1}; constant infusion, 62.5 ng kg^{-1} min^{-1})) to some degree.

TNF-α plays an important role in mediating insulin resistance (IR) in a number of cell types including: hepatoma cells (FAO and KRC-7), fibroblasts, myeloid cells (32D), and rat muscle cells (L6).[5] Recent studies demonstrated that FFA produces IR and activated the pro-inflammatory nuclear factor-kappa B (NF-κB) pathway in rat liver, which could result in over-production of glucose and hyperglycemia.[34] In 3T3-L1 adipocytes, this action was mediated by c-jun-NH2-terminal kinase (JNK) and TNF-α.[35] Actually, FFA and possibly TNF-α levels were closely related to the development of IR in subjects with metabolic disorders.[36]

The effects of TNF-α on FFA production and lipogenesis in hepatic and adipose were shown in Figure 1. TNF-α exerts different effects on liver and adipose tissues. In liver, TNF-α stimulates hepatic fatty acid *de novo* synthesis through raising hepatic levels of citrate and suppression of liver peroxisomal β-oxidation by inhibiting the activity of peroxisomal fatty acyl-CoA while in adipose tissue, this might be through TG and by regulating FAT and FATP.

TNF-α induces lipolysis

Healthy young male individuals receiving rH-TNF-α showed increased systemic lipolysis with a concomitant increase in FFA clearance while the skeletal muscle fat metabolism was unaffected.[37] Both TNF-α and IL-6 applied alone stimulated lipolysis in perinodal adipocytes.[38] Intravenous injection of recombinant TNF-α to rats increased serum triacylglycerol, which was mainly due to an increased secretion of triacylglycerol by the liver.[39] Studies on adipocytes from mice lacking TNF receptor (TNFR) [TNFR1 (TNFR1(−/−)), TNFR2 (TNFR2(−/−)), or both (TNFR1(−/−) R2(−/−))] revealed that this effect was mediated mainly via TNFR1[40] and dependent on down-regulation of lipid droplet-associated protein perilipin (PLIN).[41] The downstream signals involved the activation of several kinases of the mitogen-activated protein kinase (MAPK) family, including extracellular signal-related kinase (ERK) 1/2 (or p44/42) and JNK.[42] Other evidence suggested that the lipolytic action of TNF-α could be influenced by glucose[43] and activation of the ERK pathway was an early event in the mechanism of TNF-α-induced lipolysis in 3T3-L1 adipocytes.[44] In rabbit subcutaneous adipocytes, TNF-α affected cholesterol efflux and ATP binding cassette transporter A1 (ABCA1) expression through the pathway of PPARγ-liver-X-receptor α (LXRα)-ABCA1.[45] While in rainbow trout adipocytes, TNF-α stimulated lipolysis *in vitro* and *in vivo* by down-regulation of lipoprotein lipase (LPL) activity.[46] In human adipocytes, TNF-α promoted lipolysis through activation of MAPK (MEK)-ERK and subsequent increase in intracellular

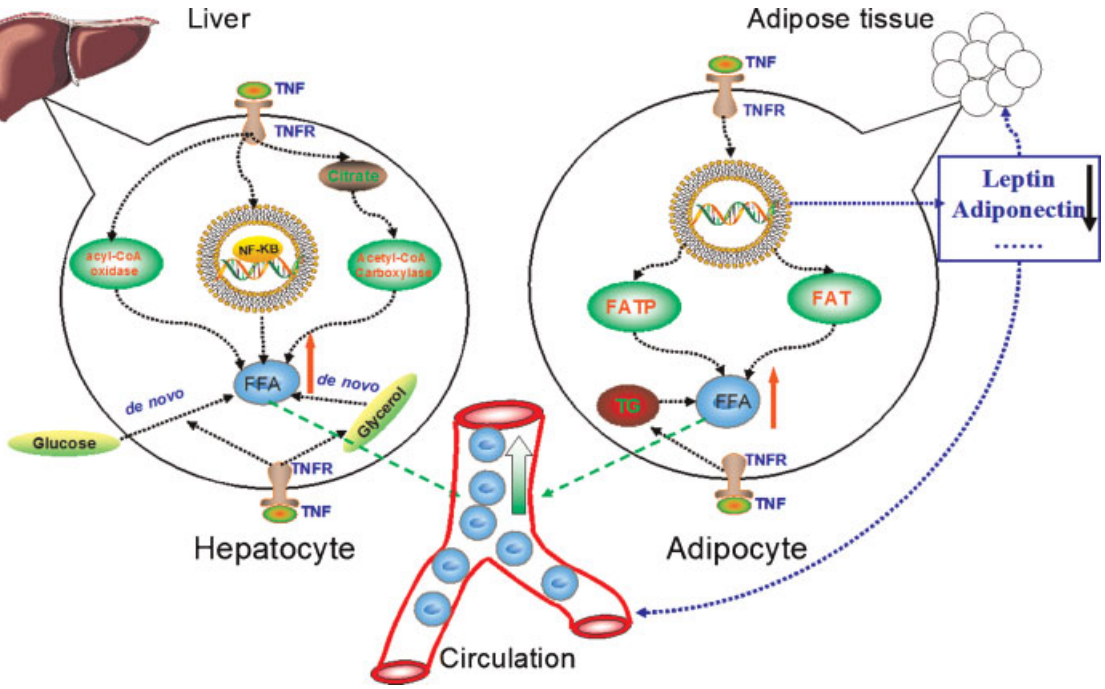

Figure 1. TNF-α increases FFA production in liver and adipose tissue. TNFR, TNF-α receptor; FFA, free fatty acid; TG, triglyceride; FATP, fatty acid transport protein; FAT, fatty acid translocase

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cAMP.[47] Treatment of adipocytes with metformin could attenuate TNF-α-mediated lipolysis by suppressing phosphorylation of ERK1/2 and reverse the down-regulation of perilipin protein.[48] Another study indicated that TNF-α-induced lipolysis by blunting endogenous inhibition of lipolysis and Gi protein down-regulation might also be involved.[49]

However, results from subcutaneous administration of a polyclonal goat anti-rat TNF antibody to Zucker rats revealed that anti-TNF treatment could not alter lipid metabolism in the obese animals. Lipolysis measurements in adipose tissue slices from the anti-TNF-treated animals also did not show any significant effect of the treatment.[50] In isolated rat adipocytes, though pre-incubation with TNF increased adrenaline-stimulated FFA release, it did not stimulate lipolysis.[51] In RAW 264.7 cell line, TNF-α increased the rate of lipolysis by a mechanism that did not involve increased expression of hormone sensitive lipase (HSL) suggesting a TNF-induced post-translational modification of the enzyme.[52] In 3T3-F442A adipocytes, TNF enhanced lipolysis, decreased LPL activity, and induced prostaglandin (PG) production. However, the lipolysis effect of TNF was independent of PG.[53]

In short, though there are still some controversies about TNF-α-induced lipolysis *in vivo*, most of the present researches confirmed that TNF-α stimulates lipolysis *in vitro*, which might be mediated by TNFR1 and through multiple pathways.

Effects of TNF-α on lipid-metabolism-related enzymes

Another mechanism through which TNF-α can affect plasma lipid metabolism is the regulation of several lipid-related enzymes. It had long been noticed that exposure of fully differentiated 3T3-L1 adipocytes to recombinant TNF resulted in a dose- and time-dependent suppression of the activity of LPL[54] and an increase in intracellular lipolysis.[55,56] TNF also inhibited LPL activity in cultured myocytes and in the Langendorff rat heart.[57] In cultures of a human osteosarcoma cell line, rh-TNF-α suppressed synthesis, activity, and secretion of LPL and inhibited LPL-mediated supply of non-esterified fatty acids as an energy source for growth, which might partly account for the anti-proliferative activity of TNF-α.[58] Furthermore, a synergism between interferon gamma and TNF-α in the regulation of LPL in the macrophage J774.2 cell line was observed.[59] In brown adipocytes, the down-regulation of LPL activity induced by TNF-α was mediated by nitric oxide (NO).[60] In addition, TNF-α could suppress LPL expression in J774.2 macrophages at the transcriptional level,[61] which might be through tyrosine kinase and the phosphatidylinositol-3′-kinase (PI3K) signaling pathways.[62]

HSL is an ''old'' enzyme expressed in multiple tissues and plays a number of roles in lipid metabolism. In adipose tissues, it is rate limiting for the degradation of triacylglycerol. In 3T3-L1 adipocytes, TNF inhibited the gene expression of HSL and depressed the activities of both LPL and HSL.[63] One potential mechanism involved might be TNF-α-mediated NF-κB activation.[64] More recently, a study revealed that a cell-permeable peptide that inhibits NF-κB signaling could abolish the nuclear translocation of NF-κB and effectively abrogated TNF-α-induced lipolysis in a concentration-dependent manner. This was combined with reduction of both HSL and PLIN protein suggesting that NF-κB was important for TNF-α-induced lipolysis in human adipocytes.[65]

Adipocyte triglyceride lipase (ATGL), also called PNPLA2/destnutrin/iPLA2zeta/TTS2.2, is a novel adipose-enriched lipase that catalyzes the initial step in triglyceride hydrolysis in adipocyte lipid droplets. TNF-α treatment decreased ATGL transcription in a time-dependent manner in 3T3-L1 cells and pharmacological inhibitory study revealed that p44/42 MAPK, PI3K, and p70 ribosomal protein S6 kinase signals involved in this process. These results suggested that ATGL is a target for transcriptional activation by TNF-α.[66] However, another study showed that treatment adipocytes with 30 ng mL^{-1} TNF-α significantly decreased ATGL mRNA to 17% of control level, which was not mediated by p44/42 MAPK.[67] Hence, it is certain that TNF-α has negative effect on ATGL mRNA expression while the involvement of p44/42 MAPK is still controversial.

Early studies showed that TNF inhibited the accumulation of acetyl-CoA carboxylase, the rate-limiting enzyme for long-chain FA biosynthesis, mRNA expression, and decreased its activity in a pre-adipocyte cell line, 30A-5.[68] This regulation was supposed to be achieved by decreasing the rate of acetyl-CoA carboxylase gene transcription during pre-adipocyte differentiation.[69] However, another study found that fatty acid synthetase and acetyl-CoA carboxylase increased 35 and 58%, respectively, after 16 h treatment of rats with TNF and that TNF acutely regulated hepatic FA synthesis *in vivo* by raising hepatic levels of citrate.[27] This was further confirmed by another study, which demonstrated that citrate, an allosteric activator of acetyl-CoA carboxylase, mediated changes in the rates of FA synthesis induced by TNF.[70] Although in diabetic rats TNF administration increased production of triglyceride by 2-fold, it did not alter either the amount or activation state of hepatic acetyl-CoA carboxylase.[70] In 3T3-F442A adipocytes, it was found that TNF decreased LPL, acetyl CoA carboxylase, HSL, and fatty acid synthase mRNA levels[71] without altering the activities of different enzymes of glucose and alanine metabolism such as hexokinase, phosphofructokinase, pyruvate kinase, glucose-6-phosphate dehydrogenase, and alanine transaminase.[72] These divergences about the effect of TNF on acetyl-CoA carboxylase might result from the difference between the adipocytes and the liver and further studies need to be done to provide more reasonable interpretation.

In summary, most of the important enzymes involved in lipid metabolism such as LPL, HSL, ATGL, and acetyl-CoA carboxylase could be regulated by TNF-α. In most cases, this regulation might be through affecting the mRNA expression at transcriptional level. Sometimes, direct inhibition of enzyme activity might also be involved.

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Effects of TNF-α on cholesterol metabolism

Effects of TNF-α on cholesterol metabolism differ between rodents and primates. Whereas the administration of TNF-α to rodents was followed by a delayed increase in serum concentrations of TC and hepatic cholesterol synthesis, non-human primates, and humans showed either no change or a decrease in serum cholesterol and LDL-C levels.[4]

In C57Bl/6 mice, TNF increased serum cholesterol. Moreover, TNF produced a 2.1-fold increase in hepatic HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis activity. Pre-treatment with anti-TNF antibodies blocked the effect of LPS on serum cholesterol, hepatic cholesterol and FA synthesis, and hepatic HMG-CoA reductase activity.[22] It is interesting to note that TNF and IL-1 combination showed synergistic effect on both serum cholesterol and HDL-C level and HMG CoA reductase mRNA levels in Syrian hamsters.[73]

TNF-α may also affect cholesterol metabolism and excretion by inhibiting the expression and activity of cholesterol-7α-hydroxylase (CYP7A1), the rate-limiting enzyme in the classic pathway of bile acid synthesis.[74] Besides, the activities of mitochondrial sterol 27-hydroxylase and oxysterol 7α-hydroxylase, the rate-limiting enzymes in the alternative pathway of bile acid synthesis, were also down-regulated by TNF-α in human hepatoma cell lines.[75]

Reverse cholesterol transport (RCT) plays a crucial role in preventing and reversing the development of hyperlipidemia and formation of atherosclerotic lesions. Several important proteins are involved in this process such as ABCA1, ATP binding cassette transporter G1 (ABCG1), cholesteryl ester transfer protein (CETP), lecithin cholesterol acyltransferase (LCAT), etc. CETP was a new therapeutic target for atherosclerosis,[76,77] and CETP blocking agents were supposed to increase HDL and decrease cardiovascular risk.[78,79] Administration of TNF-α and IL-1 individually did not significantly affect serum CETP levels while the combination of them significantly decreased serum levels of CETP in Syrian hamsters. Furthermore, TNF-α reduced the levels of mRNA for CETP in muscle, heart, intestine, stomach, and kidney, but not in adipose tissue while IL-1 was administered together they were much more effective than the individual cytokines and decreased CETP mRNA expression in all the tissues.[80]

Injection of TNF to cynomolgus monkeys decreased plasma LCAT activity, plasma cholesterol level, and decreased content of cholesterol ester in LDL and HDL particles.[81] In HepG2 cells, rH-TNF-α dose dependently decreased the concentrations of apolipoprotein (apo) A-I, apoB, and LCAT activity in the medium after 24 h of incubation.[82] In Syrian hamsters and cultured rat H35 hepatocytes, TNF treatment decreased plasma LCAT activity and LCAT mRNA expression.[83] In cynomolgus monkeys, injection of LPS caused a 2-fold increase in plasma triglyceride and a 25% reduction in plasma cholesterol 48 h after injection. Similar results were observed with injection of rH-TNF-α.[84] TNF-α induced both ABCA1 mRNA and protein expression in primary cultured peritoneal, THP-1 derived, and J774 murine macrophages,[85–87] which was mediated by NF-κB.[86] While in rabbit subcutaneous adipocytes, the expression of ABCA1 was increased by low concentration of TNF-α and was inhibited by higher concentration, which might be mediated by PPARγ-LXRα-ABCA1.[45]

Effects of TNF-α on lipid-metabolism-related adipokines

Recent advances regarding the biology of adipose tissue, especially the discovery and study of a serial of novel pleiotropic adipokines such as leptin, adiponectin, resistin, etc., have revolutionized our traditional view of adipose tissue. Adipose tissue is no longer considered as an inert tissue mainly devoted to energy storage but is emerging as an active endocrine organ and an important mediator that is involved in many physiologic and pathologic processes regarding energy metabolism. Current evidence suggested that the inter-regulation of these adipokine and TNF-α might be involved in TNF-α-mediated lipid metabolism.

Leptin, a 16 kDa protein encoded by the *ob* gene, is mainly secreted by adipose tissue.[88] The circulating leptin level is 5–15 ng mL^{-1} in lean subjects,[89] which directly correlate with adipose tissue mass.[90] Control of appetite is the primary role of leptin and its regulation and important role in controlling of food intake, body weight, and energy homeostasis have been firmly established.[91–93] Besides, few reviews have been published describing its direct potent role in lipid metabolism both *in vivo* and *in vitro*[94–96] such as decreases food consumption via modulation of hypothalamic neuropeptide, changes the fuel source from which ATP is generated, stimulator of lipolysis, and fatty acid oxidation.[94] These actions of leptin may be mediated by its binding to its receptor with succeeding activation of the Jak/Stat pathway or by direct stimulation 5-AMP-activated protein kinase (AMPK), which will phosphorylate and thereby inhibit acetyl CoA carboxylase activity and lipogenesis.[97]

Previous review summarized that acute exposure to TNF-α stimulates production of leptin at both mRNA and protein levels, which was mediated through a direct interaction between soluble TNF-α and p55 TNFR found on adipocytes.[98] However, some studies suggested that TNF-α stimulates the release of pre-formed intracellular pools of leptin but actually decreases leptin gene expression and secretion in 3T3-L1 and mouse brown adipocytes[99,100] which might be mediated by protein kinase C (PKC).[100] Another study revealed that short-term (24 h) exposure of isolated rat adipocytes to TNF-α does not affect leptin secretion while prolonged exposure produces a concentration-dependent inhibition of leptin secretion and gene expression.[101] These paradoxical results showed that TNF-α might exert dual effects on leptin synthesis and release. TNF-α stimulates the release of leptin from human mature adipocytes and existing differentiated pre-adipocytes, which may contribute to obesity-/infection-linked hyperleptinemia, while TNF-α inhibits leptin synthesis via inhibition of

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pre-adipocyte differentiation and induction of adipocyte de-differentiation.[102]

Another adipokine deserved notice is adiponectin. Adiponectin (also called Acrp30, adipoQ, ApM1, GBP28), a 30 kDa secretory protein synthesized in adipose tissue and secreted into serum, was identified in 1995.[103] Adiponectin is a unique adipokine since (1) the plasma concentration of adiponectin is very high, ranging between 0.5 and 30 mg L^{-1},[104] which accounts for about 0.01% of all plasma proteins in humans and 0.05% in rodents. This concentration is about 3 orders of magnitude higher than leptin and about 6 orders of magnitude higher than IL-6, which measured in ng mL^{-1} and pg mL^{-1}, respectively; (2) adiponectin exists in six forms *in vivo*: the gAPN (globular adiponectin), fAPN (full-length adiponectin), LMW (low molecular weight adiponectin), MMW (middle molecular weight adiponectin), HMW (high molecular weight adiponectin), and Alb-LMW (serum albumin bounded form adiponectin).[105] Its multiple beneficial effects in obesity, atherosclerosis, and metabolic syndrome[104,106] strongly supports its potential role in lipid metabolism regulation. Similar to leptin, regulation of adiponectin expression and secretion by TNF-α was well documented: Neutralization of TNF-α and anti-TNF-α therapy reduced ConA-induced liver damage in mice and improve endothelial dysfunction in patients with RA, respectively. In the meantime, the circulating levels of adiponectin were restored.[107,108] A more recent study reported that C57BL/6J mice treated with TNF-α for 7 days significantly down-regulates both PPARγ and ATGL mRNA expression in adipose tissues as well as ATGL protein levels in plasma. Moreover, adipose mRNA expression and plasma protein levels of adiponectin were significantly down-regulated.[109] In human visceral adipose tissue, TNF-α treatment dramatically decrease adiponectin expression and secretion,[110] which might be through insulin-like growth factor-binding protein-3[111] and JNK signal transduction pathways.[112] In addition, induction of hyper-adiponectinemia was observed following long-term treatment of patients with RA with infliximab, an anti-TNF-α antibody.[113]

In summary, present documented data has demonstrated that at least four signal pathways might be involved in TNF-α-mediated lipid metabolism: through ERK/JNK to cAMP to PKA and then to HSL; through Gi to cAMP; and through PI3K/NO to LPL. Furthermore, TNF-α could also regulate some lipid-metabolism-related enzymes activity and/or expression such as LPL, HSL, ATGL, acetyl-CoA carboxylase, LCAT, HMG-CoA, etc. In addition, TNF-α-meditated regulation of adipokines might also be of importance (Figure 2).

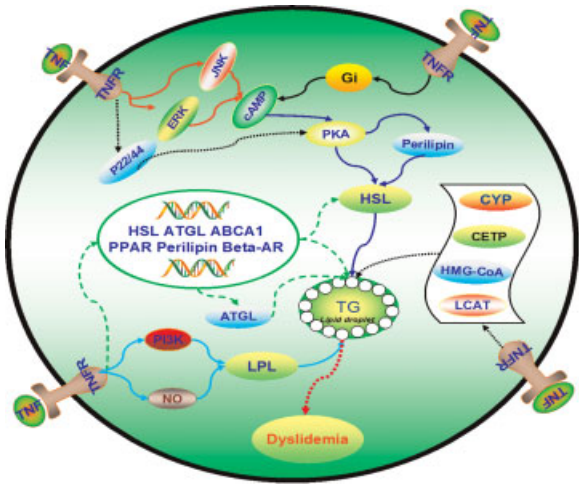

Figure 2. Effects of TNF-α on lipid metabolism. TNFR, TNF-α receptor; TG, triglyceride; ERK, extracellular signal-related kinase; JNK, c-jun-NH2-terminal kinase; PKA, protein kinase A; HSL, hormone sensitive lipase; CYP, cholesterol-7α-hydroxylase; CETP, cholesteryl ester transfer protein; HMG-CoA, hydroxy-3-methylglutaryl-coenzyme A; LCAT, lecithin cholesterol acyltransferase; ABCA1, ATP binding cassette transporter A1; ATGL, adipocyte triglyceride lipase; PPAR, peroxisome proliferator-activated receptor; Beta-AR, beta adrenoceptor; LPL, lipoprotein lipase; PI3K, phosphatidylinositol-3′-kinase

Effects of infliximab on lipid metabolism – human studies

As mentioned above, direct evidence for the effects of TNF-α on lipid profile in human subjects is limited. However, TNF-α pathway inhibition by blocking TNF-α mRNA synthesis and secretion, or by blocking TNF-α activation of their receptors (via monoclonal antibodies or soluble receptors) provides indirect evidence for the role of TNF-α in human lipid metabolism.

Infliximab, a chimeric anti-TNF-α human IgG1κ antibody linked to a variable region of a murine anti-human TNF-α antibody was developed by Junming Le and Jan Vilcek in last 1990s.[114] Now infliximab has been widely prescribed for the treatment of psoriasis, Crohn's disease, ankylosing spondylitis (AS), psoriatic arthritis (PA), RA, sarcoidosis, and ulcerative colitis.

Early studies reported that in patients with RA and PA, intravenous infliximab therapy (3 mg kg^{-1} at weeks 0, 2, and 6) leads to significant increase in TG levels, decrease in HDL-C levels but no significant difference in TC and LDL-C levels.[115] Decrease in HDL-C levels, peripheral arteries diameters, and increase of blood wall shear stress in RA patients received infliximab therapy were also observed.[116] However, another study suggested that in active RA patients, infliximab therapy (3 mg kg^{-1} at weeks 0, 2, and 6) was associated with a significant increase of both TC and HDL-C levels, which correlated with decreasing disease activity.[19] While in patients with refractory, infliximab administration (3 mg kg^{-1} at weeks 0, 2, 6, 14, 22, and 30) associated with important increases in TC, LDL-C, HDL-C but has no significant beneficial effect on the atherogenic index (TC/HDL-C, LDL-C/HDL-C).[117] A long-term investigation (2 years) of infliximab treatment in RA patients (3 mg kg^{-1}, , at 0, 2, 6 weeks and thereafter every 8 weeks for 2 years) revealed that there was an initial increase in plasma levels of TC, HDL-C, LDL-C, which significantly decreased after 6 months while the atherogenic index remained significantly

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raised.[118] Similar increase of the atherogenic index was also observed in another study in a 1-year treatment but the plasma levels of TC and LDL-C were increased.[119] While active RA treated with infliximab (3 mg kg^{-1}, at 0, 2, 6, and 14 weeks) for 14 weeks improve IR, increase TC, HDL-C, LDL-C, and TG without changing the atherogenic index.[120]

Infliximab administration to RA and AS patients (3 mg kg^{-1}, at 0, 2, 6 weeks, and every 8 weeks thereafter for RA and at 5 mg kg^{-1} body weight for AS, respectively) for 6 months showed no effect on LDL-C level, TC/HDL-C, and TG/HDL-C ratios, which suggests that infliximab might exert neutral effect on lipid profile.[121] Forty-eight weeks ($3 \sim 7.5$ mg kg^{-1}, at 0, 2, 6, and then every 8 weeks) and 14 weeks infliximab infusions showed similar effects on the lipid profile.[122,123] In addition, anti-TNF-α treatment in combination with methotrexate (MTX) and corticosteroid therapy in patients with active RA for 3 months increase both TC and HDL-C levels, without affecting the atherogenic index.[124] A study assessed the effect of infliximab on lipid profile induced by chronic inflammatory arthritides in RA, PA, and AS patients in the meantime. Six months of infliximab treatment induced a sustained increase of serum HDL-C while the TC and the atherogenic index was significantly increased and decreased, respectively, only after the first month of treatment.[20] In a case report of a patient with RA and PA, a single infusion of infliximab developed a marked increase in TG and TC levels[125] which was confirmed by a 6-month study in RA patients.[126] Infliximab treatment preferentially induced extra high levels of VLDL-TG.[126] Popa *et al*.[127] reported that treating RA patients with infliximab (3 mg kg^{-1}, at 0, 2, and 6 weeks and then every 8 weeks) for 6 months increase TC, HDL-C, apoA-I, and the atherogenic index. But the beneficial effect of infliximab was supposed to be through changes in the composition of the HDL particle leading to improved anti-oxidative properties.

In patients with inflammatory bowel disease, infliximab treatment (5 mg kg^{-1} intravenously over 2 h at weeks 0, 2, and 6 and a maintenance dose of 5 or 10 mg kg^{-1} every 8 weeks) increased TC, HDL-C, and apo-AI levels without affecting TG, LDL-C, and apoB100.[128] In patients with Crohn's disease, infliximab therapy increase in both TC and HDL-C concentrations. Furthermore, a rapid and large increase in visceral and subcutaneous abdominal fat during infliximab therapy was also observed.[129]

From discussed above, it is hard to make a definite conclusion about the effect of infliximab on lipid profile in patients and it is even harder to confirm the effect of TNF-α on lipid metabolism in human beings since the conflicting clinical results make it more elusive rather than explicit. However, it is reasonable to think that infliximab therapy exerts potent effects on lipid metabolism.

CONCLUSION

In summary, TNF-α plays an important role in energy metabolism and is an effective lipid homeostasis regulator. Recent advances have unveiled many new aspects of TNF-α action on lipid metabolism though the exact components and molecular mechanisms of these effects remain to be elucidated. However, our present view of TNF-α in lipid metabolism might be superficial since there are inconsistent and even controversial results in nearly every aspect of its action. These conflict observations might be due to the different cells/cell lines used such as the adipocytes and hepatocytes, the mature adipocytes, and pre-adipocytes, different species such as human, rodent, non-human primates, and different experimental conditions. Furthermore, the potency, the dosages, and the sources of TNF-α might be account for such inconsistence. As far as the clinical observations are concerned, large-scale, hospital-based studies in RA patients and in normal healthy subjects need to evaluate the exact effects of infliximab on lipid profile. In addition, application of proper randomized placebo and standardization of inclusion and exclusion criteria might also be considered. The molecular dissection of TNF-α signaling pathways in lipid metabolism might offer novel targets for the treatment of dyslipidemia.

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