



## Mini Review

# IL-6 and lipid metabolism

Misato Hashizume and Masahiko Mihara\*

Product Research Department, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan.

Interleukin-6 (IL-6) plays essential roles not only in the immune response, but also in hematopoiesis, and in the central nervous system. Dysregulated production of IL-6 has been found in chronic inflammatory autoimmune diseases such as rheumatoid arthritis (RA). Many reports have indicated that lipid levels, such as total cholesterol and triglyceride levels, are changed under inflammatory conditions; this is also observed in RA patients. It is well-established that IL-6 affects lipid metabolism in animals and humans, and it has been reported that blockade of IL-6 decreases lipid levels in RA patients. Based on the above findings, we investigated how IL-6 may change lipid metabolism. We conclude that it is likely that these IL-6-mediated changes in lipid metabolism are at least partly responsible for the lipid profile changes following IL-6 blockade in RA patients.

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\*Correspondence should be addressed to:

Masahiko Mihara, PhD. Product Research Department, Chugai Pharmaceutical Co. Ltd., 1-135, Komakado, Gotemba, Shizuoka, 412-8513, Japan. Tel: +81-550-87-6379, Fax: +81-550-87-6782, E-mail: miharamsh@chugai-pharm.co.jp

**Key words:**

lipid metabolism, interleukin-6, total cholesterol, triglyceride



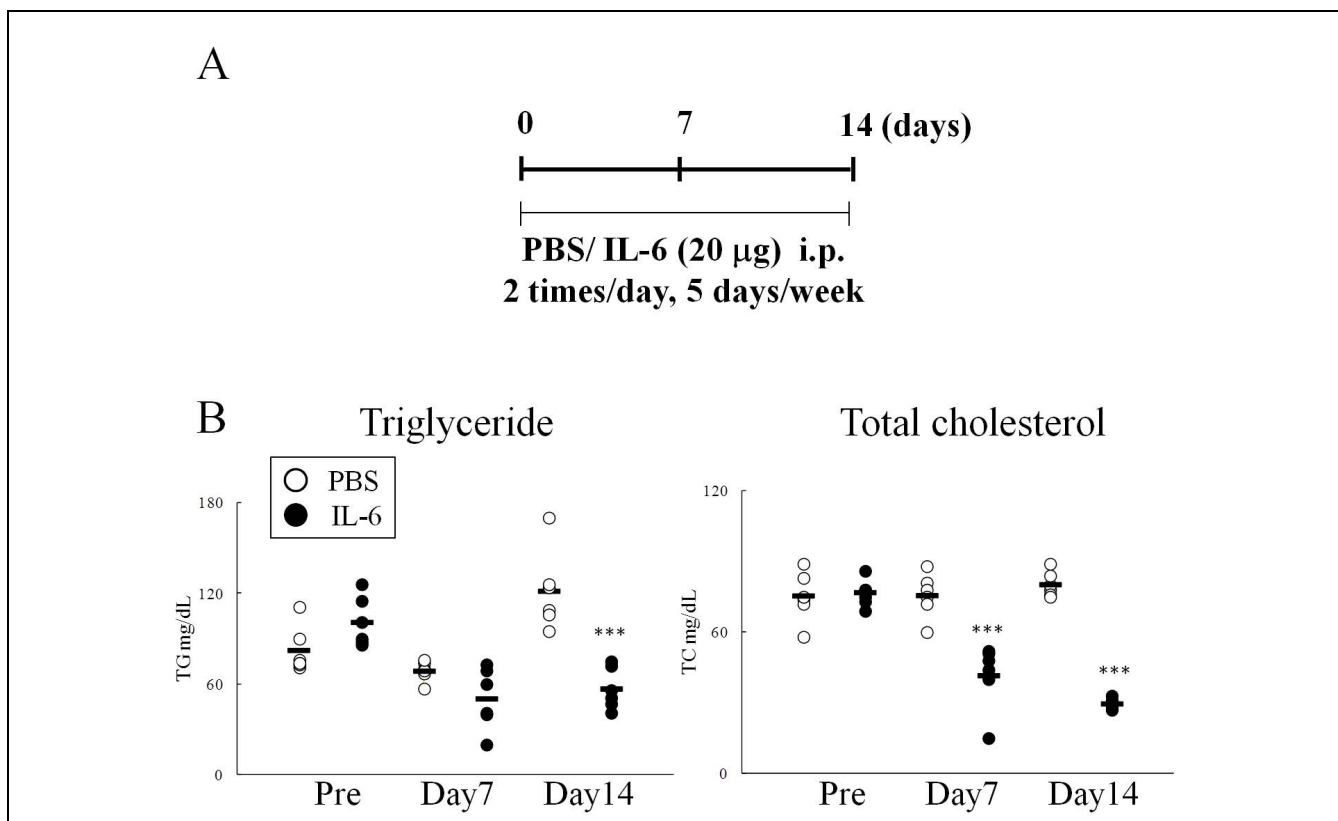
## Introduction

Interleukin-6 (IL-6) exerts many different effects on a broad range of cells and is a central player in the regulation of inflammation, hematopoiesis, the central nervous system and host defense<sup>1</sup>. IL-6 also acts on the adipose tissue and skeletal muscle as an adipokine which modulates lipid metabolism, hemostasis, blood pressure and glucose metabolism, and influences atherosclerosis<sup>2</sup>. Moreover, 10–35% of circulating IL-6 is derived from adipose tissue<sup>3</sup>. These lines of evidence arouse interest in IL-6 as a possible mediator of metabolic processes. In this review, we summarize the effects of IL-6 on lipid metabolism.

## The effect of IL-6 on serum lipid levels

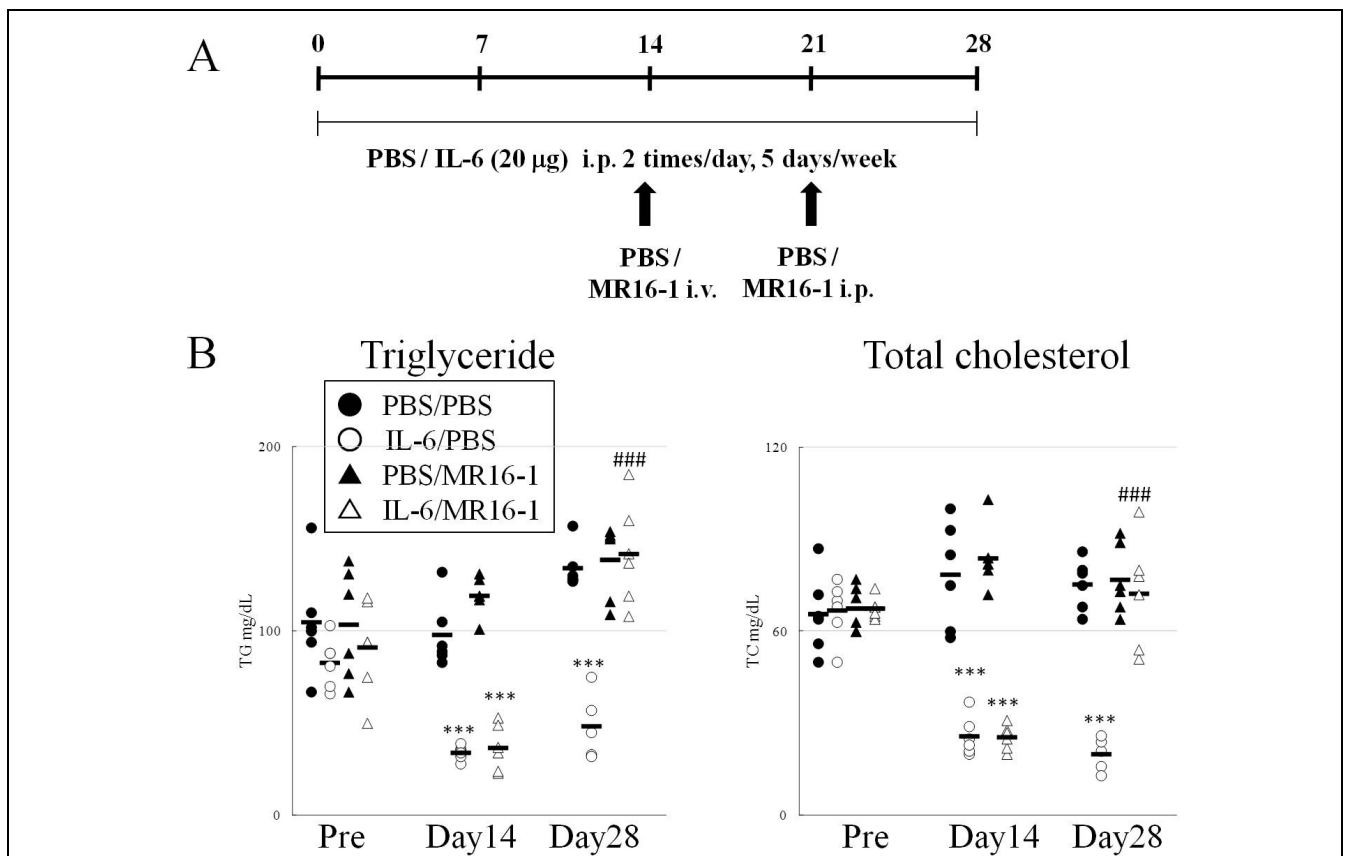
We previously reported that IL-6 transgenic mice have low total cholesterol (TC) and triglyceride (TG)

levels compared with their littermates<sup>4</sup>), suggesting that IL-6 influences lipid levels in the circulation. To confirm this, we investigated female C57BL/6 mice receiving 20  $\mu\text{g}$  of human IL-6 intraperitoneally twice a day for 14 days, after which we measured TC and TG in the blood. As shown in Figure 1, IL-6 significantly reduced the levels of TC and TG in the blood, whereas PBS treatment (control) had no effect. Furthermore, we tested whether anti-IL-6R antibody (MR16-1) treatment could reverse this IL-6-induced decrease in lipid levels (Figure 2). Again, we treated mice for two weeks by injecting IL-6 which decreased serum TC and TG. The animals were then treated with antibody MR16-1 weekly for 2 weeks. This MR16-1 treatment resulted in restoration of the TC and TG levels to those seen in control mice. Interestingly, however, administration of MR16-1 to normal mice did not result in any changes in TC and TG levels.



**Figure 1. Serum lipid levels in IL-6-treated mice**

- A) Experimental protocol. Mice ( $n=6$ ) were given i.p. IL-6 (20  $\mu\text{g}$ ) or PBS twice a day 5 times per week for 2 weeks.
- B) Serum total cholesterol and triglyceride were measured using an automatic analyzer. Closed and open circles indicate control and IL-6-treated mice, respectively. Statistical significance of differences between the PBS group and the IL-6 groups on days 0, 7 and 14 was analyzed by the unpaired t-test (\*\*\*,  $p<0.005$ ).



**Figure 2. Anti-IL-6 receptor antibody reverses the lipid level changes in IL-6-treated mice**

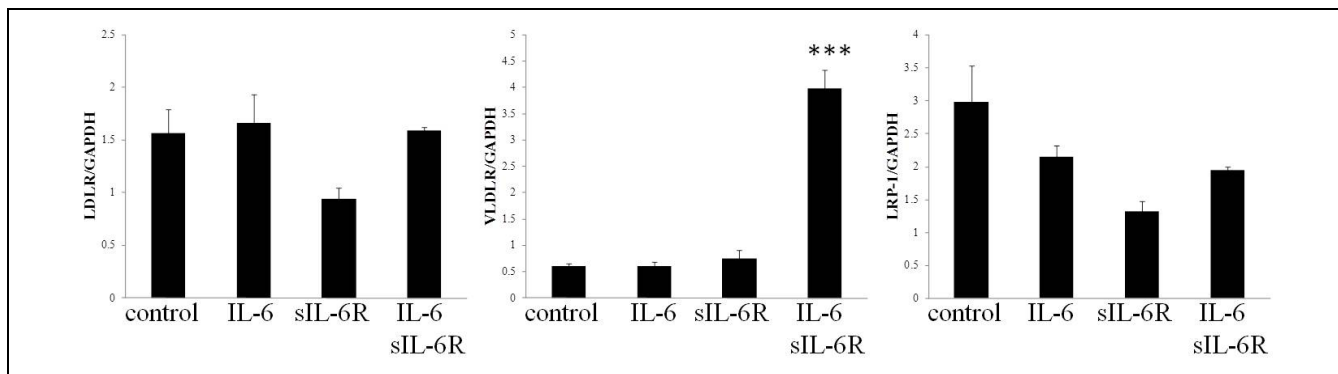
- A) Mice (n=6) received i.p. IL-6 (20 µg) or vehicle twice a day 5 times per week for 4 weeks. Anti-IL-6 receptor antibody (4 mg) or vehicle was injected intravenously once at day 14, and then anti-IL-6 receptor antibody (1 mg) or vehicle was injected intraperitoneally at day 21.
- B) Closed and open circles indicate PBS/PBS and IL-6/PBS-treated mice, respectively. Closed and open triangles indicate PBS/anti-IL-6 receptor antibody and IL-6/anti-IL-6 receptor antibody-treated mice, respectively. Statistical significance of differences between groups on days 0, 14 and 28 was analyzed by the unpaired t-test (\*\*\*,  $p < 0.005$  vs PBS/PBS, ###,  $p < 0.005$  vs PBS/IL-6).

Similar phenomena have been reported in humans. In phase I-II clinical trials of recombinant human IL-6 as a thrombopoietic drug in patients pre-chemotherapy, a single injection resulted in a rapid decrease of the cholesterol level<sup>5</sup>. Furthermore, Castleman's disease patients have abnormal production of IL-6 from germinal center B cells<sup>6</sup>. It is also reported that patients with Castleman's disease have hypolipidemia<sup>7</sup>. These lines of evidence strongly support the idea that IL-6 influences lipid levels in blood.

### Influence of IL-6 on expression of low density lipoprotein receptors

The low-density lipoprotein receptor (LDLR) family includes the LDLR, the LDL receptor-related protein (LRP) and the very low-density lipoprotein

receptor (VLDLR). The latter is most abundantly expressed in heart, skeletal muscle and adipose tissue, but only to a slight extent in the liver, whereas LDLR is abundantly expressed there. Because heart and skeletal muscle use fatty acids (FAs) as an energy source and adipose tissue uses FAs for energy storage, the VLDLR was hypothesized to play a role in the delivery of FAs derived from VLDL-triglyceride to peripheral tissues from blood. It has been reported that VLDLR-knockout mice fed a normal chow diet had 2.2-fold greater levels of TC and TG in plasma than wild-type mice<sup>8</sup>. Another group reported that VLDLR-transgenic mice under conditions of LDLR deficiency had decreased TG levels, whereas VLDLR and LDLR double-knockout mice showed an increase<sup>9</sup>. These findings imply that the VLDLR plays a crucial role in lipid metabolism.



**Figure 3. VLDLR, LDLR and LRP-1 mRNA expression in vascular smooth muscle cells induced by IL-6**  
Vascular smooth muscle cells were cultured with IL-6 (100 ng/mL), sIL-6R (100 ng/mL) or IL-6 (100 ng/mL) + sIL-6R (100 ng/mL) for 24 h. After culture, relative expression levels of VLDLR, LDLR and LRP-1 mRNA were measured by real-time PCR. Each column and vertical line indicates mean and SD of triplicate cultures. Statistical significance was analyzed by unpaired t-test (\*\*\*,  $p < 0.005$ ).

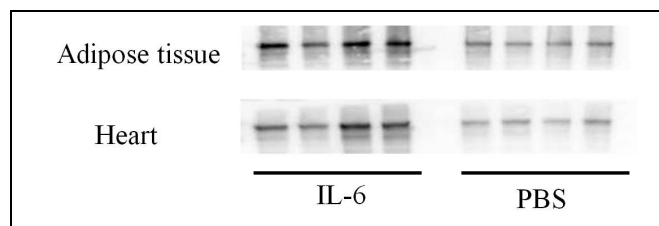
To analyze the mechanism of IL-6-induced reduction of blood lipid levels, we firstly examined the effects of IL-6 on the induction of lipoprotein receptors such as VLDLR, LDLR and LRP-1 in human vascular smooth muscle cells. Co-addition of IL-6 + soluble IL-6R (sIL-6R) strongly induced expression of VLDLR mRNA, but IL-6 or sIL-6R alone did not do so (Figure 3). In contrast, neither LDLR nor LRP-1 mRNA were induced by IL-6 + sIL-6R.

IL-6 exerts its biological activities through two membrane molecules, a ligand-binding 80 kD chain (IL-6R) and a non-ligand-binding signal transducer gp130. After binding of IL-6 to membrane-bound IL-6R, the IL-6/IL-6R complex associates with gp130, resulting in signal transduction. In addition, sIL-6R, which lacks trans-membrane and cytoplasmic domains, can associate with gp130 in the presence of IL-6 and transduce the signal through gp130. Thus, both membrane bound IL-6R and sIL-6R play essential roles in IL-6 signaling<sup>10</sup>.

IL-6 + sIL-6R, but not IL-6 alone, induces VLDLR in vascular smooth muscle cells, suggesting that these cells express gp130, but not membrane IL-6R. Levels of sIL-6R in the blood are sufficient for the phenomenon seen in this study to be likely to occur in vivo.

Next, using Western blotting, we determined the expression of VLDLR in several tissues such as heart and adipose tissue from mice treated with 20  $\mu$ g/day of IL-6 (Figure 4). PBS group showed that VLDLR expression levels were in the same range in heart and adipose tissue, whereas IL-6 treatment augmented VLDLR expression in both tissues. Reg-

ulation of VLDLR gene expression has been investigated, revealing that CCAAT/enhancer-binding protein- $\beta$  (C/EBP- $\beta$ ) and nuclear factor-Y bind to regulatory elements in the VLDLR promoter region<sup>11</sup>. C/EBP- $\beta$  is down-stream of IL-6 signaling and plays a role in the regulation of energy homeostasis and in adipocyte differentiation<sup>12,13</sup>. These findings raise the possibility that C/EBP- $\beta$  induced by IL-6 plays an important role in the regulation of VLDLR expression. These lines of evidence clearly document that decrease of blood lipid levels was brought about by VLDLR induced by IL-6.



**Figure 4. VLDLR expression in heart and adipose tissue of IL-6-treated mice**

The mice were sacrificed and heart and adipose tissues were collected on day 14 after injection with PBS or IL-6 (20  $\mu$ g). Total protein was extracted from the tissue, and Western blotting performed.

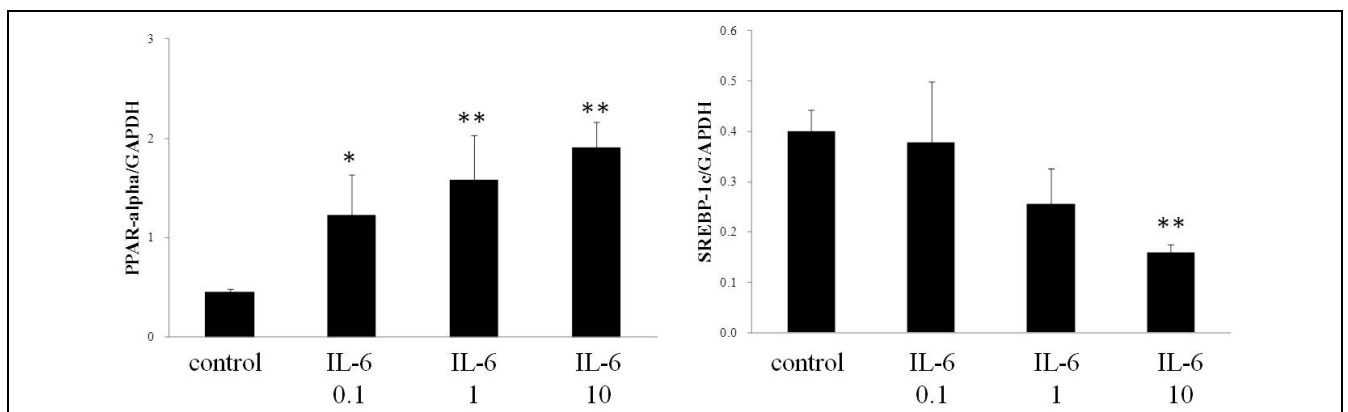
### Effect of IL-6 on transcription factors related to lipid metabolism

PPAR $\alpha$  (peroxisome-proliferator-activated receptor  $\alpha$ ) is a member of the nuclear hormone receptor family of transcription factors. It is activated by un-



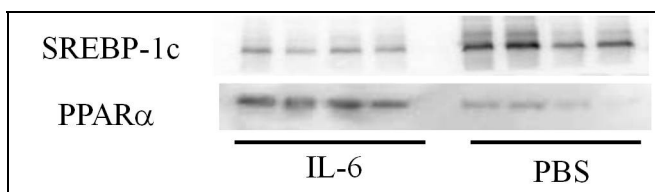
saturated fatty acids and their derivatives, and by pharmacological ligands that include the fibrate group of drugs. PPAR $\alpha$  is expressed in the liver, heart, skeletal muscle and brown adipose tissue, where it regulates genes that control mitochondrial and peroxisomal fatty acid oxidation<sup>14</sup>). It has been shown previously that PPAR $\alpha$  deficiency abolishes the normal diurnal variations in the expression of lipogenic genes, such as those encoding fatty acid synthase, acetyl-CoA carboxylase and 3-hydroxy-3-methylglutaryl-CoA reductase, in the liver<sup>15</sup>).

SREBP-1c is particularly abundant in the liver where its expression is regulated by insulin and glucagon, and where it plays a major role in controlling hepatic lipogenesis and glucose use<sup>16,17</sup>). The absence of SREBP-1c was shown to ameliorate fatty liver development in ob/ob mice<sup>18</sup>). The SREBP family is a group of transcription factors that activate genes encoding enzymes regulating cholesterol and fatty acid biosynthesis. In particular, SREBP-1c preferentially enhances transcription of genes associated with fatty acid synthesis, including fatty acid synthase<sup>19,20</sup>).



**Figure 5. PPAR $\alpha$  and SREBP-1c mRNA expression in Hep3B induced by IL-6**

Hep3B cells were cultured with IL-6 (0.1, 1, 10 ng/mL) for 24 h. After culture, relative expression levels of PPAR $\alpha$  and SREBP-1c mRNA were measured by real-time PCR. Each column and vertical line indicates mean and SD of triplicate cultures. Statistical significance was analyzed by Dunnett test (\*;  $p < 0.05$ , \*\*;  $p < 0.01$ ).



**Figure 6. PPAR $\alpha$  and SREBP-1c expression in livers of IL-6-treated mice**

The mice were sacrificed and livers were collected on day 14 after injection with PBS or IL-6 (20  $\mu$ g). Total protein was extracted from the tissue, and Western blotting performed.

We therefore investigated whether IL-6 affects the induction of PPAR $\alpha$  and SREBP-1c in a human liver cell line, Hep3B, in vitro by real-time PCR. When Hep3B cells were cultured with IL-6 for 24 hours, significant induction of PPAR $\alpha$  but reduction of SREBP-1c, mRNA was observed (Figure 5). Next, we asked whether these phenomena were also ob-

served in mice treated with 20  $\mu$ g/day of IL-6. In liver from such mice, PPAR $\alpha$  expression was indeed increased and SREBP-1c was decreased (Figure 6).

Recently, Yamaguchi et al. reported that anti-IL-6 receptor antibody treatment increased SREBP-1 in the livers of mice fed a methionine choline-deficient diet<sup>21</sup>). This diet also decreased the levels of PPAR $\alpha$  protein, and anti-IL-6 receptor antibody treatment further accelerated this. This report reinforces our conclusion that IL-6 plays an important role in the regulation of PPAR $\alpha$  and SREBP-1 expression in both normal and pathological conditions.

### Other effects of IL-6 on lipid metabolism

Adipose tissue and skeletal muscle are the major organs of lipid metabolism regulated by adipokines. Several reports have described the function of IL-6 in lipid metabolism in adipose tissue, skeletal muscle and liver. Interstitial IL-6 concentrations in adipose tissue are ~100-fold higher than in plasma, implying an important auto- and paracrine regulatory function



in this tissue<sup>22</sup>). IL-6 has lipolytic properties and increases lypolysis of adipose tissue and adipocytes *in vitro*<sup>23,24</sup>. Consistent with these *in vitro* studies, IL-6 infusion in humans increased free fatty acid and whole body fat oxidation<sup>25</sup>. In the skeletal-muscle, physical exercise is accompanied by an increase of plasma and muscular IL-6 concentrations up to 100-fold<sup>26</sup>. The main contributor to IL-6 elevation is skeletal muscle. It has been reported that IL-6 directly promotes skeletal-muscle differentiation of primary human skeletal-muscle cells and promotes lipid degradation<sup>27</sup>. Additionally, IL-6 treatment increased fatty acid oxidation in both isolated rat muscle and cultured myotubes<sup>28,29</sup>. In the liver, IL-6 acts directly on hepatocytes, inducing apolipoproteins which bind to lipids (oil-soluble substances such as fat and cholesterol) to form lipoproteins, which transport the lipids through the lymphatic and circulatory systems and regulate lipid concentrations in the blood<sup>30</sup>. It has also been reported that IL-6 stimulates the catabolism of TG and changes liver phospholipid metabolism<sup>31</sup>.

### Lipid changes in rheumatoid arthritis

Cholesterol and TG levels appear normal or even low in patients with early active rheumatoid arthritis (RA) and high-grade inflammation<sup>32</sup>. Myasoedova et al reported that patients with RA had shown a significant decrease in TC and LDL levels during the 5 years before RA manifestation, as compared with

non-RA subjects<sup>33</sup>. Inflammatory cytokines such as IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) play crucial roles in the pathogenesis of RA. The blockade of IL-6 and TNF- $\alpha$  in RA patients increased blood levels of TC, TG and HDL-cholesterol, which were inversely related to RA disease activity<sup>34,35</sup>. As we showed here, IL-6 reduced blood TC and TG levels. On the other hand, many reports have described that TNF- $\alpha$  increased TC and TG, followed by increase of cholesterol synthesis and reduction of the expression of lipid metabolism-related enzymes<sup>36,37</sup>. It is also reported that the persistent inflammatory condition reflected by elevated serum TNF- $\alpha$  levels results in low levels of TC and TG in RA<sup>38,39</sup>. Therefore, it remains to clarify why TC and TG level are reduced in RA. Further studies are necessary to explain the responsible mechanisms for the lipid changes in RA patients.

### Conclusions

IL-6 reduced TC and TG in animals and humans. Hence, inflammation reduces circulating lipid levels via the induction of IL-6. The exact mechanism by which IL-6 induces these changes still remains unknown. However, we showed that IL-6 affects lipid metabolism by stimulating lipid uptake via VLDLR induction, increasing hepatic and adipose tissue lipolysis and decreasing hepatic lipid synthesis. Further work is necessary to reveal the mechanisms responsible for the lipid changes induced by IL-6.

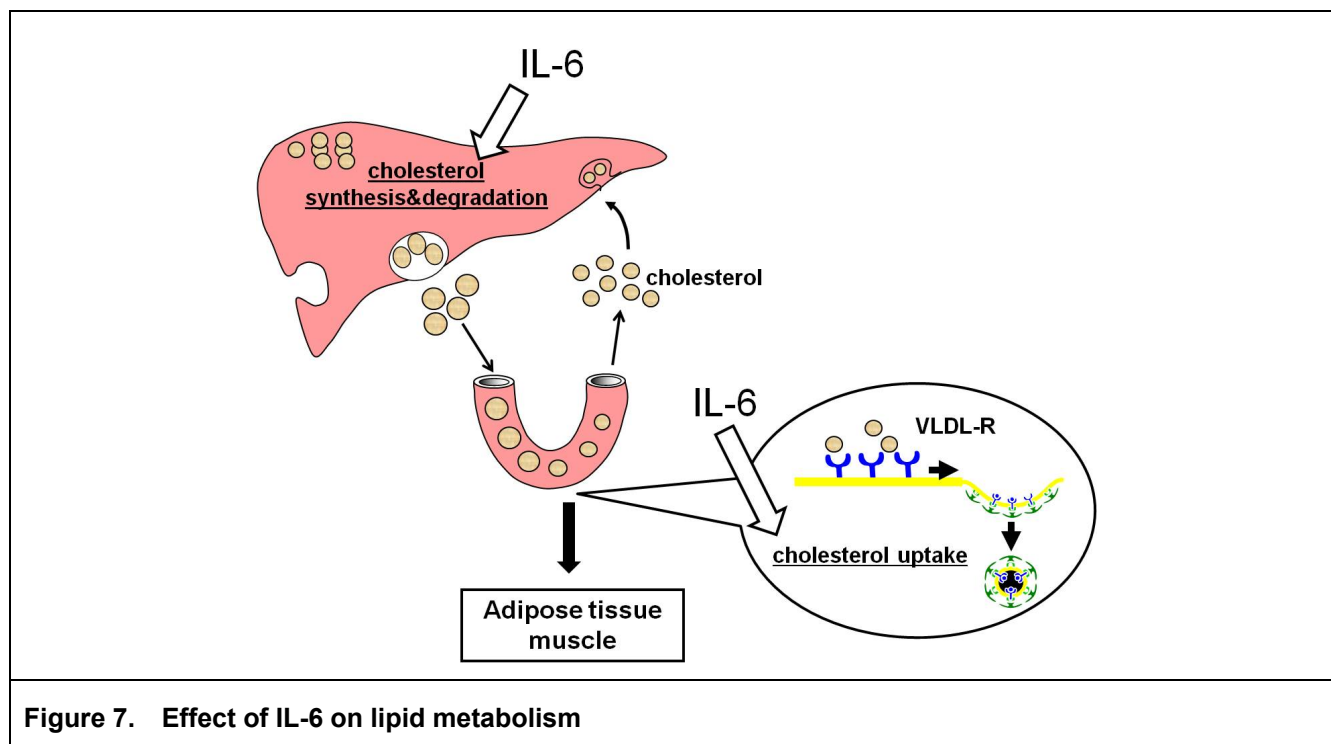


Figure 7. Effect of IL-6 on lipid metabolism



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