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Review Article

Interleukin-6 signal transduction and its role in hepatic lipid metabolic disorders

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ABSTRACT

Hepatic lipid dysregulation can lead to spectrum of metabolic disease conditions including metabolic syndrome (MS), fatty liver and diabetes. Liver lipids are regulated by a complex set of extra-hepatic and intra-hepatic factors including cellular cross-talk with variety of cells, inducing various cytokines. Interleukin 6 (IL-6) is a pleiotropic cytokine that exerts both pro-inflammatory and anti-inflammatory effects on hepatic system through either JNK/STAT or ERK/MAPK signaling. Although, IL-6 has shown to protect the liver from fat storage in both rodent and human models and various IL-6$^{-/-}$ studies have supported this notion yet a question remains over its deleterious pro-inflammatory effects on hepatocytes. IL-6 ability to produce reactive oxygen species (ROS) and subsequently disturb the hepatic lipid balance has created a conundrum. Furthermore, IL-6 has shown to behave differently under different disease states within hepatocytes and hence, modulating the hepatic lipids accordingly. This review deals with the role of IL-6 on hepatic lipid metabolism and analyzes various data presented on this topic.

1. Introduction

Interleukin 6 (IL-6) is a potent multifunctional cytokine that is encoded by the IL6 gene in humans [1]. It is pleiotropic and exerts diversified actions on different body organs while serving both as a pro-inflammatory and anti inflammatory cytokine.

IL-6 was initially distinguished as a B-cell differentiation factor on its discovery in 1986 by Hirano and his colleagues. It was put forward as a factor that can differentiates activated B-cells into immunoglobulin-producing cells [2]; it was, thereupon, termed as BSF (B-cell stimulatory factor)-2. In the same year Haegeman et al. noticed it as an identical factor with 26KD protein [3]. One year latter two other research teams found BSF-2 to be identical with other factors described as IFN (interferon)-β2 [4] and hybridoma/plasmacytoma growth factor (HPGF) [5] and hepatocyte-stimulating factor (HSF) [5].

IL-6 has been reported to produce by wide spectrum of cell types which includes T-cells, B-cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells, adipocytes and some tumor cells. Other cell types known to produce IL-6 are chondrocytes, osteoblasts, skeletal and smooth muscle cells, islet cells, thyroid cells, mesangial cells, certain tumor cells, microglial cells and astrocytes [6,7]. Recently, mast cells have also been included in the wide range of IL-6 producing cells [8].

IL-6 has shown to play a pivotal role in wide range of diseases like Anaemia of chronic diseases, Angiogenesis, Acute-phase response, Bone metabolism, Cartilage metabolism, Neutrophil trafficking, Immune responses, Lipid metabolism, Systemic juvenile and idiopathic arthritis [9]. Among metabolic disorders, IL-6 has been linked with amelioration of hepatic steatosis [10], hyperinsulinaemia and insulin resistance (IR) [11]. IL-6 has been also suspected in the disease pathology of multiple myeloma [12,13], rheumatoid arthritis [14], Castleman disease [15], AIDS [16], mesangial proliferative glomerulonephritis [17], psoriasis [18], Kaposi's sarcoma [19], sepsis [20] and osteoporosis [21]. IL-6 blockade by TCZ (tocilizumab), a humanized anti-human IL-6R monoclonal antibody, has been validated to recover the symptoms of rheumatoid arthritis (RA), Castleman's disease and sJIA (systemic JIA juvenile idiopathic arthritis) [22]. IL-6 is a growth factor for certain

Abbreviations: IL-6, interleukin-6; MS, metabolic syndrome; ROS, reactive oxygen species; IFN, interferon; hIL-6, human interleukin-6; SHP-2, Src homology domain-containing protein tyrosine phosphatase-2; IR, insulin resistance; JAK, Janus kinase; TCZ, tocilizumab; RA, rheumatoid arthritis; NK, natural killer; ERK, extracellular-signal regulated kinase; MAPK, mitogen-activated protein kinase; BMI, body mass index; CRP, C-reactive protein; VAT, visceral adipose tissue; SOCS, suppressor of cytokine signaling; NAFLD, non-alcoholic fatty liver disease; HFD, high fat diet; mgp130, membrane-bound gp130; sIL-6R, soluble IL-6R; sgp130, soluble gp 130; MCP-1, monocyte chemoattractant protein-1; HFHC, high fat high cholesterol diet; CMKLR1, chemokine-like receptor 1; SREBP, sterol-regulatory-element binding protein.

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tumors e.g. multiple myeloma and renal carcinoma cells. Further, IL-6 is indicated to be engaged in cancer cachexia. Cancer cachexia is a metabolic condition that is observed in several malignant disorders and it is generally recognized as progressive weight loss with depletion of host reservoirs of skeletal muscle and adipose tissue. Among other vital functions of IL-6 is the ability to stimulate B-cell differentiation [23], activate thymocytes and T-cells differentiation [24]. Further it can also activate macrophages [25], stimulate hepatocytes to produce acute-phase proteins, and activate natural killer (NK) cells [6]. It also possesses anti-inflammatory properties [26].

The IL-6 gene is cloned and sequenced for human, rat and mouse and they all have shown to possess four introns and five exons [27]. The gene for IL-6 has been positioned at 7p21 [28] and 5 [29] in the human and mouse genomes, correspondingly. Human IL-6 (hIL-6) sequence arrangement contains 212 amino acids with 27 of them as a signal peptide, and two sites of potential N glycosylation. Its isoelectric point is 5.4 while molecular weight varies from 21 KD to 30 KD) [30]. The 3D structure of mice and hIL-6 gene differ at certain points. hIL-6 consists of four-helix bundle: two pairs of antiparallel-helices with up–up, down–down orientation [31] while mouse IL-6 protein is refolded 185 amino acid polypeptide. Although hIL-6 and mouse IL-6 are almost 42% homologous but mouse IL-6 protein differs in probable number of O-glycosylation sections rather than N-glycosylation site [32].

IL-6 has been recognized by its own specialized receptor IL-6R, which is expressed in many organs of body like liver, muscles, adipocytes, heart and brain. IL-6R subunit is also overlapped by many other cytokines (Figs. 1 and 2).

1.1. IL-6 receptor (IL-6R) functional organization

IL-6 yields its biological actions via two receptor sections: IL-6R (IL-6Rα, gp80 or CD126) and gp130 (IL-6Rβ or CD130) [33]. Due to short cytoplasmic domain (82 amino acids) IL-6R can only play a limited role in signal transduction. Although this cytoplasmic tail performs a pivotal role in basolateral sorting; this is an important function in polarized epithelial cells [34]. Conversely, the cytoplasmic domain of gp130 possesses many potential motifs for signal transduction, for example, the YSTV sequence for SHP-2 (Src homology domain-containing protein tyrosine phosphatase-2) recruitment and YXXQ motifs (where X is any amino acid) for STAT

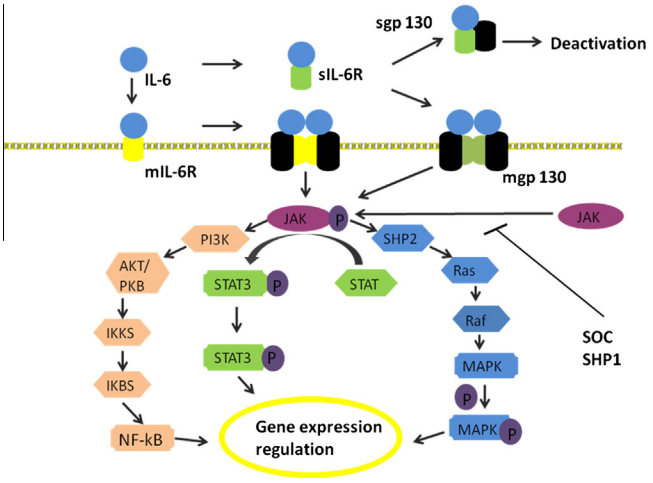

Fig. 1. Illustrating the functional organization of IL-6 receptor (IL-6R) and its downstream signal transduction. sgp130 and mgp130 serves as pivotal centers for IL-6 signaling; former serving as a feedback-sort of check on latter. Downstream, JAK presents itself as a signaling junction, regulating the various IL-6 induced protein expressions *via* ERK/MAPK, JAK-STAT3 and NF-κβ pathways.

(signal transducer and activator of transcription) activation. Unlike other cytokine receptor gp130 lacks the intrinsic kinase domain which is required for downstream signaling. Instead gp130 incorporates the location that allows the non-receptor tyrosine kinase called JAK (Janus kinase) binding and initiates the signal transduction. IL-6 attachment to mIL-6R (membrane-bound IL-6R), initiate the homodimerization of gp130, and a high affinity functional receptor complex of IL-6, IL-6R and gp130 is established. sIL-6R (soluble IL-6R), which lacks the intra-cytoplasmic portion of mIL-6R and is produced either by the enzymatic cleavage of mIL-6R by ADAM (a disintegrin and metalloproteinase)-17 or by alternative splicing, can also bind with IL-6, and then the complex of IL-6 and sIL-6R can form a complex with gp130. This unique receptor signaling system is termed IL-6 trans-signaling [35]. mgp130 (membrane-bound gp130) is expressed throughout the body. Hence, the IL-6–sIL-6R complex can, hypothetically, induce most cells in the body. However, this trans-signaling is thought to be regulated by sgp130 (soluble gp130), which exists widely in circulating blood. sgp130 binds to the IL-6–sIL-6R complex and suppresses the binding of the IL-6–sIL-6R complex to mgp130 [36,37]. Hence, sgp130 is a natural blocker of IL-6 signaling. IL-6 binds to IL-6R with an affinity of 10–9 to 10–10 mol/l and gp130 binds to IL-6–sIL-6R complex with an affinity of 10–11 mol/l [38–40]. As a matter of fact, TCZ, IL-6 signal transduction blocker, can dissociate the IL-6–sIL-6R complex, but not the IL-6–sIL-6R–sgp130 complex, indicating that the IL-6–sIL-6R complex is more vulnerable to TCZ than the IL-6–sIL-6R–sgp130 complex [41]. Gp130 is used in the signaling of many other members of the IL-6 family of cytokines, such as, CLC (cardiotrophin-like related cytokine), CNTF (ciliary neurotrophic factor), OSM (oncostatin M), CT-1 (cardiotrophin-1), leukaemia inhibitory factor (LIF), NPN (neuropoietin), IL-27 and IL-11 [42–44]. The structure of the gp130–IL-6R-IL-6 complex has been solved by X-ray crystallography. It is a hexamer comprising of two IL-6, IL-6R and gp130 proteins sections each [45]. It has been disputed, however, that the signaling mosaic is assembled by one IL-6–IL-6R complex bound to two gp130 proteins [46]. The sharing of the gp130 molecule by other IL-6 superfamily cytokines may explain their functional redundancy. A comparable system can also be observed within the other cytokine families; such as, the group of cytokines consisting of IL-3, IL-5 and GM-CSF (granulocyte/macrophage colony-stimulating factor) uses a common β receptor, and the group of ILs including IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 uses a common γ receptor component [47].

Increased levels of sIL-6R are also present in several inflammatory diseases, where pro-inflammatory IL-6 trans-signaling is particularly relevant in stromal tissue cells [48–52]. The role of sgp130 in inflammatory conditions is less clear. As an antagonist to IL-6 activity, rational would dictate that sgp130 levels would be reduced in inflammation; however, several studies documented an increase in sgp130 levels in inflammatory diseases, possibly a mechanism to attempt to counteract chronic inflammation [53,54]. The potent role of sgp130 in reducing inflammation *in vivo* is demonstrated by the ability of a synthetic version of sgp130 (sgp130Fc) to treat various inflammatory diseases [55,56]. Thus, all components of the IL-6 system i.e. IL-6, sIL-6R and sgp130 are elevated in patients with chronic inflammatory conditions.

1.2. IL-6-IL6R-GP130 signal transduction

The IL-6 receptor belongs to the cytokine class I receptor family involving JAK/STATs signal transduction pathway [57]. Janus kinase activation induces STAT phosphorylation, dimerisation and translocation to the nucleus to regulate target gene transcription [57].