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Association of retinol binding protein 4 and insulin resistance: A review on molecular mechanisms

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Retinol (ROH) and its derivatives including vitamin A are substantial for several cells' functions. Retinol Binding Protein 4 (RBP4) is known as the career of vitamin A in blood. The main receptor for RBP4 is stimulated by retinoid acid gene 6 (STRA6). RBP4 circulates in bound with Transports Thyroxine and Retinol (TTR) to form ternary ROH-RBP-TTR complex. Recently, RBP4 implicated in insulin resistance which may exerts its functions through inflammatory pathways. Although studies indicated that RBP4 may have role in inflammation as an adipocytokine, the cellular and molecular mechanisms including the interaction between Holo- or Apo-RBP4 and their receptor to induce inflammation is controversial. In this review, we focus on molecular structure of RBP4, STRA6, and their interaction to induce inflammation and insulin resistance to illustrate the potential conflicts in this area.

Introduction

Vitamin A plays important physiological roles in body including differentiation, cell growth, embryonic development, and vision [1, 2]. After vitamin A absorbs by enterocytes it is delivered to the liver ride on chylomicrons through the lymphatic system As the major storage site for vitamin A, liver synthesizes and secretes vitamin A accompanied by RBP4 [3].

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RBP4 presents in circulation in two forms: separated from vitamin A termed Apo-RBP, and the other in bound with retinol named Holo-RBP [4]. Because RBP4 is a tiny protein, it is presented in circulation in bound of TTR to form a bigger complex. This ternary complex named ROH-RBP-TTR prevents RBP4 from losing by kidney filtration [5].

Recently RBP4 have known as an adipokine which affects insulin resistance. It is reported that serum RBP4 levels are increased in patients with insulin-resistance, family history of diabetes, and obesity. RBP4 changes phosphorylation of insulin receptor substrate (IRS) to decrease glucose uptake. Moreover, RBP4 increases hepatic production of glucose

which leads to a reduction in insulin sensitivity[6].

STRA6 is known as a receptor for RBP4 in several tissues. It is not only a retinol transporter, but a surface signaling receptor. When STRA6 and RBP4 bound, a cascade of inflammatory response activates [7]. Presence of TTR in ROH-RBP-TTR complex reduces the induction of inflammatory cascade by STRA6. Hence, RBP4 with no bound to TTR is considered as a cytokine with short half-life [8]. In our knowledge there is no article which reviews the molecular aspect of structure and function of RBP4. In order to illustrate potential controversies, this article reviews recent studies cellular and molecular structure and function of RBP4 and its receptors in relation to inflammatory mechanisms.

Method

The literature search was based on PubMed listings for the term of "Retinol binding protein 4" up to September 2015. Around 350 articles were studied and 72 articles were selected for inclusion in this review.

Vitamin A

Vitamin A has been recognized as an essential factor exists in foods from many years ago. It is obtained from either animal sources in form of retinyl esters, or vegetables as carotenoids. The dietary retinol is absorbed by enterocytes and enzymatically esterified to long chain fatty acids and produced retinyl esters. In normal physiological intake, approximately 90% of retinol is esterified by Lecithin retinol acyltransferase (LRAT) but in supraphysiological or pharmacological doses diacylglycerol acyltransferase 1 (DGAT1) esterify retinol. Then retinyl esters are packaged in chylomicrons and secreted through the lymphatic system into blood[3, 9, 10]. It is estimated that liver accumulates approximately 66–75% of dietary retinol and removes 75% of chylomicron retinylesters. Chylomicron remnants are internalized and hydrolysis by hepatocytes. The majority of chylomicrons' retinol is transferred to the hepatic stellate cells for storage. The remnant chylomicrons are taken up by extra-hepatic tissues such as skeletal muscle, kidney, adipose tissue, heart, and spleen [11, 12].

As a fat soluble vitamin, retinol is an insoluble molecule in blood so it is mobilized from the liver to other tissues in the form of bounding to RBP4. Liver is the major site of synthesis and secreting of RBP4. Adipose tissue is considered as second organ, which mainly participated in RBP4 secretion. There are other tissues having a role in RBP4 production including kidney, skeletal muscle, lung, heart, eye, spleen, and testis[4].The mechanism by which liver regulates vitamin A concentrations is unknown. In normal circumstances about 75% of all RBP4 circulate. Studies on transgenic mice indicated that only liver-synthesized RBP4 can mobilize hepatic retinol stores and extrahepatic RBP4 have not been able to mobilized liver-storedretinol[12].

Tracer kinetic studies introduced retinol turnover as a process in which circulating Holo-RBP enters and exits to the liver several times before its clearance by kidney. In humans, about 50 μmol/day(14.3 mg/ day) of retinol are transmitted through plasma compared to its disposal rate which is almost 4 μmol/ day (1.14 mg/day)[13].

Retinol nutritional status is considered as a crucial factor for regulating RBP4 levels. In the state of retinol deficiency, RBP4 secretion from the liver is blocked; retinol accumulates in hepatocytes, consequently, a reduction induced in serum RBP4 levels[14]. In state of lacking RBP4 in rodents, the hepatic retinol cannot mobilize. Subsequently, mice are more potentiate to become vitamin deficient. Even in the state of sufficient dietary retinol intake, serum retinol concentrations are dramatically lower in RBP4 knockout mice compared to normal ones[15]. When dietary intake of vitamin A is not ample, the majority of the recently absorbed retinol will be secreted into the circulation in the form of Holo-RBP4 and fewer amount of them would be stored[16].

Structure of RBP4

RBP4 is a member of the lipocalin family proteins possessed a specific conformational structure to bind with its ligand- Retinol. It is the first lipocalin structure described by X-rayand regarded as reference for determination of other members of lipocalin superfamily[17, 18]. Tertiary structure of RBP4 provides a β-barrel structure composed of an eight-stranded antiparallel β-sheet folded over itself, which constitutes the ligand binding pocket. These β-barrel proteins exert essential functions in transportation and signaling pathways.

The N-terminus region of RBP4 which includes highly conserved amino acids

sequences found in lipocalins, wrap around one side of barrel capping this end. However, other end of the barrel remains open and provides a platform flanked by a single loop scaffold in the entrance to bind with ligand. In the binding site, the hydrophobic interactions between retinol inner β-ionone ring and several amino acid residues of RBP4 that lined in the inner region of pocket completely cover retinol. The hydroxyl head-group of retinol placed on the protein surface, where it causes an interaction with a water molecule at the pocket entrance. The hydroxyl group of retinol is unlikely to be regarded as crucial bonding group in stabilizing of retinol-RBP4 complex. The complex of ligand and protein stabilized primarily by the hydrophobic interactions between retinol β-ionone ring and side chains of interior hydrophobic amino acids [19-21]. Retinal and retinoic acid have high affinity for binding sites in comparison with retinol due to their dissimilar structures. The aldehyde and carboxylate groups of retinal and retinoic acid facilitate the process of binding and stabilizing at the binding site [22, 23].

RBP4 as an adipokine

Prior to 2005 the only known function of RBP4 was assisting hydrophobic retinol to circulate in blood. This retinol in tissues is turned into retinoic acid which participates in insulin responsiveness and regulating energy homeostasis. Until Yang et al introduced RBP4 as a marker of insulin resistance [6,24]. Subsequently, many studies reported a positive correlation between serum RBP4 levels and insulin resistance in mice and human[25-28]. However, some clinical investigations found no association between them [29]. There were two justifications for elevated RBP4 levels in the state of insulin resistance: some studies considered this observation merged from impaired renal clearance of RBP4 in consequence of kidney failure in the insulin resistant circumstances[30, 31]. Many other studies proved that systemic insulin resistance is a result of over expression of serum RBP4 in adipose tissue which leads to inhibition of insulin signaling in muscle and adipose tissues [5,24].

In healthy subjects' insulin signaling pathway in muscles and adipose tissues initiates with binding of insulin to IRS which results in autophosphorylation of serine and accompanied by Phosphatidyl Inositide 3-Kinase (PI3K) activation. PI3K causes Protein Kinase B (PKB) activation by catalyzing Phosphatidyl Inositol 3-Phosphate (PI3P) - the second messenger. Eventually, PKB facilitates uptake of insulin by transferring Glucose Transporter Type 4 (GLUT4) through the cell membrane [32].

Yang et al observed that muscle and liver insulin sensitivity decrease and RBP4 gene expression increase in mice knockout for the gene encoding adipose GLUT4. On the other hand, injection of RBP4 to lean mice leads to insulin resistance. This result indicates that lacking RBP4 is a protective factor against insulin resistance induced by a high-fat diet in mice. It was observed that treatment of mice with RBP4 augments Phosphoenolpyruvate carboxykinase (PEPCK) expression in liver and elevated glucose production which induces reduction in insulin sensitivity [24].

Now the question is that how RBP4 exerts its effect to induce insulin resistance? It was found that RBP4 causes a reduction in insulin-stimulated PI3K activity in muscle by phosphorylation of IRS1 at tyrosine residue 612 .Tyrosine phosphorylation reduces sensitivity of insulin receptors to their ligands[33]. In the same study, RBP4 altered the phosphorylation status of PKB without affecting IRS1, cause insulin resistance by forming a protein complex with PKB[28]. In addition, RBP4 acts as an autocrine or paracrine in relation with adipose tissue. The treatment of isolated adipocytes from Type 2Diabetes Mellitus (T2DM) patients with RBP4 antibodies increased IRS1 phosphorylation at the serine 307 residue. Insulin sensitivity is carried out by serine phosphorylation [33].

It has been observed that RBP4 gene expression in adipose tissue is up-regulated in obesity, so that may prove the enhanced concentrations of serum RBP4 in obese patients [34]. The positive correlation between adiposity and RBP4 levels is indicated in visceral and subcutaneous adipose tissue [35]. Life style intervention including healthy dietary implementation, exercise, and bariatric surgery lead to lower serum levels of RBP4 and its adipose gene expression. These effects might be as a result of weight loss which may improve insulin sensitivity [36, 37].

Recently clinical studies showed a correlation between enhanced serum RBP4 levels and subclinical inflammation[38, 39]. Besides, other studies reported that RBP4 induces release of proinflammatory cytokines in macrophages co-cultured with adipose tissue during obesity,

which leads to chronic adipose tissue inflammation and insulin resistance. Both Apo-RBP and Holo-RBP can induce inflammation in endothelial cells [40, 41].

ROH-RBP4-TTR complex

RBP4 circulates in bound with TTR to form a bigger complex (an 80kDa protein) called ROH-RBP-TTR complex which prevents loss of RBP4 from circulation through renal glomerular filtration. TTR transfers thyroxine in the plasma while it is bound with RBP4. This binding has no interference with its action as thyroid hormones carrier[5]. TTR is a Tryptophan-rich protein which is utilized as a maker for nutritional assessment. It is among the acute phase proteins, which its plasma concentrations decrease during inflammation and bacterial infection[42]. In addition, TTR exerts a critical role in various CNS disorders according to its impact on protease activity in nervous system. TTR is among the 30 proteins that are associated with human amyloidosis disorders. The reasons behind these disorders are implicated as aggregation of mis-folded proteins which leads to impairment of organ function via inducing formation of extracellular sediment [43].

TTR is a homotetramer protein which is composed of two dimers. Each monomer consists of four L-strands which contribute to construct a dimer consist of an eight-stranded antiparallel L-sheet[44]. According to the 3-dimensional crystal structure of the human ROH-RBP-TTR complex, the β-barrel of the RBP4-open end is placed at the TTR 2-fold dimer axes and stabilization of this association be performed by the amino acid residues at the RBP4 C-terminal[5]. In human the complex formation of TTR: RBP results in a reduction of accessible surface area to 42 amino acids. Hence, each RBP4 or TTR shares 21 amino acids to the interface. Leucine and Isoleucine are the most amino acids in the interface .Due to hydrophobic nature of the interface, dissociation of the complex exclusively occur at low ionic strength[21, 45].

The liver and the choroid plexus in the brain are major sites of TTR synthesis and the former serving as the circulating main source. The detail of TTR and RBP4 binding including its place has not been fully understood yet. It has been suggested that the formation of ternary ROH-RBP-TTR complex is occurred in hepatocytes before their secretion into blood [46].

In vitro, two RBP4 molecules are bound to the TTR tetramer. Whereas under normal physiological conditions in human, the concentrations of RBP4 and TTR are about 2 µM and 4.5 µM. Thus, it could be concluded that ROH-RBP-TTR complex circulates at a 1:1:1 molar stoichiometryin vivo [47, 48]. Retinal or retinoic acid can bind to RBP4 with similar affinities as retinol. However, RBP4 is not be able to associate with TTR in the presence of retinoids except retinol. Both Apo and Holo-RBP are able to form the complex with TTR [45]. Meanwhile, regarding the former dissociation stability is dramatically higher. Notably serum TTR levels do not change in *RBP4*- overexpressing and *RBP4* -knockout mice as well as mouse models of insulin resistance and humans with type 2 diabetes [24].

According to TTR-deficient mice, concentrations of RBP4 protein in their livers were 60% higher than those of wild type mice. Hence, TTR not only exert a crucial function in hepatic uptake and storage of dietary retinol, but also may serves as a facilitator for secretion RBP4 by hepatocytes [12, 49].

When RBP4 and/or TTR are not available retinyl ester transferring by lipoprotein may plays a relatively more important role for delivering retinol to tissues. Recently it is reported that the rate of retinyl ester clearance of chylomicron and its delivery to tissues are not elevated in TTR-deficient mice, while delivery of retinol-RBP4 to tissues of these mice is reduced [12].

Receptors of RBP4:

STRA6 as a retinol receiver

When ROH-RBP-TTR complex reach to target tissues, separation of vitamin A and RBP4 is mediated by a cell-surface receptor named STRA. It is estimated that STRA6 has eleven [6] or nine [50] trans membrane domains with an RBP4 binding domain on an extracellular loop depend on the computer model used[51, 52]. STRA6 associates with RBP4 directly, because STRA6 over-expression in cultured cells facilitates retinol uptake from the Holo-RBP. Consequently, decreasing inexpression levels of STRA6 reduces retinol uptake [53]. Thus, STRA6 is a retinol transporter, which mediates the extraction of the retinol from Holo-RBP , not Apo-RBP, and transfers it across plasma membranes into target cells[51].

Animal studies established lack of STRA6 suppresses vitamin A uptake in mice and zebrafish [54, 55].STRA6 is responsible for about 95% of vitamin A uptake for vision[56].

Under vitamin A sufficient circumstances *STRA6-knockout* mice have primarily vision defects, similar to *RBP4- knockout* mice[15, 57, 58]. In addition Mutations in STRA6 gene are associated with some pathological phenotypes in eye, brain, lung ,and heart of humans[59].

STRA6 can function bi-directionally to not only take up retinol from the circulation but secrete the vitamin A from cells [54] indicated that STRA6-mediated vitamin A uptake is stimulated by LRAT or Cellular retinol-binding protein (CRBP)[60]. In the absence of LRAT and CRBP, retinol is released from Holo-RBP by STRA6 and is loaded into Apo-RBP. Hence, vitamin A uptake has a close link with its metabolism[54].

Pure extracellular Apo-RBP cannot only effectively mediate retinol efflux from STRA6/CRBP cells but deplete approximately all retinol taken up by STRA6/CRBP cells. Furthermore, the ability of STRA6 for catalyzing retinol efflux from CRBP to Apo-RBP4 suggests that affinity of CRBP for retinol is similar to RBP4s affinity for bounding to STRA6. However, its details are still unknown. Retinol exchanging between extracellular RBP4 molecules and intracellular CRBP cause the intracellular retinol stores to be refreshed which prevents cells from slow depletion due to oxidation occurring during long-term storage[61].

STRA6 is also able to catalyze retinol loading to Apo-RBP and retinol releasing from Holo-RBP independent of CRBP and LRAT. Even It is reported that LRAT or CRBP suppress these functions of STRA6. According to Zhong et al L255A mutation in STRA6 residue which is essential for STRA6/CRBP interaction has no effect on STRA6 ability to vitamin A uptake [58].

STRA6 and Scavenger Receptor Class B Type I (SRB-I) which mediated cholesterol uptake from high-density lipoprotein (HDL) are so similar in function, because both take up molecules bound to extracellular carrier proteins, subsequently stay outside of the cell[62]. In addition, the ability of STRA6 to mediate both retinol uptake and retinol efflux is analog with the role of HDL receptor SRB-I's in cholesterol uptake and efflux. However, there is no sequence similarity between these two receptors[63].

STRA6 is expressed during embryonic development and in the adult adipose tissue, kidney, spleen, blood-organ barriers, retinal pigment epithelial of the eye, brain, testis, female genital tract, and at lower quantities in heart and lung[5]. STRA6 expression is elevated in melanomas, wilms kidney tumors as well as colorectal, ovarian, and endometrium cancers [64]. Notably, while being the major site of production of vitamin A, which loads RBP4 to deliver vitamin to extrahepatic organs, liver has very low or no expression of STRA6[53].

STRA6 as a receptor for cytokines

Recent studies revealed that STRA6 transportation and signaling are closely related to retinol metabolism. In addition, STRA6 not only functions as a retinol transporter, it is also acts in a role as a receptor for cytokines. Binding of Holo- RBP withSTRA6 cause phosphorylation in a tyrosine residue of the STRA6 cytosolic domain, it is followed by activation of Janus kinase 2 (JAK2) which phosphorylates a tyrosine residue in the cytosolic domain of the receptor-STRA6. Subsequently, STRA6 catalyzes the phosphorylation of a tyrosine residue near the C-terminus of Signal Transducer and Activator of Transcription (STAT) protein. In consequent activated STATs form dimer to produce transcription factor then translocate to the nucleus, bind to DNA, and induce transcription of specific target genes. Hence, Holo-RBP can activate STRA6- mediated signaling, which results in up-regulation of STAT target genes[6-8].

It is indicated that cytokine receptors are activated by binding ligands to their extracellular domains. Binding of Holo-RBP to STRA6 is necessary for its role, but unlike known cytokine receptors, this association is not be able to activate the receptor. Instead, it is suggested that activation of STRA6 and following signaling cascades occurred as a result of STRA6-mediated retinol transfer from extracellular ROH-RBP to the intracellular CRBP[7].

Suppressor of Cytokine Signaling3 (SOCS3) is one of the proteins encoded by the direct STAT target genes and regulates the JAK/STAT activities cascades. Following SOCS3 up-regulation by STATs, it functions as components of negative feedback loops and blocks cytokine signaling by contending with STATs for binding to Phosphotyrosinasein activated STRA6[65, 66]. SOCS3 do this competition by having some components including a variable N-terminal domain, a central SH2 domain, and a C-terminal 40-amino-acid module termed the SOCS box[67].

Peroxisome proliferator-activated receptor -γ

(PPARγ) is another STAT-regulated gene involved in lipid metabolism, which according to recently studies, is up- regulated via JAK/STAT pathway. Many previous studies have mentioned that PPARγ gene expression changes are negatively associated with RBP4 levels. PPARγ is a nuclear receptor that serves as a 'master regulator' of adipocytes biology. PPARγ expression and activation induces the expression of some proteins which increase adipogenesis during adipocytes differentiation[68]. In mature adipocytes, the gene expressions of some proteins that involve in uptake and storage of triglyceride are regulated by PPARγ. To sum up, up-regulation of PPARγ increases lipid accumulation by promotion of the new adipocytes formation in adipose tissue[6].

STATs are key regulators of growth, migration, and survival of cells. RBP-ROH pathway also may be participated in other biological functions such as embryogenesis and cancer development. T644M STRA6 mutation that impairs RBP-ROH signaling causes defects in embryonic development and the expression of STRA6 is elevated in some types of cancers[6].

According to the recent study, STRA6 may only mediate cellular retinol uptake from free Holo-RBP which not be bounded to TTR. Hence TTR may exert a crucial role in protecting cells against Holo-RBP-induced signaling. STRA6 senses free Holo-RBP and only functions in the state of high serum RBP to TTR ratio. This observation has been made in obese animals in which serum RBP levels are elevated, while TTR concentrations are normal. Since TTR-bound RBP4 is unlikely to rapidly excrete by glomerular filtration, its half- life in circulation is short- similar to classical cytokine. This action of free Holo-RBPis dramatically differing from its role as a retinol vehicle[8, 69].

The circulation RBP4/TTR ratio can be altered by changes in the expression levels of RBP4, TTR, or both of them. Acute-phase response down-regulates expression of hepatic TTR, and cause a decrease in serum TTR levels. This process is known as a rapid response to signaling of inflammatory cytokines[70]. Releasing Holo-RBP4 from TTR may be occurred as a result of the low serum levels of TTR which is associated with acute-phase response.

Other receptors of RBP4

RBP4 exerts its effects through both retinol-dependent and retinol independent pathways via STRA6 and other receptors activation. The latter is indicated as a signaling pathway in different cell types. STRA6 expression is undetectable in endothelial and macrophages, but it is illustrated that RBP4 can induce inflammation in primary Human retinal capillary endothelial cells (HRCEC) and Human umbilical vein endothelial cells (HUVEC) via a retinol independent pathway. According to the recent study in which endothelial cells treated with both Apo- and Holo-RBP, none of them results in cellular uptake of retinoids. However, both of them induce production of proinflammatory molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), Monocyte chemoattractant protein-1 (MCP-1),E-selectin, and interleukin-6 (IL-6). It is suggested that RBP4 may induce production of proinflammatory cytokines by inducing the activation of nuclear factor kappa-B (NF-κB) which is independent of retinol /STRA6 pathway. RBP-4 induces inflammation in macrophages through toll-like receptor 4 (TLR4) signaling. Although, the receptor of RBP4 in endothelial cells has not been recognized yet, it is speculated that it might be resemble receptor of RBP4 in macrophages. In addition, RBP4 mediate induction of inflammation in endothelial via activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. In both of these pathways Apo-RBP and Holo-RBP have the same proinflammatory effects[71].

While liver is the most important organ for retinol metabolism and storage, STRA6 is not detected in liver. The receptor of RBP4 in liver was unknown until Alpatt et.al revealed their discovery of retinol binding protein receptor 2 (RBPR2), a transporter of retinol with high affinity for RBP4 expressed highly in liver. RBPR2 is also expresses in the intestine and may play an important role in dietary retinol absorption. Moreover, expression of RBPR2 is elevated during adipocytes differentiation in adipose tissue of obese patients. RBPR2 is considered as a new member of the STRA6 family because of the same structural with STRA6 and comparable kinetics toRBP4-binding and retinol uptake. There are some differences between STRA6 and RPBR2 because these receptors are expressed in different tissues. Furthermore, RPBR2 signaling pathway is unlikely to be mediated via JAK/STAT. RBP4-dependent signaling derived from lacking STRA6 C terminus Src homology 2 domain in RBPR2 is necessary for this

pathway. Hepatocytes are the main cell type which expresses RBPR2. Other liver cell types such as stellate, ductal, endothelial, and kupffer cells may express RBPR2. Collectively,RBPR2may be responsible for physiologically regulation of dietary, circulating, and storage of retinol[72].

Discussion

In summary, RBP4 is the main vitamin A transporter from liver to extrahepatic tissues, which presents in the form of ternary ROH-RBP-TTR complex in circulation. Uptake of vitamin A from RBP4 is mediated by a cell-surface receptor termed STRA6 and is stimulated by LRAT or CRBP[10]. STRA6 functions bi-directionally and can induce secretion of vitamin from cells[53]. Furthermore RBP4 is recognized as an adipocytokine which is enable to up-regulate SOCS3 and PPARϒ gene expression through JAK/STAT signaling pathway and result in insulin resistance[6]. Notably STRA6-mediated vitamin A transferring is carried out in the same time with activation of JAK/STAT inflammatory pathway. Association of RBP4 with TTR not only prevents loss of RBP4 from the circulation by the renal glomerular filtration, but also modulates receptor response to RBP4. Hence, by increasing in RBP/TTR ratio, RBP4 with short half-life functions as a classic cytokine[8]. The recently known RBP4 receptor, RBPR2, is one of the STRA6 family members which expressed highly in liver and intestine and have a crucial impact on metabolism of dietary and liver retinol[72]. TLR4 is another receptor of RBP4 expressed in macrophages and endothelial cells which induce production of proinflammatory cytokines via activation of NFk-B and NADPH oxidase [71].

Conflict of Interests

The authors declared no conflict of interests.

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Abbreviations

Retinol: ROH; Retinol binding protein 4: RBP4; Stimulated by retinoid acid gene 6: STRA6; Transports Thyroxine and Retinol: TTR; Insulin receptor substrate: IRS; Lecithin retinol acyltransferase: LRAT; Diacylglycerol acyltransferase 1: DGAT1; Phosphatidyl Inositide 3-Kinase: PI3K; Protein Kinase B: PKB; Phosphatidyl Inositol 3-Phosphate: PI3P; Glucose Transporter Type 4: GLUT4; Phosphoenolpyruvate carboxykinase: PEPCK; Type 2 diabetes mellitus: T2DM; Cellular retinol-binding protein: CRBP; Scavenger receptor class B type I: SRB-I; High-density lipoprotein: HDL; Janus kinase 2: JAK2; Signal transducer and activator of transcription: STAT; Suppressor of cytokine signaling3: SOCS3; Peroxisome proliferator-activated receptor -γ: PPARγ; Human retinal capillary endothelial cells: HRCEC; Human retinal capillary endothelial cells: HRCEC; Iintercellular adhesion molecule-1: ICAM-1; Vascular cell adhesion molecule-1: VCAM-1; Monocyte chemoattractant protein-1: MCP-1; Interleukin-6: IL-6; Nuclear factor kappa-B: NF-κB; Toll-like receptor 4: TLR4; Nicotinamide adenine dinucleotide phosphate-oxidase: NADPH; Retinol binding protein receptor 2: RBPR2.

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