

Review Article

Interplay between Cholesterol, SREBPs, MicroRNA-33 in Dyslipidemia

Abdul Hafeez Kandhro

Abdul Hafeez Kandhro, Healthcare Molecular & Diagnostic Laboratory, Hyderabad, Pakistan,
Email of corresponding author: hafeezjaan77@yahoo.com

Abstract

Dyslipidemia is characterized by elevation of plasma cholesterol, triglycerides (TGs) or both, or a low high-density lipoprotein-cholesterol (HDL-C) level that contributes to the development of insulin resistance, Diabetes mellitus type 2 (DM2) and atherosclerosis. Dietary fat and cholesterol, genetics and other risk factors are responsible for producing variations in the lipids. The cholesterol plays a major function in the body, cholesterol homeostasis mechanism is regulated by the sterol regulatory-element binding proteins (SREBPs) and firstly introduced by Brown and Goldstein. The SREBP transcription factors act coordinately with their intronic microRNAs (miRNA-33a / miRNA-33b) to regulate both fatty acid and cholesterol homeostasis. Recently, multiple studies described microRNA-33a and SREBP2 cooperation for cholesterologenic transcription to improve intracellular cholesterol levels; suggesting that therapeutic approach of miR-33 targeting antisense would imperative for reverse cholesterol transport from atherogenic macrophages, as a result reduce atherosclerosis.

Keywords

MicroRNA-33, Dyslipidemia, Cholesterol, HDL-Cholesterol, Anti-miRNA-33, SREBP

Introduction

Dyslipidemia is an important risk factor for developing Insulin resistance, DM2, and cardiovascular diseases. It is characterized by combining abnormalities of lipoproteins which includes decreased high density lipoprotein cholesterol (HDL-C), increased serum triglycerides (TG) and also increased small low density lipoprotein cholesterol (LDL-C). (Kwan, Kronenberg, Beddhu, & Cheung, 2007). Cholesterol is required for various cellular functions, and major component of cellular compartment as it performs and maintain membrane fluidity, cell proliferation; thus it is precursor of steroid hormones, bile acids and vitamin D. Therefore, cholesterol homeostasis is generally required to maintain human health; maintain cellular cholesterol by tightly regulated complex mechanism (Brown MS, 1997; S. B. Kim JB, 1996).

Cholesterol Homeostasis

Cholesterol from diet enters pool of cholesterol, which is then transported to the liver for suppression of LDLR synthesis; thus elevation in the conversion of VLDL particles and decreases cholesterol clearance from plasma, as a result LDL levels increased (MB, 2006). The whole mechanism is regulated by SREBPs, and firstly described by Brown and Goldstein (Brown MS, 1997). The SREBP family of basic-helix-loop-helix-leucine zipper transcription factors are important regulators for cholesterol and lipid homeostasis by

activating more than 30 genes of fatty acid, triglyceride, phospholipid and cholesterol metabolism (Horton JD, 2002). The SREBP gene consists of SREBP1; which is further divided into two isoforms, (SREBP-1c and SREBP-1a) and SREBP2. SREBP-1 isoforms are involved in the expression of genes like fatty acids, triglyceride, and phospholipid biosynthesis; while SREBP-2 is involved in the in the expression of genes like cholesterol biosynthesis and uptake of low density lipoprotein receptor (LDLR) gene (Horton JD, 2002).

Upon depletion of cellular cholesterol, SREBP is cleaved from the Golgi and export to the nucleus, where transcription of LDLR gene and genes encoded for HMG-CoA reductase (the rate limiting enzyme required for cholesterol synthesis). As a result, uptake & synthesis of cholesterol increases, that meet up requirements of membrane cholesterol. While dietary cholesterol reduces synthesis of LDLR by preventing SREBP cleavage, thus the low uptake of cholesterol by the cells and cholesterol synthesis decreases by enzymes, specifically HMG-CoA reductase. On the other hand, pathologically increased cholesterol synthesis such as in obesity leads to elevated circulating cholesterol which decreases LDLR synthesis and increases LDL levels, as a result decreases clearance of cholesterol (Katan MB, 1987); (Keys A, 1965). Consequently, due to already higher level of synthesized cholesterol and suppressed LDLR

activity, thus higher amount of dietary cholesterol having little or no effect. Oxysterols (oxygenated derivative of cholesterol) are produced from increased hepatic cholesterol, play important role in cholesterol excretion as well as modulates other biological processes (I, 2002). In addition, it acts as ligands for LXRs to stimulate reverse cholesterol transport and synthesis of bile acid, thus it prevents cholesterol overload in the cell (Wojcicka G, 2007). Generally, SREBPs are regulated widely on many cellular and physiologic biochemical processes for health (Osborne TF, 2009). Thus cholesterol plays role in regulation, posttranscriptional control, proteolytic processing or maturation of SREBPs. Therefore, SREBPs regulation is necessary for proper cholesterol homeostasis via feed-back loop and SREBP2 (Osborne TF, 2009).

Fatty acid Homeostasis

Elevated level of lipogenesis is associated with dysregulation of SREBP-1c. The SREBP-1c is predominant isoform in the liver and adipose tissue, where it activates monounsaturated fatty acid synthesis; regulate gluconeogenic genes, adipocyte differentiation and minor extent in FOXO1 regulation (J. D. Horton, Bashmakov, Y., Shimomura, I., and Shimano, H, 1998) ;(Tontonoz P, 1993; Yamamoto T, 2004). Evident from studies that insulin's effects on FOXO1 regulated glucogenic genes expression as well as insulin's effects on lipogenesis emerges by the transcription of SREBP-1c. In this circumstance SREBPs involved in complex regulation and posttranscriptional levels (Horton JD, 2002). Physiologically, insulin seems to be increases SREBP-1c transcription, maturation and functional activity, SREBPs level also triggers by circulating insulin in post-prandial state which leads to elevation of hepatic glucose, fatty acid uptake and triglyceride synthesis for storage. But in pathological conditions like insulin resistance; insulin increases SREBP-1c mRNA, which is mediated through the liver x receptor (LXR) binding sites in the SREBP-1c promoter thus its transcription is an insulin-dependent manner (Chen G, 2004).

Transcriptional Regulation of Cholesterol Metabolism

SREBPs have two residue sites; a tyrosine residue allowing SREBPs to bind E-box inverted repeats and direct repeat variants binding at the sterol regulatory element (SRE) (S. G. Kim JB, Halvorsen Y-D, Shih H-M, Ellenberger T, Towle HC, Spiegelman BM, 1995), SRE was first identified in the promoter region of low-density lipoprotein receptor (LDLR) via SREBP-binding site (Dawson PA, 1988). The second residue is the large C-terminal domain which has two

membrane-spanning helices that lines in that endoplasmic reticulum (ER) membrane. The N-terminal domain having transcriptional activation, while DNA-binding domains persist with the C-terminal regulatory domain on the cytoplasmic side of the membrane (Brown MS, 1999). During translation, Interaction of SCAP with the COPII machinery leads to the complex with SREBPs C-terminal domain (SCAP/SREBP complex) forms vesicle which then transport to the Golgi. In Golgi SCAP-SREBPs complex breaks by sequential two-step proteolysis process thus active SREBPs are released (Espenshade PJ, 2002).

Active SREBPs reach nucleus for activating transcription of all genes like SREBP1 activates the fatty acid, triglyceride and lipid uptake genes while SREBP2 only activates cholesterol synthesis and uptake genes (Horton JD, 2002) ;(Brown MS, 1997) ;(J. D. Horton, Bashmakov, Y., Shimomura, I., and Shimano, H, 1998). SREBP-2 also involved in the stimulating genes that encodes LDL receptor (LDLR), which is important for cholesterol uptake elevation into liver, and PCSK9 protein that degrades hepatic LDLRs, thus reducing cholesterol uptake (J. D. Horton, Cohen, J.C., and Hobbs, H.H, 2009). SCAP is necessary for processing of SREBPs; it was proved in animal studies that without SCAP, SREBPs are rapidly degraded before reaching in Golgi and thus never enters in nucleus (Matsuda, 2001). Insulin inducing genes (INSIGs) are ER membrane proteins, pushing SCAP/SREBP complex; prevent from entering the COPII-dependent ER-Golgi transportation (Sun LP, 2007). SCAP protein having membrane region that includes a conserved sterol-sensing domain, similar conserved site is also found in cholesterol regulation and signaling proteins such as HMG CoA reductase, NPC-1, and the hedgehog receptor Patched (Chang TY, 2006), thus intracellular cholesterol directly binds to SCAP and NPC-1 (Ohgami N, 2004; S. L. Radhakrishnan A, Kwon HJ, Brown MS, Goldstein JL, 2004);(Infante RE, 2008), and also binding of reductase and SCAP to the INSIG proteins (I. Y. Radhakrishnan A, Kwon HJ, Brown MS, Goldstein JL, 2007; Sever N, 2003). In sufficient level of cholesterol / oxysterols in endoplasmic reticulum is favorable for SCAP-SREBP2 complex; which results association with another protein INSIG (A. Radhakrishnan, 2007). During the SREBP2 transport and processing in the Golgi is decreased, thus SREBP-2 target genes suppressed (M.S. Brown, 2009).

The mechanism by which insulin post-transcriptional regulate SREBPs are not completely understood;

however, suggested that either INSIG/SCAP complex or the functional role of serine/threonine protein kinase AKT. SREBPs are phosphorylated by insulin acting downstream SREBPs through AKT pathway, also by inhibiting GSK3; that promotes SREBP expression thus it stimulates SREBP-dependent gene regulation (Sundqvist A, 2005). Moreover, insulin activated mTOR signaling pathway; that can enhance the SREBPs function by mTORC1-dependent mechanism (Lewis CA; Porstmann T, 2008).

Recently, non-coding RNA termed microRNAs (miRNAs) has been identified in cholesterol and lipid metabolism as a crucial regulator of gene expression and acting primarily at the post-transcriptional level of cholesterol and lipid metabolism for controlling cholesterol and lipid homeostasis. Under physiological conditions, miRNAs are implicated in biological process such as cell cycle, differentiation, proliferation, migration, secretion, aging and apoptosis. Recently, miR-33a and miR-33b was found to be involved in the regulation of intracellular fatty acid and lipid levels with their SREBPs host gene products. At first, miR-33a and miR-33b directly controls the expression of multiple proteins which are involved in fatty acid β -oxidation (I. Gerin, 2010).

Studies reported that MicroRNA-33a (miR-33a) is an intronic transcript of SREBP2 (Najafi-Shoushtari, 2010) ;(Rayner K, 2010) ;(Brown, 2010), which suggested that low level of cellular sterol results in higher SREBP2 mRNA levels as well as increased level of miR-33a. From studies showed; miR-33a specifically binds to complimentary sequences in the 3'UTR of the ABCA1 and or ABCG1 mRNAs, which leads to degradation of these mRNAs and causes low protein levels (Najafi-Shoushtari, 2010) ;(Rayner K, 2010). Thus, under depleted levels of sterols in endoplasmic reticulum not only enhances nuclear SREBP2 which then induces cholesterol synthesis genes and cholesterol-rich lipoproteins uptake, but in addition, decreases ABCA1 and ABCG1 that aids cellular cholesterol efflux (Najafi-Shoushtari, 2010) ;(Rayner K, 2010). ABCA1 are at hepatic and intestinal levels, playing role for regulation of plasma HDL levels (V.I. Zannis, 2006). Hence, alteration of hepatic miR-33a levels is significantly effects on plasma HDL (I. Gerin, 2010) ;(Horie, 2010) ;(Marquart, 2010) ;(Najafi-Shoushtari, 2010) ;(Rayner K, 2010).

During insulin resistance, elevated levels of SREBP-1c and upregulated miRNA-33b in the liver may increases VLDL and decreases HDL-C levels (both consequences are causative factors for developing of

metabolic syndrome) (Najafi-Shoushtari, 2010). In addition, higher levels of hepatic miRNA-33b in response to high carbohydrate diet in non-human primates also confirmed in recent studies.

miR-33 as Therapeutic tool

The miRNA-33 is expressed in various cells and tissues which includes; macrophages, hepatic cells, endothelial cells, brain, liver, colon, small intestine, and skeletal muscle. The antisense technology for miRNA functions inhibition has been imperative means for clarifying miRNA biology. Antisense technology is being used and reported recently, miR-33 knockdown experimental studies that controls cholesterol homeostasis, suggested that potential target for treating cardiovascular diseases and metabolic disorders (Marquart TJ, 2010) ;(Rayner K, 2010).

From reported studies, antisense miR-33 would greatly elevated levels of ABCA1 which results increases HDL levels (Marquart, 2010). In vitro studies confirmed that ABCA1 protein expression suppressed by Srebp2 intron 16 in the same way as miR-33, in this way miR-33 showed synergistic effect on ABCA1 protein through its host gene Srebp2, thus known to downregulates the transcription of Abca1 in vascular endothelial cells (Zeng L, 2004). Another in vitro studies on mice were shown significant decrease in plasma HDL levels when miR-33a overexpressed; while in increased plasma HDL levels when mice fail to express miR-33a (Horie, 2010) or after miR-33a knockdown (Horie, 2010) ;(Marquart, 2010) ;(Najafi-Shoushtari, 2010) ;(Rayner K, 2010). From these in vitro studies, thrilling prospect that hepatic miR-33a knockdown in humans will boost hepatic ABCA1 protein levels, which will result increases plasma HDL levels thus reducing cardiovascular disease. Another study demonstrated that high-fat-diet mice which were LDLR-Knockout and antisense inhibition of miRNA-33a shown reduction in the size of atherosclerotic plaque and lipid content, however, increases reverse cholesterol transport, suggested that miRNA-33a as a target therapy for cardiovascular diseases (Marquart, 2010).

In metabolic syndrome; insulin-induced increase in SREBP-1c mRNA and protein levels associated with hypertriglycemia (Chen G, 2004) Therefore, decreased plasma HDL often associated with this situation may be possible ABCA1 is the cause of reduction in plasma HDL, because of the higher expression of miR-33b from the insulin-induced induction of SREBP1c.

The efficient antisense-oligonucleotides therapy which targets miRNA-33a and miRNA-33b are efficient in elevating HDL levels and lowering VLDL triglycerides, therefore it could flourish future human clinical trials for treating cardiovascular and metabolic diseases patients (Marquart, 2010). Antisense technology using miRNA-33 knockdown in experimental studies is being used and reported recently, that control cholesterol homeostasis, and suggested possible therapeutic marker for treating cardiovascular and metabolic disorders (Rayner K, 2010); (Marquart, 2010). In this scenario, Anti-miRNA oligonucleotide against miRNA-33a/b is being developed by Regulus Therapeutics Inc. for the treatment of atherosclerosis (Rayner K, 2010). In addition, delivery of 2'F/MOE oligonucleotides (anti-miRNA-33) could penetrate in the atherosclerotic plaques lesional macrophages, where they can up-regulate ABCA1 expression to activate reverse cholesterol transport thus enhances cholesterol removal from foam cells (Rayner et al., 2011). Therefore, anti-miRNA-33 not only enhances circulating HDL and promote reverse cholesterol transport, but directly targeted to macrophages in the plaque, where upregulates cellular cholesterol efflux pathways to further enhance the reverse cholesterol transport and favorably affect lesion pathology. Together, these data, establish miRNA-33 as an attractive therapeutic target for raising HDL and regressing atherosclerosis (Rayner et al., 2011).

Conclusion

The experimental studies support the anti-miRNA-33 therapy as a potential therapeutics for dyslipidemia and cardiovascular diseases. In addition, anti-miRNA-33a/33b therapy may increase plasma HDL-C and decreases VLDL, triglycerides without any side effects.

Still more research work required to enhance the effectiveness of anti-miRNA therapy, because the behavior of the miRNA-33 expression pattern in different cell types. Further understanding needed for the relative contribution of hepatocyte and plaque (containing macrophages, smooth muscle cells) and miRNA-33 causative of atherogenesis and the antiatherogenic anti-miRNA-33 therapy. Variation in bioavailability, efficacy, and potency due to different chemistries of oligonucleotide anti-miRNA-33 therapy either in the liver or plaque / lesions. Future studies would analyze important variables, enhances the efficacy of anti-miRNA-33 therapy, and explain the complete role of miRNA-33 and their targets.

Acknowledgement

N/A

Competing interests

N/A

Funding

N/A

References

- Radhakrishnan, Y. I., H.J. Kwon, M.S. Brown, J.L. Goldstein. (2007). Sterol regulated transport of SREBPs from endoplasmic reticulum to Golgi: oxysterols block transport by binding to Insig. *Proc. Natl. Acad. Sci.*, 104, 6511-6518.
- Brown MS, G. J. (1997). The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. *Cell*, 89, 331-340.
- Brown MS, G. J. (1999). A proteolytic pathway that controls the cholesterol content of membranes, cells, and blood. *Proc Natl Acad Sci U S A.*, 96, 11041-11048.
- Brown, M. S., Ye, J. & Goldstein, J. L. *Medicine*. (2010). HDL miR-ed down by SREBP introns. . *Science*, 328, 1495-1496.
- Chang TY, C. C., Ohgami N, Yamauchi Y. (2006). Cholesterol sensing, trafficking, and esterification. *Annu Rev Cell Dev Biol*, 22, 129-157.
- Chen G, L. G., Ou J, Goldstein JL, Brown MS. (2004). Central role for liver X receptor in insulin-mediated activation of Srebp-1c transcription and stimulation of fatty acid synthesis in liver. *Proc Natl Acad Sci U S A.*, 101, 11245-11250.
- Dawson PA, H. S., Van DerWesthuyzen DR, Sudhof TC, Brown MS, Goldstein JL. (1988). Sterol-dependent repression of low density lipoprotein receptor promoter mediated by 16-basepair sequence adjacent to binding site for transcription factor Sp1. *J Biol Chem*, 263, 3372-3379.
- Espenshade PJ, L. W., Yabe D. (2002). Sterols block binding of COPII proteins to SCAP, thereby controlling SCAP sorting in ER. *Proc Natl Acad Sci U S A.*, 99, 11694-11699.
- Horie, T. e. a. (2010). MicroRNA-33 encoded by an intron of sterol regulatory element-binding protein 2 (Srebp2) regulates HDL in vivo. . *Proc. Natl Acad. Sci. USA*, 107, 17321-17326.
- Horton, J. D., Bashmakov, Y., Shimomura, I., and Shimano, H. (1998). Regulation of sterol regulatory element binding proteins in livers of fasted and refed mice. *Proc. Natl. Acad. Sci. USA*, 95, 5987-5992.

- Horton, J. D., Cohen, J.C., and Hobbs, H.H. (2009). PCSK9: a convertase that coordinates LDL catabolism. *J. Lipid Res. Suppl.*, 50, S172-S177.
- Horton JD, G. J., Brown MS. (2002). SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest*, 109, 1125-1131.
- I, B. (2002). Do oxysterols control cholesterol homeostasis? . *J Clin Invest.*, 110, 725-730.
- Gerin, L. A. C., O. Haumont, N. Lanthier, A.K. Das, C.F. Burant, I.A. Leclercq, O.A. MacDougald, G.T. Bommer. (2010). Expression of miR-33 from an SREBP2 intron inhibits cholesterol export and fatty acid oxidation. *J. Biol. Chem.*, 285, 33652-33661.
- Infante RE, A.-M. L., Radhakrishnan A, Dale JD, Brown MS, Goldstein JL. (2008). Purified NPC1 protein. I. Binding of cholesterol and oxysterols to a 1278-amino acid membrane protein. *J Biol Chem*, 283, 1052-1063.
- Katan MB, B. A. (1987). Characteristics of human hypo- and hyperresponders to dietary cholesterol. . *Am J Epidemiol*, 125, 387-399.
- Keys A, A. J., Grande F. (1965). Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet. *Metabolism*, 14, 776-787.
- Kim JB, S. B. (1996). ADD1/SREBP1 promotes adipocyte differentiation and gene expression linked to fatty acid metabolism. *Genes Dev*, 10(1096-1107).
- Kim JB, S. G., Halvorsen Y-D, Shih H-M, Ellenberger T, Towle HC, Spiegelman BM. (1995). Dual DNA binding specificity of ADD1/SREBP-1 controlled by a single amino acid in the basic helix-loop-helix domain. *Mol Cell Biol*, 15, 2582-2588.
- Kwan, B. C., Kronenberg, F., Beddhu, S., & Cheung, A. K. (2007). Lipoprotein metabolism and lipid management in chronic kidney disease. *Journal of the American Society of Nephrology*, 18(4), 1246-1261.
- Lewis CA, G. B., Santos CR, Pende M, Schulze A. Regulation of the SREBP transcription factors by mTORC1. *Biochem Soc Trans*, 39, 495-499.
- M.S. Brown, J. L. G. (2009). Cholesterol feedback: from Schoenheimer's bottle to Scap's MELADL. *J. Lipid Res. Suppl.*, 50, S15-S27.
- Marquart, T. J., Allen, R. M., Ory, D. S. & Baldan, A. (2010). miR-33 links SREBP-2 induction to repression of sterol transporters. . *Proc. Natl Acad. Sci. USA*, 107, 12228-12232.
- Marquart TJ, A. R., Ory DS, Baldán A. (2010). miR-33 links SREBP-2 induction to repression of sterol transporters. *Proc Natl Acad Sci U S A.*, 107, 12228-12232.
- Matsuda, M., Korn, B.S., Hammer, R.E., Moon, Y.A., Komuro, R., Horton, J.D., Goldstein, J.L., Brown, M.S., and Shimomura, I. (2001). SREBP cleavage-activating protein (SCAP) is required for increased lipid synthesis in liver induced by cholesterol deprivation and insulin elevation. *Genes Dev*, 15, 1206-1216.
- MB, K. (2006). The response of lipoproteins to dietary fat and cholesterol in lean and obese persons. *Curr Cardiol Rep*, 8, 446-451.
- Najafi-Shoushtari, S. H. e. a. (2010). MicroRNA-33 and the SREBP host genes cooperate to control cholesterol homeostasis. . *Science*, 328, 1566-1569.
- Ohgami N, K. D., Thomas M, Scott MP, Chang CC, Chang TY. (2004). Binding between the Niemann-Pick C1 protein and a photoactivatable cholesterol analog requires a functional sterol-sensing domain. *Proc Natl Acad Sci U S A.*, 101, 12473-12478.
- Osborne TF, E. P. (2009). Evolutionary conservation and adaptation in the mechanism that regulates SREBP action: what a long, strange tRIP it's been. *Genes Dev*, 23, 2578-2591.
- Porstmann T, S. C., Griffiths B, Cully M, Wu M, Leevers S, Griffiths JR, Chung YL, Schulze A. (2008). SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth. *Cell Metab*, 8, 224-236.
- Radhakrishnan A, I. Y., Kwon HJ, Brown MS, Goldstein JL. (2007). Sterol-regulated transport of SREBPs from endoplasmic reticulum to Golgi: Oxysterols block transport by binding to Insig. . *Proc Natl Acad Sci U S A.*, 104, 6511-6518.
- Radhakrishnan A, S. L., Kwon HJ, Brown MS, Goldstein JL. (2004). Direct binding of cholesterol to the purified membrane region of SCAP: Mechanism for a sterol-sensing domain. *Mol Cell*, 15, 259-268.
- Rayner K, e. a. (2010). miR-33 Contributes to the regulation of cholesterol homeostasis. *Science*, 328, 1570-1573.
- Rayner, K. J., Sheedy, F. J., Esau, C. C., Hussain, F. N., Temel, R. E., Parathath, S., . . . Suarez, Y. (2011). Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. *The Journal of clinical investigation*, 121(7), 2921-2931.
- Sever N, Y. T., Brown MS, Goldstein JL, DeBose-Boyd RA. (2003). Accelerated degradation of HMG CoA reductase mediated by binding of insig-1 to its sterol-sensing domain. *Mol Cell*, 11, 25-33.

- Sun LP, S. J., Goldstein JL, Brown MS. (2007). Sterolregulated transport of SREBPs from endoplasmic reticulum to Golgi: Insig renders sorting signal in Scap inaccessible to COPII proteins. *Proc Natl Acad Sci U S A.*, 104, 6519-6526.
- Sundqvist A, B.-A. M., Ye X, Lukiyanchuk V, Jin J, Harper JW, Ericsson (2005). Control of lipid metabolism by phosphorylation-dependent degradation of the SREBP family of transcription factors by SCF(Fbw7). *J. Cell Metab.*, 1, 379-391.
- Tontonoz P, K. J., Graves RA, Spiegelman BM. (1993). ADD1: A novel helix-loop-helix transcription factor associated with adipocyte determination and differentiation. *Mol Cell Biol*, 13, 4753-4759.
- V.I. Zannis, A. C., M. Krieger. (2006). Role of apoA-I, ABCA1, LCAT, and SR-BI in the biogenesis of HDL. *J. Mol. Med*, 84, 276-294.
- Wojcicka G, J.-W. A., Horoszewicz K, Beltowski J. (2007). Liver X receptors (LXRs). Part I: structure, function, regulation of activity, and role in lipid metabolism. *Postepy Hig Med Dosw*, 61, 736-759.
- Yamamoto T, S. H., Nakagawa Y, Ide T, Yahagi N, et al. (2004). SREBP-1 interacts with hepatocyte nuclear factor-4 α and interferes with PGC-1 recruitment to suppress hepatic gluconeogenic genes. *J. Biol. Chem*, 279, 12027-12035.
- Zeng L, e. a. (2004). Sterol-responsive element-binding protein (SREBP) 2 downregulates ATP-binding cassette transporter A1 in vascular endothelial cells: A novel role of SREBP in regulating cholesterol metabolism. *J Biol Chem*, 279, 48801-48807.