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Cell Signaling in Diabetic Dyslipidemia

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Abstract

Diabetes accompanies several metabolic complications and poor production and clearance of lipoprotein is one of them. Type 2 diabetes mellitus is linked with atherosclerosis, though exact mechanism is still unclear. There are different complications of type 2 diabetes mellitus. Dyslipidemia is one of them. It has been documented that deranged lipid profile is caused by insulin resistance. Dyslipidemia arises due to low level of high density lipoproteins and high level of triglycerides. Diabetic dyslipidimia occurs due to imbalance in reverse cholesterol transport mechanism which is a major risk for cardiovascular diseases. Reverse cholesterol transport is regulated by cell surface receptors scavenger receptor B1 and ATP binding cassette protein-1. These are HDL binding receptors and help to maintain balance of HDL. Genetic and epigenetic factors influence the regulation of cell surface receptors. It plays a significant role in lipid homeostasis. HDL receptors are encoded by SCARB1 and ABCA1 genes. Peroxisome proliferator activated receptor alpha (PPARα) is a down-stream transcriptional activator of SCARB1, ABCA1 and ApoA1 genes.

Introduction

World Health Organization (WHO) reported that diabetes accounted for 6% deaths in 2012 and reached to 9% prevalence in 2014. According to WHO, 90% (312 million) diabetic cases were diagnosed as type 2 diabetes mellitus in 2015. Diabetic dyslipidemia is characterized by increase in blood triglyceride and decrease in blood HDL-cholesterol level. The anomalies in plasma a lipoprotein are associated with insulin resistance and type 2diabetes. These anomalies are linked with increased threat of cardiovascular diseases. Poor glycemic control and hypertension are the predictors of dyslipidemia in type 2 diabetes mellitus [1, 2]. Type 2 diabetes mellitus indicates to an increase production of very low-density lipoproteins, change in HDL metabolism as well as production of LDL particles. In T2DM, exchange of cholesterol between LDL and HDL by the help of cholesterol ester transfer protein is increased and results in decrease in HDL-cholesterol in T2DM [3, 4]. Hypertriglyceridemia also accelerated cholesterol ester transfer protein (CETP) facilitated interchange of VLDL-triglyceride for HDL-cholesteryl esters. The replacement of triglyceride for cholesteryl-ester in the core of the particle leads to decrease in HDL level [5, 6]. The change in lipoprotein trafficking and receptor signaling by insulin resistance is still unclear.

The HDL is an important precursor of reverse cholesterol uptake and performs this function through help of scavenger receptor B1 and ATP cassette binding protein 1. The SRB1 cell surface receptor is encoded by SCARB1 gene resides on human chromosome 12q24.31. It is abundantly expressed in hepatocytes and adipocytes [7]. ABCA1 accelerates transport of cholesterol from cells to apoA-1 and prevents atherosclerosis [8]. The ABCA1 gene resides on chromosome 17p11.2. ApoA1 gene encodes ApoA1 protein chief component of HDL.

Peroxisomes proliferator-activated receptor alpha (PPARα) are nuclear receptors and regulate the transcription of SRB1, ABCA1 and ApoA1 proteins [9]. PPARα binds to peroxisome proliferator activator receptor response element by DNA binding domain and activates transcription [10]. PPARα is involved in several independent enzymatic and DNA dependent molecular pathways in skeletal muscles, adipose tissue and liver [11]. The alterations in PPARα ultimately result in atherosclerosis due to change in HDL turnover [12]. The PPARs govern myocardial metabolism by transcriptional regulating genes, which encode enzymes that are involved in fatty acid and glucose utilization [13]. PPAR receptor agonists have been developed in humans.

Dyslipidemia is a chief risk factor of macro-vascular complications in T2DM [14]. Diabetic dyslipidemia (DD) is a significant factor contributing to increased risk of cardiac vascular diseases [15]. It is identified that HDL-C is reduced in diabetic dyslipidemia and upsurges the risk of cardiovascular disease. A strong association between PPARα polymorphism and reduce level of glucose in T2DM has been identified [16]. PPAR is being targeted to investigate cancer proliferation and cell apoptosis [17, 18]. The reduced expression of SCARB1 gene found linked with raised HDL levels and lesser cholesteryl esters uptake [19]. The overexpression of SCARB1 gene decreases HDL levels and also induces the hepatic uptake of cholesteryl esters [21].

ABCA1 is a trans-membrane protein. It is highly polymorphic, which mediates the cellular efflux of cholesterol to lipid poor HDL apolipoproteins [21]. ABCA1 gene variation is at high risk of cardiovascular disease, in the overall population [22]. ABCA1 is vital for cholesterol export. Hepatic SR-BI has a dynamic role for the selective uptake of cholesteryl esters from HDL [23]. Regulation of ABCA1 and SR-BI expression by nuclear receptors got great consideration as a pharmaceutical target [24].

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