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Mini-review

Some molecular targets for antihyperlipidemic drug research

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ABSTRACT

High levels of cholesterol and other lipid constituents are major risk factors in the development of atherosclerosis as well as diseases and disorders associated with it. Though, drugs of various categories acting through different mechanisms are available for antihyperlipidemic therapy, there are limitations associated with each of them, keeping the interest in discovery of newer and better antihyperlipidemic drugs alive. Identification and exploitation of novel molecular targets for discovery of new antihyperlipidemic drugs is an important area of research. Twenty such drug targets are elaborated herein, for their biochemical roles, structures, estimations, as well as, exploitation for new drug discovery research. Few recently discovered drugs are based on such molecular targets are also discussed.

1. Introduction

Cardiovascular diseases (CVD's) are among the major causes of deaths in the world today and shall continue to be so even by 2020 [1–3]. Hyperlipidaemia, leading to atherosclerosis is the major underlying factor for CVD's [1,4]. Elevated low-density lipoprotein cholesterol (LDLC) levels are the best indicators of the atherosclerotic risk [5]. Many novel molecular targets, on which new drugs could act and control hyperlipidaemia, are being identified and evaluated for new antihyperlipidemic drug discovery research [6].

The rising tide of obesity, diabetes and hypertension are collectively attributed to our reluctance to exercise and desire for fast food [7]. Atherosclerosis may be defined as degenerative changes in the intima of medium and large arteries. This degeneration includes accumulation of lipids, complex carbohydrates, blood and blood products, as well as, cellular debris leading to plaque formation [8]. As more plaques build up in the intima, arteries become narrow and stiffen. Eventually, enough plaques may build up to reduce blood flow through the arteries. This results in blocking a blood vessel or vessels that feed the heart, precipitating a heart attack. If plaques block blood vessels that feed the brain, it can cause a stroke. On the other hand if blood supply to the arms or legs is reduced, it can lead to gangrene or paralysis [9]. Treatment of the atherosclerotic conditions of cardiovascular systems with procedures such as coronary artery by-pass graft (CABG), insertion of stents as well as use of various pharmaceutical agents to treat hypertension, diabetes, dyslipidaemia, pose an enormous economic, as well as, social burden on the society.

Cessation of smoking, control of blood pressure and blood levels of glucose, low density lipoprotein cholesterol (LDLC), as well as, elevation of high density lipoprotein cholesterol (HDLC) levels remain the most effective long-term options for controlling atherosclerosis [6]. More emphasis has been focused on the management of cholesterol, primarily through lifestyle and drug therapy. Drug therapy offers numerous options, with each drug class dealing with the disease state through its own unique mechanism of action. In addition, different cholesterol lowering drugs or non-pharmacological treatments can significantly reduce morbidity from CVDs and the related coronary events.

Two different classifications for hyperlipidaemias are; the Fredrickson classification [10] and the WHO classification [11], both based on the levels of lipoproteins, triglycerides and chylomicron in the blood.

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Lipoproteins are small spherules that transport fats in the body and consist of cholesterol, triglycerides and phospholipids.

Lipoproteins are classified as chylomicrons, very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), LDL and HDL [12] based on their electrophoresis, density and composition [13–20], the HDL being the smallest, but most dense amongst various lipoproteins [12]. Apolipoproteins found on the outer surface of lipoprotein, make them soluble in plasma [21].

The terms “good” and “bad” cholesterol refer to HDL and LDL, respectively. High levels of LDL are associated with coronary atherosclerosis, whereas, high levels of HDL appear to protect against CVD's [22–26].

2. Pathways of lipid transport

Cholesterol is essential for the production of hormones and vitamins in the body, as well as, for the integrity of cell membranes. The lipid metabolism and transport involves exogenous and endogenous pathways in the body. Liver and intestine are the main organs involved in the lipid and lipoprotein metabolism [27]. Various enzymes namely, lipoprotein lipase [28], hepatic triglyceride lipase [29], lecithin cholesterol acyl transferase (LCAT) [30], cholesterol ester transfer protein (CETP) [31], microsomal triglyceride protein (MTP) [32] and acyl CoA cholesterol acyl transferase (ACAT) [33] are involved in these lipid metabolic processes.

In the exogenous pathway [34], chylomicrons transport dietary lipids that are absorbed from the intestine *via* the systemic circulation. In the endogenous pathway [35], the liver assembles and secretes triglyceride-rich VLDL particles, which transport triglycerides from liver to the peripheral tissues.

In reverse cholesterol transport (RCT) pathway cholesterol is transported from atherosclerotic plaques or other lipids back to the liver to be excreted into the feces through bile [35]. The cholesterol from cells and their turnovers are recovered and reincorporated into IDL pool or returned to the liver [36].

3. Antihyperlipidemic agents currently used in therapy

Antihyperlipidemic drugs are broadly classified into 5 main types (Table 1) [5].

Though drugs of various categories acting through different mechanisms are available for the management of hyperlipidaemia, there are a few limitations [37] associated with the anti-hyperlipidemic therapy as enlisted below;

a) Drugs like clofibrate, nicotinic acid, D-thyroxine etc., are not very effective therefore, new drugs are required for treatment of the hitherto untreatable cases of Type II hyperlipidaemia.
b) New drugs, able to block the stimuli responsible for the formation of an atherosclerotic lesion need to be developed.
c) Furthermore, specific drugs, which could bring about regression of the already existing atherosclerotic lesions, in the blood vessels are the need of the hour.
d) The most widely used “Statins” suffer from limitations like, intolerance and adverse effects, often achieving only 40% risk reduction and sometimes even ineffective.

Therefore, novel potential molecular targets for new drug discovery research (NDDR) for antihyperlipidemic therapy are being searched and investigated. Though, earlier this topic has been reviewed [37], the interest in antihyperlipidemic research, as well as, the constant development in the field, makes it necessary to have a periodic update on this subject.

This review covers in details the roles of these twenty different molecular targets in the biochemical and biosynthetic lipid pathways, literature reports on their recent studies till 2013, as well as, information on some molecules identified as their agonists/antagonists, to help design novel new chemical entities (NCE's). The X-ray crystal structures of many of these molecular targets are also dealt with and could be useful for molecular docking studies. Further, the biochemical assay procedures for the *in vitro* evaluation of potential leads against these targets have also been provided.

4. Current drug targets for antihyperlipidemic therapy

4.1. Molecular entities involved in absorption of cholesterol [inhibition of cholesterol absorption]

Identifying entities in the body responsible for absorption of the dietary cholesterol and blocking them specifically, is an area of

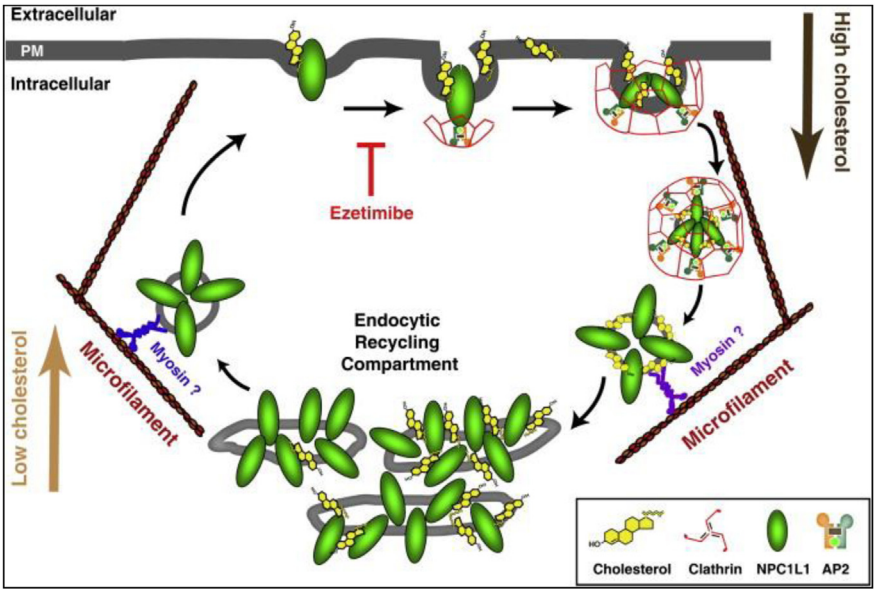

Fig. 1. NPC1L1 protein and ezetimibe as its blocker.