Models to Study Atherosclerosis: A Mechanistic Insight

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Abstract: The recent failure of candidate drugs like cholesterol ester transfer protein (CETP) and acyl-CoA:cholesterol acyltransferase (ACAT) inhibitors calls for a revised approach for screening anti-atherosclerotic drugs and development of new models of atherosclerosis. For this it is important to understand the mechanism of the disease in a particular model. Models simultaneously showing hyperlipidemia, inflammation and associated complications of diabetes and hypertension will serve the purpose better as they mimic the actual clinical condition. Besides this, analyzing candidate molecules *in vivo*, *in vitro* and at various levels of atherosclerosis progression is important. Models based on various cells and process involved in atherosclerosis should be used for screening candidate molecules. The challenge lies in bridging the gap between genetically friendly small animal and human-like bigger animal models. Sequencing of the mouse and human genome, development of a single nucleotide polymorphism (SNP) database and in silico quantitative trait loci (QTL) linkage analysis may enhance the understanding of atherosclerosis and help develop new therapeutic targets.

Keywords: Atherosclerosis, mechanism, animal, cell, model, target, assay, complication.

INTRODUCTION

Atherosclerosis is a complex disorder [1-4]. Initial events include endothelial injury and monocyte activation [5, 6]. However the type and stimulus of injury triggering atherosclerosis is still an area of active research [5, 6]. With the help of various cell adhesion molecules and gap junctions, leukocytes adhere and migrate in to the endothelium [5, 6]. Monocytes differentiate into macrophages inside the vessel wall and form macrophage foam cells [5-7]. These cells interact with other cells like T lymphocytes [5, 6] and vascular smooth muscle cells (VSMCs) [5, 6], which migrate [5, 6], differentiate [5, 6] and proliferate [5, 6] and take positions in close proximity to these cells [5, 6]. Amplification of the inflammatory response [5, 6] coupled with enhanced migration, proliferation and differentiation of inflammatory cells accounts for atherosclerosis progression [5, 6]. Secretion of various extra cellular matrix proteins by VSMC ultimately leads to the formation of fibrous plaque [5, 6]. Vessel microenvironment is compromised due to extensive biochemical and molecular changes and beneficial processes like phagocytic clearance of lipid-laden macrophages is hampered [5, 6]. Under such conditions cells undergo necrotic death and release various inflammatory cytokines, lipids, and cellular content to form a lipid rich necrotic core [5, 6]. All these processes contribute to the formation of an atherosclerotic plaque [5, 6]. Unstable plaques are prone to rupture due to degradation of extracellular matrix proteins by released metalloproteases [5, 6] leading to various complications, depending on the site of vessel blockage [5, 6]. This leads to exposure of blood to tissue factor (TF), thus activating the coagulation cascade and fibrin deposition and activating and recruiting platelets to form a thrombus [5, 6].

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This review covers all the aspects of models of atherosclerosis. This includes animal models [8-12], lower organisms [13] genetic models [14], in silico [14, 15], analytical [16], kinetic models [17], *in vitro* models and also target-based models. The importance of target-based models can be derived from the mechanism of atherosclerosis discussed in the review. Thus, it addresses not only the model but also the mechanism of disease manifestation in them. It also describes in brief how these models can be used for the assessment of various drugs. Although reviews on animal models of atherosclerosis have been published [18-24], there are almost none for the *in vitro*, cell and target based models, which this review will cover. Besides updating all the models, the present review approaches the models in a mechanistic way and thus blends classical animal models with recent biochemical and molecular findings. This will help in understanding the disease process and designing better strategies including models to study atherosclerosis.

ATHEROSCLEROSIS: COMPLICATIONS AND FAILURES

Failure of ACAT [25-28], and CETP [29] inhibitors are a setback in the treatment of atherosclerosis. These observations emphasize the fact that a candidate molecule should show a protective effect in several models of atherosclerosis. Furthermore, studying a disorder in isolation may not lead to clinically relevant benefits. It is often observed that those suffering from atherosclerosis, also have diabetes and insulin resistance [4, 30-32]. More evidence for this concept comes from many basic [33, 34] and clinical observations [4, 32, 35, 36]. Dyslipidemic patients suffering from diabetes and insulin resistance may show better cardiovascular improvement than the dyslipidemic alone, when treated with PPAR (peroxisome proliferator-activated receptor) α agonists [6, 37]. Similarly thrombotic events observed in atherosclerosis [38-42] and the common use of anti-platelet drugs in patients who have undergone balloon angioplasty emphasizes that

1570-1611/09 $55.00+.00

thrombosis is central to atherosclerotic complications [43-46]. Similar findings have shown that anti-platelet drug-eluting stents to be more protective against restenosis in atherosclerotic patients suffering from diabetes [47]. However, it can also be argued at the same time that since the incidence of restenosis is more in diabetics, the chances of seeing protection is more.

The existence of hypertension along with atherosclerosis is common [48-50] with evidence that shear stress influences the development of atherosclerosis [49, 51, 52]. Activation of the renin-angiotensin system (RAS) in adipose tissue may represent an important link between obesity and hypertension [53]. Plasma-derived angiotensin II (AngII) exerts potent vasoconstrictor effects on resistance arteries. In addition Ang II releases aldosterone from the adrenal glands, which in turn enhances renal tubular sodium reabsorption resulting in an increase in the effective plasma volume [54, 55]. Other proatherosclerotic effects of angiotensin have also been recognised [55, 56]. The potential link between Ang II and atherosclerosis is strengthened by the Heart Outcomes Prevention Evaluation (HOPE) trial where ACE (angiotensin converting enzyme) inhibition reduced the rates of death, myocardial infarction, and stroke in patients with atherosclerosis [57].

The effectiveness of statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors] faces the fact that many patients who develop atherosclerosis have cholesterol below risk levels [58]. At the same time there is evidence that the protection exerted by statins is not only due to cholesterol lowering but also to other actions like inflammation, which plays a role in atherosclerosis progression [59, 60]. Thus, it is important to develop models of atherosclerosis that comprehensively reflect the clinical situation. A different mechanism of atherosclerosis in different animals may explain certain failures. For example, drugs affecting the reverse cholesterol transport (RCT) that are also in clinical trials [61, 62]. However, while screening these candidate drugs in animals one has to be careful of the interpretations. An example of this is CETP. This is a protein involved in human RCT but it is absent in mice [63, 64]. It follows that a candidate drug showing good results with respect to RCT in a mouse model, may behave differently in humans. Attractive molecules like the CETP inhibitor torcetrapib have faced failure in clinical trialls and it is still being debated whether it was the mechanism or the structure of the molecule, which lead to its failure [29]. A combination of atorvastatin with torcetrapib lead to increased myocardial infarction, angina, heart failure, revascularization procedures when compared with atorvastatin alone [29]. However, in an other study, although there was no protection with the candidate drug, no major adverse effects were noticed [65]. This may be a structure specific effect. At the same time lipoprotein a [Lp(a)] is absent in mice and many other animals [66]. Therefore, the species specific presence/absence of these proteins will affect the candidate drug is unknown until evaluated in a clinical setting.

ACAT inhibitors are facing failures in clinical trials even after more than 2 decades of research [25-28]. ACAT2 esterifies the free cholesterol that forms the core of lipoproteins assembled in hepatocytes and intestinal epithelium, whereas ACAT1 acts in macrophages [25]. Several ACAT inhibitors failed in clinical trials after showing very promising results in animal models [25-28]. This raises the question about the suitability of the models used. Time of animal sacrifice and the sites of lesion analysis may determine outcome [25, 67-72]. Evidence suggests that different lesion sites may respond differently to the same drug [67]. Therefore, it is important that the lesion being analyzed should be similar to humans in its nature and location [67]. Equal importance to plasma lipid levels has to be given and mere significant changes are not sufficient [67]. Lesion analysis at varying plasma lipid levels may yield variable results. These points are also important when comparing data from 2 different studies. Answer to the failures also comes from the data regarding the overall effect of these inhibitors [25, 67-72]. Although ACAT inhibitors make more cholesterol available for RCT, too much of it can induces macrophage apoptosis and plaque rupture in atherosclerosis [73-76]. Screening of these inhibitors in animals, which can take care of excess cholesterol easily or have upregulated RCT and cholesterol efflux may provide inappropriate projections about the candidate molecules [25]. Therefore, while screening for ACAT inhibitors it also becomes important to ascertain the extent of cholesterol-induced apoptosis. However, if used in combination with inhibitors of apoptosis or activators of cholesterol efflux, these inhibitors may work but this also requires clinical testing.

Therefore, understanding the mechanism of atherosclerosis is a key factor.

MECHANISM OF ATHEROSCLEROSIS

Different biochemical and molecular events control the various processes of atherosclerosis, making it a very complex process [5, 6]. Activated monocytes adhere to the endothelium with the help of cell adhesion molecules and receptors like intercellular cell adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), selectins, very late antigen-4 (VLA-4) [5, 6]. This process involves distinct signaling mechanisms which leads to upregulation of cell adhesion molecules and receptors and gap junctions like connexin (Cx) 37 on the endothelium and monocytes [5, 6, 77]. Leukocyte rolling (L-selectin, P-selectin), arrest (E-selectin, Cx57, VCAM-1, ICAM-1) and diapedesis [ICAM-1, Platelet/endothelial cell adhesion molecule-1 (PECAM-1), junctional adhesion molecule-A (JAM-A), Cx 43] leads to their accumulation inside the endothelium [78, 79]. These adhesion molecules and gap junctions are potential therapeutic targets as are the cellular signaling like activation family of protooncogenic tyrosine kinases (src kinases), phosphoinositide 3 (PI3) kinase -AKT, p38 mitogen activated protein kinase (p38 MAPK) and nuclear factor-kappa B (NFkB) that are associated with their upregulation [6, 80-85].

Macrophage chemotactic protein-1 (MCP-1) and macrophage migration inhibitory factor (MIF) play an important role in monocyte activation, migration and differentiation [6, 81, 82, 86-90]. MCP-1 receptor, C-C motif chemokine receptor–2 (CCR2) knockouts show reduced atherosclerosis [82]. MIF and chemokine receptor also play an important role in the chemotaxis and upregulation of cell adhesion molecule [6, 84, 91] and are areas of future therapeutic intervention [6, 78, 92]. An inflammatory response seems to am-

plify these processes [5, 6]. Once inside the vessel wall monocytes differentiate into macrophages in presence of macrophage-colony stimulating factor (M-CSF), granulocyte macrophage colony stimulating- factor (GM-CSF) and modified lipids [5, 6]. These differentiated macrophages accumulate modified lipids *via* specific receptors like macrophage scavenger receptor (SR) A, CD36 and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) [5, 6] and pinocytosis [93]. All of these are areas of active research and being developed as targets of atherosclerosis. Enzymes like lipoxygenase (LOX) 15, 5LOX and inducible nitric oxide synthase (iNOS) bring about oxidation of low density lipoprotein (LDL) to form oxidized low density lipoprotein (Ox-LDL) [5, 6]. iNOS, NADPH oxidase, cyclooxygenase (COX), LOX12/15 and mitochondrial dysfunction contribute to free radical generation and protein modifications observed during atherosclerosis [5, 6]. Since oxidative stress contributes to atherosclerosis progression, several antioxidants are in clinical trials for this disorder [94]. Use of COX-2 inhibitors is often accompanied with myocardial infarction and thus it has a major drawback [95]. It is believed that selective COX-2 inhibition disturbs the thrombotic equilibrium and creates an imbalance between anti and pro-thrombotic factors by inhibiting endothelium-derived prostaglandin (PG) I_2 while sparing platelet-derived thromboxane [95].

The endothelium [96] promotes anti-thrombotic events by releasing nitric oxide (NO), prostacyclin (PGI2), adenosine nucleotides which inhibit platelet adhesion and aggregation [96]. Tissue factor pathway inhibitor (TFPI), thrombomodulin (TM), heparans and dermatans released by the vessel wall are inhibitors of the coagulation pathway [96]. Tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) bring about fibrin cleavage [96] and NO and interleukin (IL)-10 suppresses adhesion and aggregation of blood platelets [96]. However, at the same time mediators like von Willebrand factor (vWF), P-selectin and IL-8 released by the endothelium promote platelet activation and prothrombotic events [96]. TF, factor Va, phosphatidylserine activate the coagulation cascade [96]. Plasminogen activator inhibitor-1 (PAI-1) is involved in fibrinolysis [96]. Adhesion molecules, inflammatory mediators like tumor necrosis factor (TNF) α and CD40L released by platelets and endothelium promote formation of platelet leukocyte co-aggregate and thrombosis [96]. Platelet activation, besides creating a prothrombotic environment [36, 97] also leads to an increase in platelet-derived growth factor (PDGF), lysophosphatidic acid (LPA) and 5-hydroxytryptamine (5-HT). These agents promote smooth muscle cell (SMC) migration and proliferation [36, 97].

Inside the macrophages, the enzyme ACAT-1 converts free cholesterol, released as a result of lysosomal degradation, into cholesterol esters [7]. These give macrophages the characteristic foamy appearance and hence the name "foam cell" [7]. All cells including endothelium, macrophages and VSMCs accumulate these lipids to form foam cells, which ultimately contributes to the formation of atherosclerotic plaque [98, 99]. Oxidative stress contributes to foam cell formation by generating more oxidized lipids [5, 100]. Recently c-jun-N-terminal kinase-2 (JNK2) has been postulated to play a role in macrophage foam cell formation and atherosclerosis progression [6, 101]. A similar enzyme, ACAT2, present in the intestine, facilitates the uptake of chylomicrons [27]. Cholesterol inside the macrophages is routinely expelled by transporters like ATP-binding cassette transporter A1 (ABCA1), ATP binding cassette transporter G1 (ABCG1), SR B1, caveolins and sterol 27-hydroxylase to acceptors like HDL and apolipoprotein (Apo) A-1 [102]. This forms an important step of RCT a process by which excess cholesterol is removed from the macrophage and vessel wall to the liver or intestine for metabolism and excretion [102]. Although several proteins mediate the processing and uptake of effluxed cholesterol before it is finally excreted from the liver, HDL takes center stage in this process and therapeutic interventions targeting this process have a bearing on the plasma HDL-cholesterol levels [103-106]. It is well understood that from the early days of the Framingham Heart Study, that HDL-cholesterol levels are a more potent risk factor for coronary artery disease than LDL-cholesterol, total cholesterol or plasma triglyceride [107, 108]. Therefore, strategies affecting the RCT in such a way so as to increase the HDL-cholesterol are being actively pursued [103-106]. Apo A1 forms nascent discoidal HDL (ndHDL) particles on reacting with serum phospholipids [102]. This is an acceptor of effluxed cholesterol from macrophages and endothelium and is esterified by the enzyme lecithin: cholesterol acyl transferase (LCAT) [102]. Further action by enzymes like phospholipid transfer protein (PLTP) leads to formation of more mature HDL particles (HDL2) [102]. PLTP also has a role in generating pre β-HDL, which is an important acceptor of cholesterol at the plasma membrane of the effluxing cells [102, 107]. Since PLTP contributes to the transport of the surface remnants after lipolysis of triglyceride rich food and ultimately helps in generation of pre β-HDL, it also contributes to lowering the atherosclerotic burden [102, 107]. Similarly enzymes like lipoprotein lipase (LPL) and hepatic lipase (HL) also contribute to generating pre β-HDL [102, 107]. HL facilitates the conversion of triglyceride rich HDL particles (HDL2) to HDL3 [102, 107]. Regulation of HL and PLTP is crucial in RCT [102, 107]. The protein CETP which is secreted by liver, binds to HDL and brings about the transfer of cholesterol ester from HDL to very low density lipoprotein (VLDL) and LDL and in turn transfers triglyceride from the latter to HDL [102, 107]. Cholesterol esters can thus be removed from the liver by low density lipoprotein receptor (LDLR) [102, 107]. This calls for an anti-atherogenic effect of CETP. However, at the same time since it is leading to an increase in LDL-cholesterol, a decrease in HDL-cholesterol may lead to proatherogenic events [102, 107]. Therefore, caution is to be observed when targeting this molecule for atherosclerosis treatment. These aspects should also be looked into while evaluating the failure of CETP inhibitor, torcetrapib [102, 107].

Atherosclerosis is now considered an inflammatory disorder and inflammation is being considered as an attractive therapeutic target [59, 60]. One of the major challenges is to connect dyslipidemia with the increased inflammation observed during atherosclerosis [59, 60]. Toll like receptors (TLR) are a class of pattern recognition receptors, which besides taking part in inflammatory response also regulate cell survival and cell death of lesion macrophages [6, 109-111]. Thus, they regulate the development of the lipid rich necrotic core. Nuclear receptors on the other hand play a

dual role in atherosclerosis by mediating changes in both inflammatory and lipid pathways [6, 112-116]. The anti-inflammatory effect of liver X receptor (LXR) and PPARγ ligands is mediated by trans repression of inflammatory targets genes like TLR and NFkB [6, 112, 113, 116, 117]. However, these receptors also regulate fatty acid metabolism in a number of ways and may affect the process of atherosclerosis in several ways [6, 112, 113, 116, 117]. The problem with classical LXRs is that beside their protective anti-inflammatory effect their activation also leads to the increase in fatty acid and triglyceride synthesis [118-124]. Since nuclear receptors like LXR and PPAR heterodimerize with the retinoid receptors leading to their activation, retinoid receptors can also be targeted in atherosclerosis [125-127]. A more recent approach is to exploit the process of transrepression in case of nuclear receptors [112, 113, 116, 117]. In case of novel specific PPARγ and dual PPARα/γ agonists, safety concerns have led to their discontinuation in clinical trials [128]. These include associated carcinogenecity observed in rodents, signs of myopathy and rhabdomyolysis, increase in plasma creatinine and homocysteine, weight gain, fluid retention, peripheral edema and potential increased risk of cardiac failure [128]. The toxicological side effects observed are believed to be very compound specific [128].

Macrophages presents entitities like chlamydia pneuminiae, herpes simplex, cytomegalovirus, heliobacter pylori, and lipid derived immunogenic neo epitopes to T cells in the atherosclerotic plaques to start a series of immunological events [129]. The type of cytokine, growth factor and other cytokines released as a result of these interactions, ultimately decide the fate and the type of inflammatory response [129]. The T cell releases both anti-inflammatory [IL-5, IL-10, transforming growth factor β (TGFβ)] and pro inflammatory cytokines (interferon gamma (IFN-γ), IL-4) [129]. Which stimulus triggers which type of cytokine is the real challenge for researchers and if one could just increase the anti-inflammatory response during atherogenesis then this may be beneficial therapy wise. T cell activation also activates macrophages which in turn produce pro atherogenic mediators like proteases, show increased uptake of Ox-LDL, increased TF expression, secretion of reactive oxygen species (ROS), reactive nitrogen species (RNS) and pro inflammatory cytokines IL-1, IL-6 and TNF-α [129]. Secretion of various chemokines also amplifies leukocyte migration to the endothelium and regulate atherosclerosis progression [92]. Products released as a result of 15-LOX mediated arachidonic acid (AA) and linoleic acid (LA) acid oxidation, have been shown to be proinflammatory and prothrombotic [130, 131]. 12/15-LOX can regulate the expression of key proinflammatory, pro atherosclerotic T helper (Th)1 cytokine, IL-12 [132]. Phospholipase A_2 (PLA_2) activation also leads to the generation of lipid-derived inflammatory mediators including platelet activating factor (PAF), AA and prostaglandins (PG), all contributing to the generation and amplification of an inflammatory response [133, 134]. AA by the action of LOX and five lipoxygenase activating protein (FLAP) gets converted to leukotrienes, which play a role in inflammation and vasoconstriction thus increasing atherosclerotic load [135, 136]. They can be targeted for anti-atherosclerotic therapy. Isoprostanes released as a result of non-enzymatic degradation (lipid per oxidation) of AA, act on thromboxane prostanoid (TP) receptor to promote platelet aggregation and smooth muscle contraction [137]. AA metabolism in platelets due to COX-1 and thromboxane (TX) synthase leads to the generation of prostaglandin H2 (PGH2) and TXA2, respectively [137]. TXA2 acts on the TP receptor to promote platelet aggregation and smooth muscle contraction [137]. However, PGH2 generated from AA by the action of COX-1 and 2 in the endothelium gives rise to PGI2 by the action of PGI2 synthase [137]. PGI2 acts on the PGI2 receptor (IP receptor) to inhibit platelet aggregation and smooth muscle relaxation [137]. A disturbance in the dynamic balance of the above two processes may lead to prothrombotic changes [137]. Antioxidants also block the generation of isoprostanes by inhibiting lipid peroxidation of AA [137].

Cell proliferation in atherosclerosis leads to more complex lesions and plays a fundamental role in plaque formation and rupture [98, 99, 138-142]. Macrophage and VSMC proliferation observed during this disorder prolongs their presence in the vessel wall and hence increases the chances of plaque formation and rupture [98, 99, 143, 144]. However, increase in macrophage content is associated with unstable plaque [98, 145], the increase in VSMC content [99, 145] makes the plaque more stable due to the shielding of vessel contents from the outside environment [98, 99, 145]. However, VSMC proliferation observed after balloon angioplasty and stent implantation leads to restenosis [58, 146, 147]. Besides this vascular remodeling has also been said to be responsible for this [148, 149]. Matrix metalloproteinases (MMPs) also influence survival, proliferation and migration of VSMC [141]. VSMC apoptosis induces plaque vulnerability and apoptosis [150]. mTOR inhibitor rapamycin, which inhibits VSMC proliferation, is in effective use in clinic and is applied on stents for preventing restenosis [146, 147, 151]. Defective removal of macrophages, their necrotic cell death, releases MMPs e.g. MMP3 which degrade the extracellular matrix and result into release of TF and activation of coagulation cascade and thrombosis [152, 153].

ANIMAL MODELS OF ATHEROSCLEROSIS

A wide range of animals has been used to study atherosclerosis, as discussed below.

Hamster

Golden Syrian hamster, preferentially F1B strain is used as model for studying hyperlipidemia and atherosclerosis. Hamsters have quite a few similarities with humans which makes them a valuable model of atherosclerosis. These features include, LDL as the major circulating lipoprotein [154], similar cholesterol and bile acid metabolism [155], similar LDLR gene [156, 157] profound CETP activity[158], exclusive hepatic production of ApoB100 [159], human like lesions Ca deposits and necrosis in lesions [160]. Hamsters are also sound responders to dietary manipulations with respect to plasma lipid levels and lipid metabolism [161]. They do show influence of other metabolic disorders on lipoprotein metabolism [162, 163], and can develop extensive hypertriglyceridemia [154]. APA strain Syrian hamsters show signs of hypercholesterolemia, hypertriglyceridemia and atherosclerotic lesions under diabetic condition induced by streptozotocin (STZ) and thus is a good model to study atherosclerosis along with its complications [164, 165]. Hamsters develop diabetognic atherosclerosis characterized

by accelerated atherosclerotic plaque formation and vascular dysfunction in diabetic environment, thus providing a model to evaluate the anti-atherogenic effect of hypolipidemic drugs and antioxidants [163, 166]. Hamsters also respond to inflammatory regulations in atherosclerosis, and studies have shown changes in SRB1 expression, apolipoprotein levels and lipid metabolism after infection (endotoxin) and/or inflammatory stimulation [167-169]. Hamsters also show diet specific change in cytokines (TNF-α, IL-1α, IL-1β, IL-6) production [170]. Since this model responds well to dietary modifications, it is excellent for studying diet-induced plasma lipid levels and effect of hypolipidemic agents. Similarity with the human LDLR gene, make it ideal to study LDLR antagonists and also useful for drugs which interfere with CETP activities and RCT [171]. Hamsters can also be used to evaluate candidate drugs affecting the inflammatory pathway, since they do show signs of inflammation as mentioned above. However, the major limitations include lack of spontaneity in lesion formation and absence of advanced atherosclerotic lesions and plaque rupture. Furthermore, platelets are much less sensitive towards hyperlipidemia in this species [172].

Guinea Pig

This is a useful model of dyslipidemia and to investigate hypocholesterolemic drugs [173]. Their human-like features include, RCT components e.g. CETP [174], LCAT [175], LPL [176], majority of circulating cholesterol as LDL [177] and moderate rates of hepatic cholesterol synthesis [177] and catabolism [178]. They respond well to dietary cholesterol [179], fibres [178] and saturated fat [180]. Mechanism of apical sodium dependent bile acid transporter (ASBT) inhibitors [181], statins [182] and drugs interfering with triglycerides metabolism can also be explored [183,184]. Guinea pig models also exhibit elevated level of atherosclerosis linked inflammatory components (IFN-γ, TNF-α, IL-1β, IL-8, and MCP-1) in diet-induced atherosclerosis [185]. A study showed that polymorphonuclear leukocytes (PMN) obtained from hyperlipidemic guinea pigs are associated with an augmented generation of ROS by increasing the expression of protein kinase C (PKC) alpha, betaI and gp91phox and pitavastatin has an inhibitory effect [186]. Ovariectomized guinea pigs have a plasma lipid profile similar to postmenopausal women [187]. High plasma Lp(a) is associated with coronary heart disease and other forms of atherosclerosis in humans, and the presence of Lp(a) in guinea pigs [188], makes them useful to assess the role of this lipoprotein in atherosclerosis. Guinea pigs are a model for dietary interventions and provide an opportunity to study the influence of gender and hormones on lipid metabolism [187]. The major limitation of this model is the requirement of vitamin C [189] as dietary supplement, which has antioxidant activity and may interfere in atherosclerosis development [190]. They do not develop advanced atherosclerotic lesions, and are not a well-established model for atherosclerosis progression [190].

Rabbit

Rabbits are the most frequently studied animal model for spontaneous [191, 192] as well as diet-induced atherosclerosis [193]. New Zealand White (NZW) rabbits are the strain commonly used [194]. Although they have low plasma total cholesterol concentrations and HDL as dominant lipoprotein [195], βVLDL becomes the major class of plasma lipoproteins when exposed to cholesterol rich diet [196-198]. In conjunction with chylomicron remnants βVLDL becomes highly atherogenic [199]. Besides the presence of pronounced CETP activity [200, 201], these animals show human-like Apo B [202], low HL activity [203] but lack an analogue of human Apo A-II [202, 204]. The NZW rabbit rarely shows spontaneous lesions [11] and on feeding with diet rich in saturated fat and cholesterol they form lesions rich in foam cells with some fibrous component in the ascending aorta and aortic arch along with xanthomatosis [205]. The Watanabe heritable hyperlipidemic rabbit develops spontaneous hypercholesterolemia [206, 207], has high plasma LDL, fibrous lesions which are rich in foam cells [208] and develop spontaneous myocardial infarction [209]. St. Thomas' Hospital strains manifests endogenous hypercholesterolemia and hypertriglyceridemia, and develops atherosclerosis with certain features closely resembling human disease [210, 211]. Availability of transgenic models such as human ApoE2 and Apo (a) rabbits [212, 213] provide a basis to understand disease progression and its correlation with the lipid environment and associated complications such as plaque rupture and aneurysm formation [127]. The expression of various inflammatory mediators IL-1β, MCP-1, 5LOX, PGE_2 [214, 215], COX-2 [216, 217], VCAM-1 [218], have been studied in this model and are said to be responsible for plaque formation and rupture. Lipid lowering in rabbit reduces TF expression, proteolytic and prothrombotic potential [219, 220]. Increased platelet aggregation have been found in hyperlipidemic rabbits [172]. This model has been used in restenosis studies arising as a result of balloon angioplasty [221, 222].

Low HL activity, and lack of an analogue of human Apo A-II, provides a unique system to assess the effects of these human transgenes on plasma lipoproteins and atherosclerosis susceptibility [223]. Due to their large size, imaging techniques such as ultrasound computed tomography and magnetic resonance imaging can be effectively applied to determine the plaque composition, distribution pattern, and somehow its vulnerability [224]. This model is also suited to study the effect of atherosclerosis associated complications such as hypertension [225] and diabetes [226] on disease progression. Since this model does not produce spontaneous plaque rupture, various manipulations (balloon injury) have been applied to study various aspects of plaque rupture [227]. The rabbit model can be used to study the expression of adhesion molecules, and production of cytokines and other inflammatory mediators in the presence or absence of candidate drugs. Among the major drawback is the absence of important RCT component, HL [203], spontaneous atherosclerosis is not observed and occurrence of cholesterol storage syndrome depends on high cholesterol feeding. At the same time the formed lesions are more fatty and macrophage rich than human and also differ in location [228]. Rabbits are not an effective model for drugs having activity on HL and Apo A-II [203, 204].

Mouse

Naturally mice are resistant to atherosclerosis progression [229], but due to the availability of an atherosclerosis susceptible strain and provision for generating knockout/trans-

genic lines, they are sought after models [230, 231]. Advanced genetic manipulations in this model have helped in generating information regarding atherosclerosis initiation, progression, advanced plaque formation and rupture [232]. The genetically engineered mice lacking genes involved in lipid transportation, metabolism help to elaborate their role in atherosclerosis and other cardiovascular disorders [229]. One susceptible strain C57BL/6 got major attention from researchers for atherosclerosis progression [233] and principally for generating knockout/transgenic lines. Many transgenic mice like ApoC-III [234, 235], ApoE3 Leiden [236, 237], CETP [230], sPLA2 [238, 239], ApoB100 [240], CETP- ApoB100 [240], LDLR-/- ApoB100 [241], hApoM transgenic [242] have been created and are useful in understanding the mechanism of the disease and candidate drug molecules. The major limitation with transgenic models is the non-physiological high expression levels, which may not be similar to humans. Knockout models like ApoE-/- [231, 243-247] and LDLR-/- [231, 247-250] have great utility in deciphering the molecular events of atherosclerosis and screening candidate drugs for anti-atherosclerotic effect. Mice models are well characterized for various aspects of disease progression like macrophage foam cell formation, the involvement inflammatory mediators [251-256], cell adhesion molecules [257, 258], smooth muscle cell proliferation [259], apoptosis [260] nitric oxide synthase regulation [261], endothelial function impairment and NO production [262-264]. Plaque rupture is also seen in ApoE -/- mice especially when exposed to western type diet [265]. These models can also be used to study atherosclerosis progression along with diabetes [9, 266] and obesity [267]. Since mice are well characterized and researcher friendly, they are strong tools to characterize the progression of atherosclerosis and study the involvement of various inflammatory mediators. With the help of transgenic and knockout lines, the role of various signaling proteins in atherosclerosis progression can be easily studied. Diabetes and hypertension both have a synergistic effect on atherosclerosis development in the mouse model and thus offers a tool to study the combination of these metabolic disorders. Various approaches applied to develop hypertension in atherosclerosis prone species (such as deoxycortisone acetate salt induction, AngII administration) resulted in accelerated atherosclerosis [268]. Another finding suggests increased plaque necrosis and atherothrombotic vascular disease in insulin resistant syndromes [269].

Major disadvantages of mice are that they are highly resistant to atherogenesis, need genetic manipulations and have high HDL. The RCT component CETP is absent [12] and there are difficulties in blood collection sampling and dissection of miniature vessels. Correlation with human populations is as yet unknown in some transgenic models [238]. Some knockout models need dietary modifications to develop atherosclerosis [231]. The high cost of experiment and lesions not very much similar to human are another disadvantage [245]. The model is not valuable for studies assessing dietary effects on lipoprotein metabolism [247]. Even genetically manipulated mice develop lesions very slowly with chow diet supplement and supplementation with high fat is necessary [250].

Swine

This animal has remarkable similarities of lesion distribution, pathogenesis, and morphology with humans [11]. These are commonly used for studying atherosclerosis and related complications [270, 271]. Lesions formed in swine are characterized by necrotic cores, calcification, neovascularization, and intraplaque hemorrhage that closely mimic advanced human atherosclerosis [272, 273]. Porcine species can develop atherosclerosis without cholesterol feeding [274]. On being fed a high cholesterol high fat diet swine show close resemblance with human lipid profile [275]. Familial hypercolesterolemic swine with elevated level of the Apo C-III, B, and E are also available [276]. This is an efficient model to study the exercise-induced changes in lipid metabolism [277] and to study vascular function [278]. Porcine platelet aggregation resembles humans [279] thus making them useful for inducing atherothrombotic complications. Miniature pigs that are fed with high cholesterol, high fat, high sucrose diet show elevated expression levels of various cytokines (EOTAXIN-2, granulocyte colony stimulating factor (G-CSF), ICAM, IFN-γ, I-309, IL-1α, IL-1β, IL-6SR, IL-8, IL-10, IL-11, IL-12P40, IL-12P70, IL-13, IL-15, IL-16, IL-17, IP-10, MCP-1, MCP-2, gamma interferon-induced monokine (MIG), macrophage inflammatory protein (MIP)-1δ, TGF-β, TNF-α, TNF-β, regulated upon activation normal T-cell expressed and secreted (RANTES) and tumor necrosis factor receptor-I (sTNFRI) [280, 281]. VCAM-1, ICAM, IL-1α, IL-1β, IL-6SR, MCP-1, MCP-2, TNF-α, TNF-β, were predominantly involved in the development of diabetes mellitus and atherosclerosis in this model [280, 281]. The effect of dietary cholesterol withdrawal on vascular inflammation, C reactive protein (CRP) level, and plaque stabilization has also been evaluated in miniature pigs [282]. Swine models can thus be effectively used to study the effect of drug/candidate molecules on lipid metabolism, inflammation, lesion formation and plaque rupture. The swine model can be used to study atherosclerosis-associated hypertension [270] and diabetes [271]. Large size swine are the effective model to study carotid artery stent techniques [283], and invasive therapies for the treatment of atherosclerosis [284, 285]. Availability of miniature pigs is another advantage for studies where size is a problem. Major limitations include requirement of high cholesterol diet (4–5% w/w) to induce atherosclerosis and very low baseline cholesterol level [12]. Spontaneity in development of metabolic syndrome and insulin resistance, is not common in this species [22, 286]. The difficulties in care and high maintenance cost has been overcome to some extent by the development of micropig and miniature swine [287, 288].

Avian

Avian species attracts many researchers by its ability to develop atherosclerosis spontaneously and/or diet induced [289-291]. Principally studied avian species include pigeon, chicken, Japanese quail, turkey [11] and parrots [292]. Pigeons got special attention due to relatively high plasma cholesterol levels [293]. Although basal plasma HDL levels are on the higher side, β VLDL and LDL become major lipid carriers when these animals are fed cholesterol rich diet

[293, 294]**.** Pigeons show similarity to humans in lipid metabolism and lesion progression [12]. Avians are susceptible to both spontaneous and diet-induced atherosclerosis [295]. Pigeons also have resemble humans in increased platelet adherence, thrombosis, and impaired vascular smooth cell and endothelial function [12, 296, 297]. Platelet factor-4 activation, elevation in thrombocyte adhesiveness, endothelial damage and sterol accumulations are the earliest events in the pathogenesis of spontaneous pigeon atherosclerosis [296-298]. White Carneau (WC) strain develops spontaneous atherosclerosis with defined lesions [12]. WC pigeon aortic smooth muscle cells (SMCs) lack a functional LDLR pathway and in this way resemble cells from human beings with homozygous familial hypercholesterolemia or from Watanabe rabbits [299]. Monocyte chemoattractants have also been analyzed in cholesterol fed WC pigeons [300].

African Grey and Amazon parrots are susceptible to atherosclerosis [211, 301, 302]. Risk factors to develop atherosclerosis include elevated cholesterol level, diet composition [301, 302], social stress and inactivity [292]. Parrots also show increased platelet aggregability and elevated plasma cholesterol level [301, 302] and polyunsaturated fatty acids ameliorate severe atherosclerosis in these birds [301, 302]. Limitations in parrots include, less information [292] and clinical signs are seldom seen [292]. In general, avians are non-mammalian and mechanism wise atherosclerosis is not well characterized. HDL is the major circulating lipoprotein. There is lack of Apo E [303], B48 [12], and chylomicron formation [12] as well as a large variation in time (12-16 weeks to 9-27 months [304-309] and cholesterol amount (0.5-5%) needed to develop atherosclerosis [304, 305, 310].

Dog

This species do not develop spontaneous atherosclerosis [11]. Besides dietary supplement rich in cholesterol and saturated fat, thyroid suppression is also required for atherosclerosis development [11]. On cholesterol rich diet treatment animals develop lesions throughout the arterial tree and coronary vessels accompanied with prominent vascular changes [311, 312]. Beagles show useful similarities with human in cholesterol synthesis, and lipoproteins level [313] and this model has been successfully used to demonstrate the effect of statins on cholesterol synthesis [313, 314]. Dogs treated with colestipol (a bile acid sequestrant) and mevinolin (a cholesterol synthesis inhibitor) produced a 3-fold increase in LDL binding activity on liver membrane [315]. The role of vascular NAD(P)H oxidase-derived superoxide anion (O^{2-}) in endothelial dysfunction in dogs with tachycardia-induced congestive heart failure (CHF) and the therapeutic effect of statins [316], the effect of antioxidant in hyperlipidemic dogs [317] has been studied. Miniature Schnauzer dogs have been used in various studies involving analysis of solid intraocular xanthogranuloma formation [318] and the prevalence and severity of hypertriglyceridemia with age [319]. Since this model has close resemblance with humans in cholesterol synthesis and lipoprotein level, it can be useful to screen HMG CoA reductase inhibitors. Due to size, dogs are imaging friendly. In addition, this model can be of good predictive value regarding hypocholesterolemic effect on disease progression in humans [313, 315, 320, 321]. Hypotensive, anti-atherogenic and coronary dilating effect of plant extracts has been evaluated in dogs [322]. A study conducted to find out the association between diabetes mellitus, hypothyroidism and atherosclerosis in dog, showed that diabetes mellitus and hypothyroidism are more prevalent in dogs with atherosclerosis compared to dogs without atherosclerosis on postmortem examination [323].

A study conducted on mongrel dogs showed that IL-10 has protective effect on cerebrovascular dysfunction induced by inflammation and significantly depressed adherence of monocytes to cerebrovascular endothelial cells and inhibited up-regulation of ICAM-1 and VCAM-1 [324]. Due to their large size, they can be easily applied to *in vivo* detection of vulnerable plaques [325] and other invasive techniques. Major limitations are absence of natural atherosclerosis development, poor response to dietary cholesterol [12] not well-characterized, large amount of experimental agents needed and ethical issues.

Rat

Generally rats are highly resistant to the development of atherosclerosis [22]. HDL is dominating lipoprotein in these animals. Sprague-Dawley rats develop hyperlipidemia by triton administration [326]. Lymphatic cholesterol transport system [327] and the rate of hepatic secretion of VLDL in triton-induced hyperlipidemic rat [328] has been explored. Corpulent rats strain developed by cross between Sprague–Dawley rats and spontaneously hypertensive rats (SHR) are hypertensive, obese, hyperlipidemic and hyperinsulinemic [22, 329, 330]. Advanced atherosclerotic lesions, reflecting aortic aneurysms are also observed [329, 330]. Another strain JCR:LA-cp is prone to atherosclerosis development and insulin resistance [331]. The cp/cp male phenotype develops extensive atherosclerotic lesions [332-334], displays increased activity of PAI-1, vascular dysfunction [335] characterized by impaired NO production and metabolism [22]. The CETP transgenic Fisher rat, shows large increase in non-HDL lipid when fed with high-sucrose diet with implications for RCT and atherosclerosis [336]. Increased expression of the inflammatory cytokines (TNFα, IL-1β, IL-8 and VCAM-1) and augmented foam cell formation found in chronic infection induced by chlamydia pneumoniae [337] in white-rats (*Rattus norvegicus*). The role of P-selectin in vascular inflammatory processes, has been evaluated in balloon injured rat carotid arteries [338]. Rats are potentially useful model for studying hypercholesterolemia along with hypertension. They exhibit augmented thrombotic response and develop coronary atherosclerotic lesions under hypertensive and hyperlipidemic conditions [339-341]. Elevated plasma cholesterol level and coagulation factors shows good correlation in these animals [342]. They can be good model for angioplasty restenosis [285]. Rats lack physiological resemblance on many aspects with humans that are pathophysiologically important [285]. Rat platelets are generally resistant in hyperlipidemic condition [172].

Sand rat (*Psammomomys obesus*), naturally become obese, insulin resistant and develop VLDL hyperlipidemia with energy rich (chow) diet [343-345, 22] and correlates with human type2 diabetes mellitus [22]. This can be an effective model to study the nature of hyperlipidemia and vascular reactivity in the insulin resistant state [346-348]; especially type 2 diabetes mellitus [347].

Non-Human Primate

Non-human primates (NHPs) are an excellent model to study cardiovascular disease plus metabolic syndrome [22], since they are phylogenetically close to humans, eat a similar omnivorous diet, have similar metabolism, and develop both metabolic syndrome and cardiovascular disease (CVD) as they age [349, 350]. Commonly used models are Macaques species (stumptail, rhesus, cynomolgous, and the pigtail), Squirrel monkey, green monkey and African baboon [11]. They develop spontaneous (in some species) and high fat high cholesterol diet-induced lesions [351]. Lesions are similar to those in humans and show plaque mineralization and calcification [352, 353]. Hypertension in these models shows deleterious effect on atherosclerosis development [354], thus they are extensively used to study the effects of hypertension on atherosclerosis [351, 354, 355]. African green monkey and other primates have been used to study the effects of oral contraceptives on plasma cholesterol [11, 356, 357]. The close resemblance of plasma lipoprotein-lipid level, plaque development and its calcification and mineralization with humans makes them an excellent model to study the correlation between plasma lipids and plaque development. The effect of the caloric restrictions on atherosclerosis development has also been evaluated in the rhesus monkey [358]. Squirrel and rhesus monkeys exhibit augmented (mild) platelet aggregation in hyperlipidemic condition [172]. NHPs can also be used to study atherosclerosis along with diabetes-hyperinsulinemia [359]. *Macaca nigra* is very valuable in studies focused on the interactions between atherosclerosis and diabetes [360]. Interactions between atherosclerosis and hypertension can also be studied effectively in NHPs [360]. Monkeys show good correlation between the levels of many coagulation factors and serum cholesterol [342], that may play role in atherogenesis. Lp(a) in conjunction with proinflammatory oxidized phospholipids act in atherosclerosis, coronary artery disease and cardiovascular events [361, 362]. Lp(a) is also potentially involved in atherosclerosis plus thrombogenesis [363-365]. The presence of Lp(a) in NHPs (particularly in rhesus monkeys and baboons) resembling that in humans [366, 367] represents a good model for the study of the structure and biology of Lp(a) and its involvement in atherosclerosis [368]. The major limitations include variations in site of lesions, expensive, difficult to house and handle, limited availability and ethical concerns.

Lower Organisms

Lower organisms like worms (*Caenorhabditis elegans*), fly (*Drosophila melanogaster*) and zebrafish (*Danio rerio*) are good tools to study metabolic disorders and atherosclerosis and past research has helped in the elucidation of genetic and biochemical background of metabolic disorders such as obesity diabetes and atherosclerosis [13, 369-371]. The insulin and insulin-like growth factor signaling pathway has been characterized in great detail in Drosophila and *C. elegans* [13]. ApoB (AI964937) is the main beta lipoprotein in zebrafish and whole animal protein levels are up-regulated in response to high fat feeding [13, 372]. As a vertebrate, zebrafish possesses many structural similarities with humans [372]. These animals are lab friendly and can be manipulated genetically. Easy genetic manipulation in lower organisms and the availability of genetically manipulated variants like mutant flies can deliver valuable information just like in mice [13, 373]. *Caenorhabditis elegans* and *Drosophila melanogaster* being invertebrates, have less similarity with humans.

CELL BASED MODELS

A wide range of cells participate in the process of atherosclerosis and can be used to study atherosclerosis progression and the effect of candidate anti-atherosclerotic compounds.

Macrophages

The recruitment of monocytes/macrophages to the arterial wall is an initiating event leading to atherosclerosis progression. This process is facilitated by the expression of endothelial adhesion molecules namely, ICAM [374-376] VCAM [374, 377-379] endothelial-leukocyte adhesion molecule (ELAM), as well as P and E selectins. The conversion of macrophages to foam cells by the accumulation of modified LDL, especially acetylated low density lipoprotein (AcLDL) and Ox-LDL, is another critical step in atherosclerosis development [380-382]. Since monocytes differentiate (MCSF, GMCSF, Ox-LDL) [383], proliferate (Ox-LDL,) [6,383] and die (Ox-LDL) [383], during the process of atherosclerosis, they can be tested on these aspects for the anti-atherosclerotic effect of candidate drugs. Macrophage infiltration, LOX-1 and MCP-1 are reduced by chronic HMG-CoA reductase inhibition by simvastatin (20 mg/kg) in common carotid artery of stroke-prone spontaneous hypertensive rats (SHR-SP) [384]. Olmesartan and pravastatin additively reduce the development of atherosclerosis in ApoE3 Leiden transgenic mice [236]. Atorvastatin inhibits macrophage accumulation of oxidized lipids by inhibiting endothelial and LPL expressed in human acute monocytic leukemia cell line, THP-1 macrophages [385]. Similar results have been obtained with simvastatin [386]. Fibrates have also been shown to inhibit cholesterol esterification in macrophages [387]. Inhibitory effects of fluvastatin on cytokine and chemokine production by peripheral blood mononuclear cells has been observed [388]. Any test compound can be evaluated in a similar way for its protective effect in atherosclerosis.

T Lymphocytes

The presence of activated T lymphocytes (principally CD4+ cells) in all stages of atherosclerotic lesion, give a potential clue for their participation in this disease [389]. The complete absence of lymphocytes reduces lesion formation in hypercholesterolemic condition [390, 391], which reveals their active participation [392]. The Th1 cell attracted attention regarding atherosclerosis progression because of the presence of its potential inducer IFN-γ, and IL-12 in lesions. Various reports suggest that Th1 cells are atherogenic [393, 394] whereas Th2 cells are atheroprotective [129, 395, 396]. One recent finding showed activation of LXRα and β on CD4 positive lymphocytes which reduces Th-1 cytokine expression in these cells [397]. The CD40-CD40L system in conjunction with T lymphocyte mediates various inflammatory responses in atherosclerosis [398]. The atherogenic (Th1), and atheroprotective (Th2) involvement of T lympho-

cytes in atherosclerosis are a valuable tool to study the cytokine regulated inflammatory pathways in atherosclerosis. Statins have an inhibitory effect on T cell activation [399, 400]. Production of inflammatory (IFN-γ,IL-12,IL-18,IL-4, TNFα) and anti-inflammatory (IL-10, TGFβ,IL-5) cytokines in the presence of modified lipids, and in co-cultures with macrophages, VSMC in the presence of test compounds can be used to screen potential candidate drugs [401].

Lovastatin inhibits T-cell antigen receptor signaling [402]. Statins also decrease T cell activation, the recruitment of monocytes and T cells into the arterial wall, and enhance the stability of atherosclerotic lesions [403]. Beneficial effects of anti-diabetic PPAR activators on atherosclerotic plaque development may be partly explained by their repression of MHC-II expression and subsequent inhibition of T-lymphocyte activation [404].

Natural Killer T (NKT) Cells

NKT cells are a specific type of lymphocytes that play protective role in many autoimmune disorders [405]. Their immune responses are mainly mediated *via* up regulation of Th2 (principally) and Th1 cells [406-408], suggesting their role in atherosclerosis development [405, 409]. The presence of CD1d-expressing cells in human atherosclerotic plaques suggest NKT cells presence in lesions [410]. This has been well characterized in lipopolysaccharide treated ApoE-/- mice [243, 411]. A significant reduction in atherosclerotic lesion in NKT cell–deficient CD1d-/- mice and in CD1d-/- -LDLR-/- mice has been reported when exposed to atherogenic diet [412]. Lovastatin, has been shown to inhibit mitogen-stimulated proliferation of natural killer cells *in vitro* [413] and test compounds can be screened in a similar way for their effect in atherosclerosis.

Vascular Smooth Muscle Cells

VSMCs synthesize fibrous protein (collagen) elastin and proteoglycans that provide extra strength to arteries. The death of SMCs in core of atherosclerotic plaques is critical to the weakening of plaque and its rupture. The migration of SMCs from media to intima and its cross talk with foam cells, Th cells, and cytokines (such as IFN-γ, IL-10) complicates atherosclerosis progression [5]. Human pulmonary artery smooth muscle cells (PASMC) can be used to assess the effect of inflammatory mediators on the expression of vascular adhesion molecules [414] and thoracic aorta derived SMCs are used to define the PDGF survival signals on vascular smooth cells [415]. In the presence of statins VSMCs decrease their binding affinity for LDL [416]. Statins also reduce the proinflammatory activation of human VSMCs [417]. The protective effect of N-3 PUFAs in atherosclerosis has been attributed to their ability to modulate VSMC proliferation, migration, and apoptosis [418]. Candidate drugs or test compounds can be evaluated in a similar way for their anti-atherosclerotic effect.

Endothelial Cells

Endothelial cells are unique. They prevent clot formation and act as barrier between circulating blood component and underlying tissue components. The interaction of circulating monocytes and expression of adhesion molecules on vascular endothelial cells are the initiating events of atherosclerosis and is an attractive target [5]. Endothelial-dependent relaxation is hampered in atherosclerosis due to impaired NO bioavailability produced from endothelial nitric oxide synthase (eNOS), which is important for vascular homeostasis and has anti-atherogenic action [419, 420]. This can be evaluated in a simple organ bath system [421]. Human umbilical vein endothelial cells (HUVEC) are used to define the role of various surviving factors such as hepatocyte growth factor, NF-κB in atherosclerosis [422] and to explore the involved signaling event [423]. Recently HUVEC was used to explore the anti-inflammatory effect of aspirin in presence of oxidized LDL [424]. Endothelial progenitor cells (EPCs) attracted special attention because of their ability to repair endothelium and initiate neovascularization. Circulating EPCs are markers for cardiovascular risks [425]. EPCs have also been proposed as heredity markers of atherosclerosis susceptibility [426]. Since endothelial cells secrete prothrombotic, anti-thrombotic and thrombolytic agents, they can be set up for evaluation of such activities in the presence and absence of test compounds [96, 427]. Simvastatin exerts a protective effect by regulating the chemokines and chemokine receptors on endothelial cells [428]. Fluvastatin exerts a protective effect on the endothelium through lipid-lowering independent effects [429, 430]. Rosuvastatin increases vascular endothelial PPARγ expression and corrects blood pressure variability in obese dyslipidaemic mice [431]. Adverse balance of NO/peroxynitrite in the dysfunctional endothelium can be reversed by statins [432]. Fluvastatin inhibits up-regulation of TF expression by anti-phospholipid antibodies on endothelial cells [433].

Adipocytes

Various experimental findings indicate that adipocytes act as a source of hormones and endocrine molecules known as adipokines [434], many of which have a potential role in atherosclerosis [435]. Adipocytes also have a potential role in cholesterol homeostasis [435]. Adiponectin has anti-inflammatory and atheroprotective properties [436]. Its plasma levels are low in obese individuals and weight loss restores levels [437]. Another adipokine, leptin, has atherogenic and thrombotic properties [435, 438]. The leptin receptor has been confirmed on human atherosclerotic lesions and its role has been explored regarding atherosclerosis and thrombosis in mice models [439, 440]. Leptin and adipocytokines seem to bridge the gap between immunity and atherosclerosis [441]. Adipocytes can be set up in presence and absence of candidate anti-atherosclerotic drugs for the secretion of such adipokines, which can be estimated by conventional methods [441-444]. Atorvastatin reduces TF expression in adipose tissue of atherosclerotic rabbits [445]. Atorvastatin also reduces PAI-1 expression in adipose tissue of atherosclerotic rabbits [446]. Atorvastatin can inhibit IL-6 secretion in adipocytes possibly through upregulating PPARγ, which may help to explain the anti-inflammatory effects of statins [447]. Adipocyte LPL expression is also induced after statin treatment [97]. Assays using the above parameters can be set up in the presence and absence of test compounds.

Hepatocytes

In mammals, hepatocytes play a key role in the whole body cholesterol homeostasis by fine tuning of plasma lipoprotein concentrations and cholesterol synthesis, relocation, and regulation [448]. HL, ACAT2, LDLR, CETP, ApoA-I, ApoE, SRB1, LXR are the principal components of hepatic cells which regulate cholesterol homeostasis. A recent finding indicates the role of nuclear receptors [LXR, and hepatocyte nuclear factor-4*α,* (HFN-4α)] in cholesterol efflux pathway [449]. Bile acids synthesized in liver, are key players in lipid absorption and excretion [450-452]. Hepatocytes can be used for lipid uptake studies and clearance from the body, lipid metabolism, lipid transportation, and cholesterol synthesis [453-459]. Fibrates down-regulate hepatic SRBI protein expression in mice and thus inhibit atherosclerosis progression [460]. The anti-inflammatory activities of PPARα activators and statins have been explored in hepatocytes [461]. It is believed that by preventing the reabsorption of bile acids, a minimally absorbed ASBT inhibitor would lower serum cholesterol without the potential systemic side effects of an absorbed drug [462]. A series of novel benzothiepines (3R,3R'-2,3,4,5-tetrahydro-5-aryl-1-benzothiepin-4-ol 1,1-dioxides) were synthesized and tested for their ability to inhibit the ASBT-mediated uptake of [^{14}C] taurocholate (TC) in H14 cells [462]. A transfected baby hamster kidney cell line (H-14) that constitutively expresses human ASBT can be used [463]. ASBT inhibitory activity is assessed on the basis of the ability of compounds to inhibit the cellular uptake of 5 μM [^{14}C]taurocholate during a 2 h incubation. Selectivity is tested in the same assay system using 5 μM [^{14}C]alanine instead of taurocholate to determine the effect on another cellular sodium-dependent cotransporter [462]. Hepatocytes can be tested for hypolipidemic effect by incubating them in presence or absence of test compound or statin and estimating the VLDL levels (measured by Apo B100) in HepG2 cells [464].

Mast Cells

Mast cells are involved in allergic and innate immune response and recent studies reported their presence in human atherosclerotic lesion [465]. Various *in vitro - in vivo* studies have shown their active participation in atherogenesis [466] by releasing proteases (interfere with arterial remodeling) [467], cytokines (activate vascular cells) [468], and chemokines (attract leukocytes) [469]. With the help of various inflammatory mediators released from mast cells these cells can be involved in atherogenesis [470, 471]. Few reports suggest the participation of mast cells in the genesis of vulnerable plaques [472, 473]. These cells can be set up in the presence of various candidate drugs and secretions of various mediators can be monitored by conventional methods. Mast cell accumulation has also been reported at the site of deep venous thrombosis, liver vein thrombosis and pulmonary embolism [474-476]. The inhibitory effect of statins on the growth and function of human mast cells and may be one of the beneficial pleiotropic effects of statins [477].

Dendritic Cells

Dendritic cells (DCs) are specialized antigen-presenting cells which initiate the primary immune response by the activation of T-lymphocytes [478]. The presence of DCs in early [479-481] as well as in advanced [482] atherosclerotic lesions potentially indicates their involvement in atherosclerosis progression. Endothelial dysfunction in atherosclerosis, regulates the DC adhesion and migration [483]. *In vitro* experiments show an increase in migration of DCs when endothelial cells are exposed to atherogenic conditions [483]. The presence of activated DCs alone or as cluster with T cells in atherosclerotic and rupture prone regions indicate their importance in atherogenesis and plaque rupture [482, 484, 485]. As majority of them are present in rupture prone areas of advanced plaques, DCs can be a useful marker for plaque vulnerability and any candidate drugs decreasing their population can stabilize plaques. Mature DCs express CD83 and they can be detected immunochemically in the lesions [486]. Besides this CD197, CD1a, CD4, CD8, CD80 are a few other markers of this cell [487, 488]. Maturation of DCs is suppressed by statins [489]. Preincubation of DCs with statins decreases their adhesion as well as recruitment to human microvascular endothelial cell line (HMEC-1) [490]. The immunomodulating effect of simvastatin on DCs is by favouring Th2 and inhibiting Th1 cell development [491].

Enterocytes

Enterocytes mediate the ingested and biliary cholesterol uptake and this serves as the rate limiting step in cholesterol absorption [492] and is a useful target for lipid-lowering approaches [493]. Ezetimibe, an inhibitor of intestinal cholesterol absorption, acts at the brush border of the small intestine and inhibits the uptake of dietary and biliary cholesterol into the enterocytes [494, 495]. Caco2 cells an intestinal cell line used in several studies to explore mechanistic aspect of dietary and biliary cholesterol uptake has been used to assess the efficacy of various inhibitors such as ezetimibe [494], SCH5803 [327], SC-435 (ASBT inhibitor) [463]. The effect of test compounds on lipoprotein production in Caco2 human intestinal cells can be evaluated by incubating for 24h with test agent or 10 μmol/L of atorvastatin. Chylomicron levels (measured by ApoB48) in Caco2 cells were measured using western blotting. Intracellular cholesterol levels can be measured using gas chromatography [464].

KINETIC MODEL

This model is based on the principle that a transition from one state to another, leading to a cardiovascular event obeys a simple exponential law [17]. This model keeps in mind the 2 concepts of atherosclerosis development [17]. Physical concept takes into account the magnitude of vascular stenosis causing functional cardiovascular ischemia [17, 496] and the biochemical concept is based on the inflammatory process associated with atherosclerosis progression and plaque rupture [17, 497]. According to the kinetic model, the normal, stenotic, inflammatory and event states can transition between each other [17]. The transition between the states is governed by rate constants, which in turn depend on many pathophysiological events taking place in atherosclerosis [17]. This model considers simultaneously the physics of anatomic stenosis and the chemistry of plaque instability for determining the dynamic processes that lead to atherosclerosis [17, 498, 499]. Kinetic data like time required for state-to-state transition is required for this model to be exploited to

its full potential. However, some observational data is available on the basis of which the utility of this model has been checked [500-503]. An example of this model is development of heart failure as the event state resulting from hypertension or ischemia as the intermediary states [17]. The drawback of this model is that it fails to consider genetic and environmental factors such as insulin resistance [17, 504]. Some support for this kinetic model also comes from experimental findings [17, 505-507]. This model needs validation and is very preliminary but it tries to blend the laws of physics and chemistry with biology.

ANALYTICAL MODEL

Importance of hemodynamics in atherosclerosis has been realized from the response to injury findings [508, 509]. Since atherosclerotic lesions are developed only in particular regions of the vessel wall, the structural aspects and fluidics become important aspects [510]. Atherosclerosis involves nanoscale fluid dynamics and macromoleculer transport at the arterial endothelium and thus the importance of thermodynamics and shear stress is taken into account while predicting the probability of atherosclerosis progression [510].

Thermodynamic Model

This model is based on the hemodynamic force exerted by the flowing blood on the endothelium [16]. This force affects the endothelium's physical and biochemical properties leading to its dysfunction [16]. The probability of its formation depends on the kinetic and static energy of a lesion [16]. It is based on the principle that to form a lesion there is some minimal energy required. At the same time since the blood flow will follow the principles of conservation of energy, there will be some kinetic energy associated with lesions, which depends on the interfacial shear resistance and the adhesive length over which the lesion is supposed to form [16]. At the same time the energy that is needed for lesion formation (static energy) will depend on the work done by the axial transient inertial force 'f' to get deposited on the vessel [16]. If static energy is more than the dynamic/kinetic energy, LDL will get deposited on the endothelium and in case of vice versa, it will keep flowing [16]. In such type of models factors like the rate at which blood flows, the stickiness of the endothelium will ultimately determine whether the lesion will form or not [16].

Dynamic Boundary Value Model

This model is based on the fact that atherosclerotic lesions are usually located in regions of reduced shear stress of the fluid [511-518]. The shear stress is often associated with flow separation and turbulence [511-518]. Reduced shear stress leads to the formation of a transient boundary layer in atherosclerotic lesion forming regions [511-518]. Atherosclerotic lesion formation depends on the plasma viscous flow in the transient boundary layer near the inner tube wall at an arterial branch point [511-518]. The model takes into account the Navier-Stokes equation for deriving the probability of lesion formation [16]. Parameters like velocity vector of the fluid, body force vector, pressure vector and viscosity, density of fluid are important for lesion development [16]. Factors like the axial velocity of the plasma fluid and the thickness of the transient boundary layer [16] may determine the ultimate outcome [16].

On the basis of the above models it can be concluded that the probability and location of a lesion depends upon regions of increased transient boundary layer and reduced surface energy of adhesion which answers why lesions are formed only in small regions of the entire vascular system [16]. Arterial branch points due to their structure tend to have an increased eddy velocity of the fluid and reduced viscous shear stress. This is responsible for reduced surface energy of adhesion, which brings LDL from the plasma fluid to the plasma – endothelial interface resulting in lesion formation. Although this model finds support in the literature [16], it needs more validation.

QTL ANALYSIS

QTL linkage analysis is aimed to find correlations between genotype and phenotypes by crossing inbred mice strains and using specific QTL softwares and identify genes contributing to the polygenic trait [519]. The result is expressed in the form of log of the odds (LOD) score. In this model 2 mouse strains of distinct phenotypes are crossed to yield F1 and then subsequently F2 progeny [519]. The F2 generation strains are subjected to genomic scans and linkage analysis for their genotype determination. This leads to the defining of chromosomal map loci by strain specific polymorphic marker, which spans the genome at small intervals [519]. After this initial mapping, secondary congenic lines are created by repeated intercrossing of inbred strains that differ significantly in the measured phenotypes to isolate the QTL locus from one strain onto the genetic background of another strain [519]. Recombinants selection helps in narrowing down the QTL locus for the identification of strain specific polymorphism and functional expression difference in specific genes [519]. Major disadvantage of this technique is that it is laborious and many intercrosses for determination of genotypes and phenotypes of hundreds and or thousands of mice. This may take years for analysis.

IN SILICO QTL MODEL

This model takes advantage of the mouse SNP database containing allele information of 15 inbred mouse strains [15, 519, 520]. Phenotype data of a particular trait is analyzed against the SNP database for the identification of SNP patterns that are similar among strains with similar phenotypes, but different among strains with different phenotypes [15, 519]. A further analysis is done to pin point the gene and mutation within the QTL [15, 519]. Critical advantages of this model includes reduced time of analysis and quick generation of data, no intercrosses to be performed and by the help of this model multiple strains instead of just 2 in classical QTL analysis can be analyzed [15, 519]. Using this model already 5 genetic loci associated with atherosclerosis in ApoE-/- mice have been defined [15, 519]. As a consequence of the sequencing of the mouse genome and availability of a more detailed mouse SNP database this model will get high impetus.

In silico method has the limitation due to the unequal distribution of marker information but with the increasing number of SNPs in the database this will be less of a prob-

lem in the near future. This method also fails to account for the epistatic genetic interactions and may also not detect phenotype-altering mutations that occurred after the strains diverged from each other since it relies on evolutionary derived genetic differences between the strains [15, 519].

PROCESS OF ATHEROSCLEROSIS AS MODEL

The process of atherosclerosis consists of many steps, which can be used to study atherosclerosis progression and the protective effect of test compounds, as discussed below.

Reverse Cholesterol Transport

This important process of atherosclerosis can be monitored by evaluating the activities of various proteins facilitating it. These include Apo A, HL, PLTP, CETP, HDL, ABCA1, to name a few. An increase in this process should ultimately increase the plasma HDL levels [61, 62, 521], which can be estimated by regular methods [521-523]. Animal models of atherosclerosis can be screened in the presence or absence of test compounds for increased level of plasma HDL and improvement in LDL/HDL ratio [524]. The LXR agonist T0901317 promotes the RCT from macrophages by increasing plasma efflux potential [523]. RADAR (Rosuvastatin and Atorvastatin in different Dosages And RCT) study showed that 10, 20 and 40 mg of rosuvastatin was significantly more effective than 20, 40 and 80 mg of atorvastatin in improving the LDL-C/HDL-C ratio in patients with cardiovascular disease and low HDL-C. However both drugs showed similar and significant increase in HDL-C levels [61, 525]. Since it is expected that an activation of the RCT pathway will ultimately lead to an increase in HDL-C levels, the benificial effects on the HDL levels seen in the RADAR study may be due the activation of RCT pathway.

Formation of Atherosclerotic Lesions

Assesment of atherosclerotic lesion formation is an important parameter for evaluating the protective effect of all anti-atherosclerotic drugs [42, 526-528]. Atherosclerotic animals with and without test compound are sacrificed and the aortic arch is removed, cleaned and cut open with the luminal surface facing up [101, 529]. It is immersion-fixed in 10% neutral buffered formalin overnight or 2-3 days [101, 529]. After rinsing in water, the aortic arch is thoroughly cleaned of adventitial fat. The inner aortic surface is stained with oil red O (1.0% w/v in 60% isopropanol) for 25 min at room temperature. After rinsing with 60% isopropanol and distilled water, the aorta is mounted on a glass slide with a glass coverslip and aqueous mounting medium containing glycerin [101, 529]. The oil red O-stained area was observed using zoom microscope and stained area was analyzed by image analysis software [101, 529]. Immunohistochemistry with macrophage, T cell or VSMC specific and inflammatory marker tells about the composition of the lesion [530-532]. In human advanced imaging techniques are required for monitoring lesion progression and regression [533]. On the basis of above parameters, statins have been shown to reduce atherosclerotic lesions both in animals and humans [236, 534, 535].

Angiogenesis

Besides its overall role in vascular remodeling, neovascularization within the vessel wall plays an important role in plaque destabilization and vulnerability [536-538]. Patients on statin treatment have reduced intraplaque angiogenesis in their carotid endarterectomy specimens when compared with patients not receiving this kind of drug [538, 539]. Migration and proliferation of endothelial cells in response to VEGF play an important role in angiogenesis associated to pathologies such as atherosclerosis, diabetes and tumor development [540]. PPARα agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition [541]. By using HUVEC and chick chorioallantoic membrane (CAM) models *in vitro* and *in vivo* respectively, angiogenesis can be evaluated in the presence of test compounds [540]. In this model fertile eggs are cracked on Day 4 of incubation and individually cultured in a covered glass dish at 37°C and 3% CO_2 in air and saturated humidity. Test substances are applied to the surface of the CAM within silastic rings. Digital images of the live CAM are captured using a binocular dissection microscope [542]. Similarly HUVEC cells are seeded on Matrigel and formation of vascular (tube) like structures is monitored in the presence or absence of test compounds. Pictures are taken by microscope and degree of cord formation is quantified by measuring the area and length occupied by the tubes [543-545].

Cell Differentiation

Since differentiation of monocytes to macrophages is one of the most important events of atherosclerosis, candidate drugs inhibiting this process can be suitable for atherosclerosis treatment [546]. For this assay, various monocytic cell lines like THP and Raw 264.7 can be taken. Cells are differentiated in presence of phorbol 12-myristate 13-acetate (PMA), Ox-LDL, MCSF or GMCSF [5-7, 547-551]. Up regulation of differentiation markers like CD11, CD14, type-I SR can be monitored for assessing differentiation [552-554]. In case of floating cells like THP, induction of differentiation leads to their attachment and this can be monitored biochemically or microscopically. *In vivo* differentiated macrophages can be detected by staining immunochemically with differentiated cell specific markers [532]. Lovastatin (5-15 μM) caused a significant dose-related reduction in steady state levels of type-I SCR mRNA in PMA-treated THP-1 cells [552].

Macrophage Foam Cell

Peritoneal animal macrophages or PMA differentiated THP cells are treated with Ox-LDL (40-100 μg/ml) for 24-48 h in the presence or absence of test compound [6, 7, 383]. Cells are stained with Oil Red O to assess the amount of lipid inside the cell [555, 556]. This can be assessed spectrophotometrically at 518 nm also after lysing the cells [216]. Cell surface receptors like CD36, SRA or LOX-1 can be monitored for increased macrophage foam cell formation [6]. An inhibition in their expression reflects in the inhibition of the process of atherosclerosis. Similar immunohistochemical staining can be done in animal aortic tissues [6, 101, 529, 532, 557]. Atorvastatin-mediated inhibition of macrophage

foam cell is accompanied by inhibition of Ox-LDL induced increase in the expression of SR CD68 and that of fatty acid binding protein 4 [558].

Leukocyte Migration Assay

This can be set up as any other migration assay. For assessing the migration of cell in response to endothelium activation, THP-1 monocyte migration can be assayed by using the ChemoTx kit (Neuro Probe) or Boyden chambers [559]. The lower chamber is filled with medium obtained after Ox-LDL or TNF-α treatment of endothelial cells (HUVECs). Monocytes are incubated in the presence or absence of test compound and after incubation for around 6h at 37°C; cells that migrate into the lower chamber are counted by flow cytometry or conventional methods [557]. Test agents like KR-31378 have been found to inhibit monocyte recruitment [557]. Simvastatin inhibits the migration and adhesion of monocytic cells and disorganizes the cytoskeleton of activated endothelial cells [560]. Lovastatin inhibits endothelial-monocyte cell interaction by down-regulating the expression of VCAM-1 and E-selectin by inhibiting the phosphoinositide 3 kinase (PI3-kinase)/protein kinase B (Akt)/NF-kappaB pathway in endothelial cells [561]. Similar types of assay can be set for SMCs [559].

Proliferation Assay

Macrophage proliferation can be determined by counting the numbers of macrophages 24 h after exposing them to varying concentrations of the drug, as described earlier [562, 563]. Briefly, peritoneal macrophages can be harvested and allowed to adhere in 6-well plates for 2 h [564]. Candidate drug can be added to 2 x 10^5 cells in siliconized polypropylene tubes. After overnight incubation, 10 µl of trypan blue solution is added to each tube followed by gentle shaking during incubation, for 2 min, and a 10-µl aliquot can be used for counting the number of cells in a hemocytometer. Proliferation can also be studied using MTT assay using MTT kit from ATCC following manufacturer's protocol [565]. Briefly, after plating the cells for 6-24 h, 10µl of MTT reagent is added followed by incubation for 2-4 h until a purple precipitate is visible. This is followed by addition of 100 µl of detergent reagent and left at room temperature for 2 h [565]. Absorbance is read at 570 nm. Simvastatin, lovastatin and mevastatin inhibit proliferation and invasion of melanoma cells [566]. Pitavastatin inhibits LPA-induced proliferation and MCP -1 expression in aortic SMCs [567].

Cell Adhesion Assay

Adhesion of THP-1 cells to HUVEC cells can be assayed as previously described [559, 568]. Briefly, HUVEC cells can be plated in a 6 well culture plate at a cell density of $1x10^5$ per well and cultured to 90% confluency. The cells can be treated with various drugs for appropriate times. THP-1 ($2x10^4$ cells/ml) cells in an exponential growth phase is added to each well and incubated with HUVEC cells for 30 min at 37^0C.The unbound cells are washed 3 times with the RPMI media and the total number of cells adhered are counted randomly in 4 randomly selected optical fields per well. Fluvastatin, inhibits expression of adhesion molecules on human monocyte cell line [569]. Similarly adhesion of platelets can be done in presence or absence of test compound by performing static or flow adhesion assays [570]. In these assays washed platelets are added to laminin, collagen, fibrinogen or fibronectin-coated plates [571, 572]. Unadhered platelets are washed off and adhesion can be calculated by doing simple protein estimation of the adhered platelets [573, 574]. Under flow condition, platelet adhesion is monitored by using parallel plate rectangular perfusion chamber. Prewarmed blood is perfused through the chamber by the help of a peristaltic pump [571]. Platelets adhered in the presence or absence of test compound can be monitored microscopically [571]. Inhibition in platelet adhesion during the process of atherosclerosis and restenosis is an attractive therapeutic strategy being pursued actively.

Apoptosis Assays

Apoptosis can be quantified by common staining by Hoechst H33342 and propidium iodide using immuno fluorescence microscopy as previously described [575]. Nuclei of apoptotic cells will be stained brightly with H33342 dye and stained negatively with propidium iodide. Analysis can be done using conventional tool programmes. Apoptosis can also be confirmed with a DNA laddering assay, as previously described [576]. Intracellular caspase-8 and -9 can be measured using a colorimetric assay with *p*-nitroaniline-labeled substrates, as previously described [576] or by western blotting. Apoptosis can also be measured by Flow Cytometry using AnnexinV and PI dyes. Briefly, the cell size and PS (phosphatidylserine) exposure is analyzed by flow cytometry using a fluorescence activated cell sorter (FACS) and appropriate software. PS exposure is estimated by FITC- or Cy3-conjugated Annexin V staining [577]. FITC- and Cy3-Annexin V can be purchased from commercial vendors [577]. Candidate drug treated THP-1, VSMC cells can be analyzed for apoptosis studies. Lovastatin-induces apoptosis in macrophages through the Rac1/Cdc42/JNK pathway [578] and lipophilic statins induce apoptosis of human VSMCs [579].

Thrombosis Potential

Thrombosis goes hand in hand with atherosclerosis and blood coagulation, platelets and endothelium contribute to this [38, 580]. Since platelets are involved in atherosclerosis progression as well as thrombus formation [581], so assessment of platelet behavior in hypercholesterolemic condition provide an important tool to predict atherogenicity of the subject/model. Commonly available parameters/methods of assaying platelet function are, optical (turbidometric), impedance and whole blood platelet aggregometry [582-584], platelet activation markers (such as platelet-activating factor-4 [585], β-thromboglobulin [586-588], P-selectin [589, 590], CD63 [591, 592], CD40L [593, 594], conformational changes in the GPIIb/IIIa receptor [595-597], binding of secreted proteins (thrombospondin) [598] and Platelet Function Analyzer-100 (PFA-100) [581]. Platelet-mediated, thrombin release [599], augmented plasma fibrinogen level [600] and low level of antithrombin-III [601-604], reflect the hypercoagubility of blood in hyperlipidemic condition [600]. The status of coagulation pathways/factors can be evaluated by estimating the coagulation parameters which include thrombin time (TT), prothrombin time (PT), activated partial

thromboplastin time (aPTT), fibrinogen time (FT) by coagulation analyzer [605, 606]. The hemostatic markers (fibrinogen, vWF, antithrombin –III, plasmin-antiplasmin complexes, thrombin-antithrombin complexes) can be assayed by commercially available assay kits [607]. The effect of niacin, warfarin and antioxidant vitamin cocktail on coagulation parameter has been evaluated in peripheral arterial disease patients [608]. The effect of hormonal regulation on hemodynamic parameters and atherosclerotic risk factors have also been assessed in womens taking progestin containing contraceptives [606], and testosterone treated rabbit model [609]. Besides this many animal models of thrombosis are also available which can be used to assess the hypercoaguability and thrombogenecity of blood under hyperlipidemic conditions in the presence and absence of test compounds [339, 340, 445, 610-612].

Autophagy Assay

Autophagy is a process that directs cytoplasmic material and organelles to the lysosomes. In this process, portions of cytosol and organelles are encircled by autophagosomes. This is followed by fusion between autophagosomes and endosomes/lysosomes, culminating in the formation of autolysosomes and degradation of their contents [613, 614]. Since autophagy is more for survival than death, its occurrence in VSMC may increase plaque stability however at the same time in macrophages it may be detrimental [615]. The classical ways to measure autophagy are quantitative electron microscopy and the degradation rate of long-lived proteins in presence of standard autophagy inhibitor (3-methyladenine or wortmannin) [616]. An assay developed by Seglen measures the sequestration of a soluble cytoplasmic marker to a membrane-bound and thus sedimentable cell fraction [617, 618]. Microtubule-associated protein 1 light chain 3 (LC3) was introduced as the first protein that localises specifically to autophagosome membranes and can be detected by conventional microscopy or western blotting in the presence and absence of test compounds [619].

Phagocytosis Assay

Phagocytosis has varied implications in atherosclerosis [6]. Phagocytic efficiency of monocytes can be assessed by monitoring uptake of labeled (fluorescein) bacteria, yeast, AC (apoptotic cell), lipids in simple *in vitro* test systems [620-622]. Adherent Cells are incubated with S. cerevisiae in the presence or absence of test compund like pravastatin in a wet chamber for 30 min at 37 °C in 5% CO_2 in air [621, 622]. Washing is done to eliminate non-phagocytosed S. cerevisiae, followed by fixation staining with 10% buffered Giemsa solution. The number of S. cerevisiae that are attached/ ingested are assessed by optic microscopy. The phagocytic index is calculated as the average number of attached plus ingested S. cerevisiae per phagocytosing monocytes, multiplied by the percentage of these cells engaged in phagocytosis [620]. A recent study found that pravastatin was able to decrease phagocytosis through complement receptors and caused a decrease in the production of hydrogen peroxide by monocytes. This may contribute to the inhibition of plaque development and instability [621].

Plaque Rupture

Atherosclerotic plaque rupture is the root cause of atherothrombosis disorders. No single model shows excellence in plaque rupture homology with human, but the models in focus are swine, rabbit, rat and mouse [623]. Spontaneous plaque rupture and hemorrhage is seen in pigs with inherited hyper-LDL cholesterolemia bearing mutant alleles for ApoB, however these complications occur in 39-54 month old animals [272, 623]. Swine model offers several advantage, for example imaging studies for the assessment of lesion site (and size), vulnerable plaque component and plaque stabilizing therapies can be easily applied [224]. Aged (42-54 week) ApoE deficient mice [624] develop interplaque hemorrhage and plaque instability features [624], and this process is accelerated by feeding westernized diet in ApoE deficient mice [265]. One study found spontaneous death in 37–59 week-old ApoE deficient mice fed with diet containing 21% lard and 0.15% cholesterol [625]. CETP transgenic Dahl salt sensitive hypertensive rat model proposed for plaque rupture is characterized by hypertriglyceridemia, hypercholesterolemia, decreased HDL, lesions in aorta and coronary vessels, premature death due to myocardial infarction (MI). Although plaque rupture is not observed but occurrence of MI indicate the potential of this model for coronary artery plaque rupture [626]. Induced plaque rupture/thrombosis can be attained in models by various manipulations. High cholesterol high fat diet fed rabbit models manipulated with balloon injury develop plaque rupture [227]. This has several advantages which include reproducible plaque formation on balloon surface, measurable mechanical strength and delivery of gene, genetically modified cells, proteins, lipids from outside for studying the role of various factors on plaque stability and fissuring [227]. Major limitation in this model is requirement of high cholesterol/fat diet for long time, around 8 months. Another means of inducing plaque rupture in cholesterol fed rabbit is to simultaneously treat them with Russell's viper venom followed by the vasopressor histamine [627, 628]. Knockout mouse model, ApoE deficient and ApoE-LDLR double knockout are being used as a model for spontaneous plaque rupture [629, 630]. Various manipulations have been used to induce plaque rupture in ApoE deficient mice. These include photochemical injury to mice vessels [20, 631], 9 week feeding with cholesterol and fat rich diet coupled with shear induction by pericarotid device (perivascular shear stress modifier) [632], implantation of perivascular cuff followed by p53 adenovirus transfection and pressor challenge with phenylephrine [633], common carotid ligation followed by polyethylene cuff placement [629], mechanical injury (compression of abdominal aorta with blunt forceps) [634] and perivascular carotid collar implantation in western type diet fed mice [635].

MOLECULAR TARGET ASSAYS

A defined molecular target is one of the characteristic features of a successful drug. Candidate drug molecules can be screened against defined targets by performing simple *in vitro* assays in the lab (Table **1A, 1B** & **1C**). A list of current and potential new drug targets in atherosclerosis is listed (Table **1A, 1B** & **1C**). The principle and the assay type of these targets are briefly mentioned and suitable references

Table 1A. Molecular Targets and Assays

	Target	Pathway	Response	Method
1	PPARα	Multiple including, Inflammation & RCT	Expression, Promoter activity	Electrophoretic mobility shift assay (EMSA) [636], Luciferase assays [637], RT-PCR [638], Immunoblotting [636], FACS [639]
2	PPARγ	Multiple including, Inflammation & RCT	Expression, Promoter activity	EMSA [640], Luciferase assays [641], RT-PCR [642], Immunoblotting [640]
3	LXR	Multiple including, Inflammation & RCT	Expression, Promoter activity	EMSA [643], Luciferase assays, RT-PCR [642], Immunoblotting [643]
4	Apo A	RCT (HDL compo-nent)	Expression, Promoter activity/levels	Luciferase assays [644], liquid-phase double-antibody radio immunoassays rocket immunoelectrophoresis [645]
5	ABCG1	Cholesterol efflux (RCT)	Expression, Promoter activity	Immunoblotting [105], RT-PCR [646]
6	CD36	Foam cell formation	Expression, Promoter activity	Luciferase assays, RT-PCR [647], Immunoblotting [648], FACS [649]
7	SRA	Foam cell formation	Expression, Promoter activity	Luciferase assays, RT-PCR, Immunoblotting [648], FACS [650]
8	COX-2	Inflammation, free radical generation	Enzymatic activity for AA metabolism to PG synthesis, Expression	Spectrophotometric [651], Immunoblotting [652], Colorimetric & flourimetric immunoassay, ELISA [651]
9	NOS	Inflammation, free radical genera-tion,vasodilation	Enzymatic activity for Nitrite formation, NO release, Expression	ELISA, radioactive, colorimetric NOS assays [653-655]
10	RXR	Multiple including, Inflammation & RCT	Promoter activity, Expression	Luciferase assays [656], RT-PCR [657], Immunoblotting [639]
11	MIF	Adhesion, migration, proliferation, In-flammation	Quantity/level	Antibody based immunoassay, ELISA [658], FACS [658]
12	HL	RCT	Enzymatic activity for fatty acid release, triglyceride substrate	Fluorimetric substrate utilization, Radioactive assay [659, 660]

Table 1B. Molecular Targets and Assays (Continued)

	Target	Pathway	Response	Method
13	ICAM	Adhesion	Expression,levels	EMSA, Luciferase assays, RT-PCR, FACS [661], Immunoblotting, ELISA [662]
14	VCAM	Adhesion	Expression, levels	EMSA [663], Luciferase assays [663], RT-PCR [663], FACS [664], Im-munoblotting [663], ELISA [662]
15	ACAT-1, 2	Foam cell	Enzyme activity, [^{14}C]oleate incorporation into cholesterol esters, expression	Radioactive assays [665, 666], ACAT activity and immunoblotting, RTPCR [666, 667]

(Table 1B) contd….

	Target	Pathway	Response	Method
16	SRB1	Cholesterol efflux, RCT	Expression, levels	RT-PCR, Immunoblotting [668], FACS [669]
17	Free radicals	Formation of modified lipids, oxidative stress	Generation of ROS&RNS	FACS-DCF&DAF response [670]
18	5-LOX	Formation of modified lipids,inflammation	Expression & Enzyme activity for hydroperoxides generated from the incubation of a 5-, 12-, or 15-LOX with either AA or LA	Spectrofluorimetric [671-673], Western blotting and Luciferase assay [674]
19	CD68	Foam cell formation	Expression, levels	RT-PCR [675], Immunoblotting, FACS [675]
20	MMP, MMP3	Plaque rupture	Enzyme activity for proteolytic cleavage self quenched peptide leading to enhanced flourescence post cleavage, Expression	Fluorimetric detection, immunoassay, immunoblotting. [676]
21	ABC-A1,A2	Cholesterol efflux, RCT	Cholesterol efflux, RCT	EMSA, Luciferase assays, RT-PCR FACS, Immunoblotting [646]
22	LOX-1	Lipid uptake, foam cell	Promoter activity, Expression	RT-PCR, Immunoblotting [677]
23	PLTP	RCT	Enzyme activity, transfer of donor fluorescent self-quenched phos pholipid to an acceptor leading to an increase in fluorescence, radioactive [^{14}C] phosphatidylcholine from phospholipid liposome (PL donor) to HDL acceptor	Fluorimetric assay [678-681]

Table 1C. Molecular Targets and Assays (Continued)

	Target	Pathway	Response	Method
24	CXCR2, CXCR1	Cell infiltration, Inflammation	Promoter activity, Expression	RT-PCR [682], Immunoblotting [683], FACS [684]
25	TXA2	Inflammation, platelet activation	TXB2 levels	Spectrophotometric [685], ELISA [686]
26	mTOR	Proliferation	Kinase activity, incorporation of phosphate	Radioactive [281], Spectrophotometric, ELISA [687,688]
27	CETP	RCT	CETP mediated transfer of donor molecule containing flu-orescent self quenched neutral lipid (from HDL) to acceptor molecule (LDL&VLDL) giving enhanced fluorescence, expression	Fluorimetric ELISA [689-692], Expression [693]
28	HDL	RCT	Quantity/levels	ELISA photometric [694]

(Table 1C) contd….

	Target	Pathway	Response	Method
29	LOX 15	Formation of modified lipids	Enzyme activity, hydroperoxides generated from the incubation of a 5-, 12-, or 15-LOX with either AA or LA	Spectrophotometric, ELISA [695-697]
30	CD-14	Inflammation	Promoter activity, Expression	Luciferase assays, RT-PCR [698], Immunoblotting [699], FACS [700]
31	Cx 37 (gap junction)	Adhesion	Expression	RT-PCR, Immunoblotting [701]
32	Phospho lipase A2	Inflammation, RCT	Enzyme activity, free thiols generated from specific substrate in presence of PLA2 are detected using DTNB reagent	Spectrophotometric ELISA [702-704]
33	HMG-CoA Reductase	Cholesterol synthesis	Enzyme activity, HMG-CoA dependent oxidation of NADPH, generation of mevalonolactone in presence of ^{14}C-HMG-CoA	Spectrophotometric ELISA, radioactive based assays [705, 706]
34	LCAT	RCT	Release of specific fluorescence after LCAT mediated hydrolysis of substrate (transfer of acyl chain from the sn-2 position of phosphatidylcholine to cholesterol)	Fluorimetric assay [707, 708]

are provided for detailed target specific methodology, which will help in setting up the assays in the lab.

FUTURE STRATEGIES

Developing new animal models and understanding the mechanism of atherosclerosis along with its complications is essential. At the same time emphasis should also be placed on selecting the best model suited for screening a particular class of drug. Since each model has its own advantages and disadvantages, the beneficial actions of a candidate drug should be documented in several models of atherosclerosis. The protective effect should be evident at the morphological, biochemical and molecular levels rather than at single level. Preferably a candidate drug should inhibit various processes of atherosclerosis and have a defined mechanism of action. Strategies like QTL analysis coupled with pharmacogenomics and in silico screening will help in the identification and design of new strategies.

Important information regarding initiation of atherosclerosis is still not clear. Deciphering the mechanism of atherosclerosis will help to address in a major way the side effects of various drugs in use. Researchers have to overcome the challenge and fact that bigger animals develop better atherosclerosis like humans however detailed molecular and genetic studies can be best carried out with smaller animals like mice. Secondly since the mouse [709] and human [710] genome are already sequenced and reagents in the market support studies in these species, to carry out molecular and other detailed studies in other animals often becomes very challenging. There is an urgent need to have good reagents for carrying out molecular studies in all types of animal models of atherosclerosis. Developing small animal models, which can develop atherosclerosis very similar to humans, can bridge the gap between small and big animals. ApoE mice and ApoE leiden mice address this issue to some extent [711, 712]. However we still need a good model of plaque rupture and it will be challenging to develop a spontaneous plaque rupture model. However it will also be better to have an animal model where initiation, progression of atherosclerosis is similar to humans. It is also very important that the animal develops lesion in area like those in humans. Sometimes the drugs are screened on lesions whose sites are not similar to humans and despite of showing protective effect in that animal, no protection may be observed in case of humans since the site of lesion is different. Here the flow of blood and shear stress may also be important for lesion formation. Imaging of small animals is very difficult and there is a need for developing sophisticated imaging techniques where animals can be monitored for atherosclerosis progression or regression. Usually a lot of work is based after animal sacrifice. Emphasis should be given to develop non-invasive im-

aging techniques for monitoring progression or regression of atherosclerosis. Simultaneously scientists can also develop several biomarkers and also surrogate markers for atherosclerosis [713]. The development of these markers will greatly tell about the mechanism of the diseased and by monitoring the levels of the surrogate markers in the animal models and also in humans we can easily monitor the efficacy of many drugs. It should also be clear that failure of one molecule should not be taken as failure of entire class of protein for atherosclerosis treatment. Evidence suggests that the effect of a compound may be very specific to its structure and mechanism of action [714]. More compounds may be designed and synthesized using information from the crystal structure of their protein. At the same time the compound should be tested in various models of atherosclerosis both *in vivo* and *in vitro*. By doing computational analysis of murine SNP database and utilizing data from inbred parental strains, can lead to rapid identification of QTL intervals. Computational identification of putative disease genes can be done by coupling information from murine SNP database, tissue specific gene expression database and phenotypic information across mouse strains as discussed in the review. Good use of QTL and in silico analysis will reduce the time for identification of genes involved in atherosclerosis progression. Since several mechanisms are responsible for the development of atherosclerosis, it is most likely that a combinatorial therapy may work in atherosclerosis rather than one alone.

ACKNOWLEDGEMENTS

Fellowship to Mr. Vishal Singh from ICMR, Mr. Rajiv Lochan Tiwari from CSIR and financial support to Dr. Manoj Kumar Barthwal from DBT, DST and CSIR Network Project NWP0034, India is acknowledged.

LIST OF ABBREVIATIONS

AA = Arachidonic acid

ABCA1 = ATP-binding cassette transporter A1

ABCG1 = ATP binding cassette transporter G1

ACAT = Acyl-CoA:cholesterol acyltransferase

AcLDL = Acetylated LDL

AngII = Angiotensin II

Apo = Apolipoprotein

ASBT = Apical sodium dependent bile acid transporter

CAM = Chick chorioallantoic membrane

CCR2 = C-C motif chemokine receptor–2

CETP = Cholesterol ester transfer protein

CHF = Congestive heart failure

COX = Cyclooxygenase

CRP = C reactive protein

Cx = Connexin

ELAM = Endothelial-leukocyte adhesion molecule

ELISA = Enzyme-Linked ImmunoSorbent Assay

EMSA = Electrophoretic mobility shift assay

eNOS = Endothelial nitric oxide synthase

EPCs = Endothelial progenitor cells

FACS = Fluorescence activated cell sorting

FLAP = Five lipoxygenase activating protein

G-CSF = Granulocyte colony stimulating factor

GM-CSF = Granulocyte macrophage colony-stimulating factor

5-HT = 5-Hydroxytryptamine

HDL = High-density lipoprotein

HFN-4α = Hepatocyte nuclear factor-4α

HL = Hepatic lipase

HMGCoA = 3-hydroxy-3-methylglutaryl coenzyme A

HOPE = Heart Outcomes Prevention Evaluation

HUVEC = Human umbilical vein endothelial cells

ICAM = Intercellular adhesion molecule

IFN-γ = Interferon gamma

IL = Interleukins

iNOS = Inducible nitric oxide synthase

IP-receptor = PGI2 receptor

JAM-A = Junctional adhesion molecule-A

JNK = c-jun-N-terminal kinase

LA = Linoleic acid

LDL = Low-density lipoprotein

LDLR = Low density lipoprotein receptor

LOD = Log of the odds

LOX = Lipoxygenase

LOX-1 = Lectin-like oxidized low-density lipoprotein receptor-1

Lp(a) = Lipoprotein (a)

LPA = Lysophosphatidic acid

LPL = Lipoprotein lipase

LXR = Liver X receptor

MCP = Macrophage chemotactic protein

M-CSF = Macrophage-colony stimulating factor

MHC = Major histocompatibility complex

MIF = Migration inhibitory factor

MIG = Gamma interferon-induced monokine

MIP = Macrophage inflammatory protein

MMPs = Matrix metalloproteinase

mTOR = Mammalian target of rapamycin

NFκB = Nuclear factor-kappa B

NHPs = Non-human primates

NKT = Natural killer T cells
NO = Nitric oxide
NZW = New Zealand White
Ox-LDL = Oxidized LDL
PAF = Platelet activating factor
PAI-1 = Plasminogen activator inhibitor-1
PASMC = pulmonary artery smooth muscle cells
PDGF = platelet-derived growth factor
PECAM-1 = Platelet/endothelial cell adhesion molecule-1
PGs = Prostaglandins
PGH_2 = Prostaglandin H2
PGI_2 = Prostacyclin
PI3 Kinase = Phosphoinositide 3 (PI3) kinase
PKC = Protein kinase C
PLA_2 = Phospholipase A_2
PLTP = Phospholipid transfer protein
PMA = Phorbol 12-myristate 13-acetate
P^{38}MAPK = P^{38}mitogen activated protein kinase
PMN = Polymorphonuclear leukocytes
PPAR = Peroxisome proliferator-activated receptors
QTL = Quantitative trait loci
RADAR = Rosuvastatin and Atorvastatin in different Dosages and RCT
RANTES = Regulated upon activation normal T-cell expressed and secreted
RAS = Renin-angiotensin system
RCT = Reverse cholesterol transport
RNS = Reactive nitrogen species
ROS = Reactive oxygen species
RT-PCR = Reverse transcriptase- polymerase chain reaction
SHR = Spontaneously hypertensive rats
SHR-SP = Stroke-prone spontaneous hypertensive rats
SMC = Smooth muscle cell
SNP = Single nucleotide polymorphism
SR = Scavenger receptor
STZ = Streptozotocin
TF = Tissue factor
TFPI = Tissue facor pathway inhibitor
TGF β = Transforming growth factor β
Th = T helper cells
THP-1 = Human acute monocytic leukemia cell line
TLR = Toll-like receptor
TM = Thrombomodulin
TNF = Tumor necrosis factor
TNFR-I = Tumor necrosis factor receptor-I
TP = Thromboxane prostanoid
tPA = Tissue plasminogen activator
TX = Thromboxane
uPA = Urokinase-type plasminogen activator
VCAM = Vascular cell adhesion molecule
VLA-4 = Very late antigen-4
VLDL = Very low density lipoprotein
VSMC = Vascular smooth muscle cell
vWF = Von Willebrand factor

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Received: July 15, 2008 **Revised: July 30, 2008** **Accepted: August 02, 2008**