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Interaction of pathogens with host cholesterol metabolism

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Abstract

Purpose of the review—Pathogens of different taxa, from prions to protozoa, target cellular cholesterol metabolism to advance own development and to impair host immune responses, but also causing metabolic complications, *e.g.* atherosclerosis. This review describes recent findings of how pathogens do it.

Recent findings—A common theme in interaction between pathogens and host cholesterol metabolism is pathogens targeting lipid rafts of the host plasma membrane. Many intracellular pathogens use rafts as an entry gate, taking advantage of the endocytic machinery and high abundance of outward looking molecules that can be used as receptors. At the same time, disruption of the rafts' functional capacity, achieved by the pathogens through a number of various means, impairs the ability of the host to generate immune response, thus helping pathogen to thrive. Pathogens cannot synthesise cholesterol, and salvaging host cholesterol helps pathogens build advanced cholesterol-containing membranes and assembly platforms. Impact on cholesterol metabolism is not limited to the infected cells; proteins and miRNAs secreted by infected cells affect lipid metabolism systemically.

Summary—Given an essential role that host cholesterol metabolism plays in pathogen development, targeting this interaction may be a viable strategy to fight infections as well as metabolic complications of the infections.

Keywords

Cholesterol; infections; metabolic diseases

Introduction

Evolutionary, cholesterol first consistently appeared in primitive vertebrates, whereas other living organisms had different, if any, sterols [1]. Cholesterol is essential, first of all, for maintaining liquid-solid structure of plasma membrane to sustain complex signalling and endocytic pathways that originate from the membrane and are key elements in interaction

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Conflict of Interests
None declared.

between an individual cell and the rest of the organism. This is not always a requirement for simpler organisms and yet many pathogens salvage host cholesterol and interfere with cellular cholesterol metabolism. In humans cholesterol metabolism plays a central role in pathogenesis of many metabolic diseases, from atherosclerosis to neurodegenerative diseases. It is therefore plausible, and in several cases (*e.g.* HIV infection) has been proven, that changes in host cholesterol metabolism inflicted by pathogens cause metabolic complications and contribute to the risk and burden of metabolic diseases. In this brief review we will attempt to analyse recent findings on how and why pathogens interact with cellular cholesterol metabolism, and how this interaction affects metabolic status of host and microbe.

Pathogens target cellular cholesterol metabolism

Many pathogens, in particular those that are parasites, evolved to take advantage of high abundance of cholesterol in host cells. A frequent way to exploit cellular cholesterol by pathogens is using cholesterol rich domains of the plasma membrane, lipid rafts, as an entry point or/and an assembly platform. One reason for this is that rafts contain large number of outward facing cellular receptors, including GPI-anchored proteins, which are exploited by pathogens as receptors. Rafts also allow viruses to position viral components in close proximity during assembly. Rafts play an important role in immunity, including phagocytosis and recognition of infected cells, so disruption of rafts during entry or assembly often “hides” pathogens from immune response. On the other hand, disruption of rafts by depleting them of cholesterol may impair the infection, making “inactivation” rather than disruption of rafts the preferred outcome for a pathogen.

One example of exploiting the rafts is the simplest pathogen, prion. A key event in the pathogenesis of the prion disease is the conversion of the host prion protein, PrP^{C}, to a pathological misfolded isoform (PrP^{Sc}). This conversion requires high local concentration of PrP^{C}, which is achieved in rafts [2]; depletion of cellular cholesterol [3] or raft modification diminishes PrP^{Sc} formation [4]. Prions, in turn, inhibit cellular cholesterol efflux by displacing ABCA1 transporter from rafts and increasing ABCA1 internalization, leading to accumulation of cellular cholesterol and possibly aggregation of rafts [5]. Similar paradigms were found in more complex pathogens.

Many viruses, both enveloped and non-enveloped, use lipid rafts to get into and/or out of the target cell [6]; HIV being one of the best studied. HIV receptor CD4 is a lipid raft protein [7], and some reports suggested that co-receptors CXCR4 and CCR5 may also localize to rafts, or may be relocated to the rafts following HIV binding to CD4 [8]. In a recent study, pluripotent stem cells were transduced with lentiviral vectors expressing CD4 mutants localized to different membrane domains, differentiated into macrophage-like cells, and assessed for susceptibility for HIV-1 infection. The analysis revealed that infection through lipid raft-associated CD4 was significantly more effective than through CD4 excluded from rafts [9]. Localization of HIV assembly is determined by the preferential association of the HIV Gag polyprotein with rafts on the plasma membrane [10], which also promotes localization of Env to these microdomains [11]. Cholesterol and sphingomyelin are a pre-requisite for fusion, as depletion of these lipids from the viral or cellular membrane inhibits

virus-cell fusion [12]; some reports suggest that lipid rafts promote fusion of the viral and target cell membranes [13]. The most likely and general mechanism of fusion regulation by cholesterol appears to be concentration of virus-specific protein molecules in one location, in rafts. Due to their mobility within the membrane, rafts are convenient sites for multimerization and assembly of large particles. Assembly of HIV in rafts inevitably modifies rafts: the size of HIV (about 100 nm) is at least twice that of the rafts; thus, rafts have to aggregate during assembly.

Another suggested effect of lipid rafts on viral infection is facilitation of formation of virological synapses. These structures represent the contact zones formed between virus-infected and target cell and facilitate cell-to-cell transmission of infection. Such mode of transmission is much more efficient than infection by cell-free virions and may be a preferred mechanism of infection *in vivo* [14]. In the case of HIV infection, the virological synapse formed between infected and target T cell is enriched in assembled or assembling virus particles [15], and is also enriched in markers for lipid rafts [15, 16].

Another example of a medically relevant virus assembled in lipid rafts is influenza. Two of influenza virus membrane proteins, HA and NA, are intrinsically associated with lipid raft domains [17]. Lipid raft association of HA is determined by palmitoylation occurring on three cysteine residues, and mutations affecting HA palmitoylation block HA association with lipid rafts and impair virus assembly [18]. HA association with rafts causes expansion of these domains resulting in huge structures, ranging in diameter from 2 to 5 μm, from which virus budding occurs and which have been termed the viral budozone [19].

Enteroviruses hijack host clathrin-mediated endocytosis pathway to move cholesterol from plasma membrane to intracellular replication organelles, broadly analogous to lipid rafts, where viruses replicate and assemble [20].

Using lipid rafts as an entry gate is not limited to viruses. *Mycobacterium tuberculosis* uses lipid rafts to enter alveolar epithelium and it was suggested that it secretes a factor causing rafts aggregation to prepare uninfected cells for new infection [21]. *Leishmania donovani* also binds to lipid rafts of the macrophages using them as an entry gate; cholesterol depletion inhibits infection *in vitro* [22].

Targeting of lipid rafts by the viruses alters raft-mediated activities including host signalling and endocytic pathways originating from rafts. In many cases this may provide considerable evolutionary advantage and be a primary reason for pathogens to recognize rafts constituents as receptors or assembly platforms. Thus, the Epstein-Barr virus (EBV) modulates lipid raft microdomains via its latent membrane protein 1 (LMP1). LMP1 increased the localization of phosphatidylinositol 3-kinase (PI3K) and its activated downstream target, Akt, to lipid rafts, thus activating signal transduction necessary for oncogenic transformation [23]. Proteomics analysis of lipid rafts in cells infected with hepatitis C virus (HCV), which neither enters nor assembles in rafts, identified 110 proteins being upregulated and 40 proteins – downregulated relative to lipid rafts of uninfected cells [24]. Majority of modified proteins were proteins involved in vesicular transport, protein trafficking, and cell signaling, and at least some regulated virus replication. HIV evolved several mechanisms to increase the

abundance of lipid rafts on the plasma membrane [25], including upregulation of cholesterol synthesis and cholesterol uptake [26], inhibition of cholesterol efflux [27], and Nef-mediated delivery of cholesterol to rafts [25]. At the same time, several raft-dependent functions, such as endocytosis and phagocytosis, were suppressed in HIV-infected macrophages [25].

L. donovani, when inside the cell, actively extracts cholesterol from lipid rafts, disrupting them and impairing multiple elements of immune response, including T-cell stimulation [28]. Experimental hypercholesterolemia, induced either by western diet or genetically in apoE$^{-/-}$ mice, restored lipid rafts structure, reversed the effect of the parasite on immune response and was broadly protective against *L. donovani* infection [28]. Plasma membrane cholesterol depletion by *L. major* inhibits assembly of IL-12-inducing CD40 signalosome and promotes assembly of IL-10-inducing CD40 signalosome, thus contributing to immune evasion [29]. It was suggested that cholesterol removed from the plasma membrane accumulates inside the cells contributing to the formation of foam cells, although this could be a result of stimulation of expression of scavenger receptors and inhibition of genes involved in cholesterol efflux by Leishmania infection [30].

There are also other strategies pathogens employ to disrupt the function of rafts. *Mycobacterium leprae* incorporates cellular cholesterol into bacteria-containing phagosome. The requirement for cholesterol in the phagosome membrane is not clear, but by doing so pathogen disrupts host cell rafts leading to T-cell hyporesponsiveness [31]. *Toxoplasma gondii* also incorporates cellular cholesterol into parasitophorus vacuole membrane (PVM) during invasion; reducing host plasma membrane cholesterol content inhibits parasite entry [32]. Once inside the cell, however, *T. gondii* salvages cholesterol from the host pathway of LDL endocytosis (for review see [33]). Specifically, the parasite hijacks host NPC1 forcing it to deliver LDL-derived cholesterol from lysosomes to the surface of PVM instead of host plasma membrane. *T. gondii* also expresses a cholesterol transporter homologous to mammalian transporters of ABCG subfamily, inserting it into PVM in an orientation suitable to transport cholesterol and phospholipids to the inside of the vacuole [34]. Furthermore, *T. gondii* expresses two enzymes similar to mammalian ACAT1 and ACAT2 that catalyze esterification of cholesterol and storing of cholesteryl esters in lipid droplets [35]. This is a likely mechanism to regulate levels of free cholesterol in PVM: inhibition of parasite's ACATs leads to collapse of the membrane due to overloading with free cholesterol [35].

Merozoites of *Plasmodium falciparum* dwell in the liver, aggressively diverting hepatocyte cholesterol from all sources, hijacking LDL receptor internalization pathway and intercepting newly synthesized cholesterol [36]. Surprisingly, blocking these pathways, while severely depleting parasite of cholesterol, does not affect its development or infectivity [36], suggesting that the objective of this activity could be to affect the hepatocyte, e.g. to deplete it of rafts, rather than to satisfy a need in cholesterol for the parasite. Trophozoites recruit cholesterol from lipid rafts of red blood cells disrupting signalling and possibly affecting immune response toward infected cells [37].

Helicobacter pylori dwells at the gastric epithelium and in order to neutralize immune defences it follows cholesterol gradient, extracts cholesterol from lipid rafts of epithelial

cells and macrophages, and disrupts rafts preventing phagocytosis by antigen-presenting cells [38]. To mitigate toxic effect of the extracted free cholesterol, *H. pylori* expresses a unique enzyme glucosylating cholesterol, which not only reduces cholesterol burden, but also inhibits phagocytosis [38]. *M. tuberculosis* also actively degrades cholesterol [39], using it as a source of carbon and energy.

Several free-living pathogens use dietary lipids and plasma lipoproteins as a source of cholesterol. For example, *Entamoeba histolitica* aquires host cholesterol to build its own lipid rafts required to attach to the intestinal wall [40] and for complex signalling regulating amoeba mobility [41].

A very different paradigm of interaction between pathogen and host cholesterol metabolism was described for HCV (for excellent recent reviews see [42, 43]). HCV hijacks hepatocyte VLDL assembly pathway incorporating itself into secreted VLDL. This allows virus to travel through the bloodstream protected from immune responses and re-enter hepatocytes through LDL receptor. To facilitate expression of LDL-receptors HCV up-regulates SREBP, causing seatosis [44].

Pathogens and systemic cholesterol metabolism

Most infections are associated with reduced levels of all or some plasma lipoprotein fractions, with best investigated pathogens being HIV. Alterations of lipoprotein homeostasis may result from direct and specific effects of the pathogens as well as from inflammation accompanying the infection.

Untreated HIV infection is characterised by low levels of total cholesterol (TC), LDL-C and HDL-C and elevation in triglycerides (TG). Treatment with HAART, especially with regimens containing protease inhibitors (PI), causes sharp elevation of LDL-C, which was attributed to the effects of PI unrelated to their effects on pathogen [45]. Hypoalphalipoproteinemia and hypertriglyceridemia persist even after treatment and are most likely due to the effect of HIV itself [45-47]. We have recently demonstrated that SIV causes similar effects on lipoprotein metabolism in monkeys [48]. Recombinant HIV protein Nef, when injected in mice, reproduced many elements of HIV-induced dyslipidemia [49], further suggesting that HIV, rather than associated factors (e.g. chronic inflammation), is responsible for changes in plasma lipoproteins. Mechanistically, HIV Nef is capable of impairing ABCA1 [25], and impairment of liver ABCA1 may account for the dyslipidemia seen in HIV patients. Further, cells transfected with Nef secrete exosomes with several miRNAs affecting systemic lipid metabolism [50]. HCV infection is also associated with dyslipidemia, evidenced by lower levels of all plasma lipids except for TG, the latter is most likely a result of severe liver steatosis caused by HCV infection [51].

Recent meta-analysis confirmed numerous previous observations that malaria is associated with low levels of plasma TC, HDL-C and LDL-C [52]; the mechanism remains unknown. *L. donovani* also reduced plasma cholesterol by a recently described mechanism involving down-regulation of hepatic MiR-122 [53].

Microbiota and host lipoprotein metabolism

Under normal circumstances gut microbiota is not a conventional pathogen, but it has been recently suggested that metabolic products produced by microbiota play a major causative role in regulating cholesterol metabolism of the host and in development of atherosclerosis. Thus, protocatechuic acid, a product of metabolism of cyanidin-3 to 0-β-glucosid occurring in the gut, reduced the expression of miRNA-10b leading to stimulation of ABCA1 and ABCG1 abundance in macrophages and to anti-atherogenic effect in mice [54]. Conversely, trimethylamine-N-oxide, also produced by gut microbiota, reduced reverse cholesterol transport and accelerated the development of atherosclerosis in mice and correlated with atherosclerotic burden in humans [55]. Gut microbiota regulated the metabolism of bile acids producing FXR antagonists thus providing a feedback to bile acid synthesis in mice [56]. Gut microbiota was also implicated in pathogenesis of obesity, and obesity status was transferred with transplantation of gut microbiota or just co-housing of mice [57].

Cholesterol metabolism as an innate immune factor anti-infection treatment target

A number of anti-viral innate immune mechanisms work through modification of cholesterol metabolism. One example is IFN-inducible transmembrane (IFITM) proteins which restrict the replication of multiple viruses, including Influenza A, SARS coronavirus, filoviruses (Ebola and Marburg viruses), flaviviruses (dengue and West Nile viruses), and HIV-1 [58-60]. IFITM proteins interact with vesicle-associated membrane protein-associated protein A (VAPA) and block VAPA interaction with oxysterol-binding protein (OSBP) [61], thus preventing formation of the VAPA-OSBP complex that regulates cholesterol transport from ER to organelles [62]. As a result, cholesterol accumulates in the endosomal compartment, blocking fusion and cytosolic release of VSV and influenza A cores [61]. Another example of IFN-inducible anti-viral factor working through cholesterol-dependent mechanism is cholesterol-25-hydroxylase [63], an endoplasmic-reticulum-associated enzyme that catalyzes oxidation of cholesterol to 25-hydroxycholesterol. Insertion of 25-hydroxycholesterol into the cellular membranes blocks virus-cell fusion and protects cells from infection by a number of enveloped viruses, including VSV, HSV, HIV, EBOV, RVFV, RSSEV, and Nipah viruses [63].

Cholesterol metabolism is an attractive target for anti-infection therapy as it may serve two purposes at once: suppress pathogen replication and correct changes in cholesterol metabolism caused by the infection and leading to chronic complications, such as atherosclerosis or obesity. An example of such treatment is stimulation of ABCA1 expression. Up-regulation of ABCA1 has long been explored as a strategy to promote formation of HDL and to prevent or treat atherosclerosis, but it can also be an effective anti-infection strategy. HIV replication has been shown to be impaired when ABCA1 was upregulated by LXR agonist [25, 64]. This effect was due to reduced number of lipid rafts and depletion of membrane cholesterol, limiting both production and infectivity of HIV virions. In addition, ABCA1 stimulation by PPARγ or LXR agonists prevented HIV capture by dendritic cells and trans-infection of susceptible T cells [65], inhibiting a key pathway in

HIV transmission. Pharmacological stimulation of ABCA1 also inhibited HCV infection by affecting virus entry [66].

Conclusions

By interfering with cellular cholesterol metabolism, pathogens simultaneously achieve several objectives: they (*i*) impair host immune response, (*ii*) procure cholesterol to organize entry, assembly and budding sites, protective membranes or as a source of carbon, (*iii*) inflict changes on uninfected bystander cells and systemically to generate metabolic milieu advancing spread of infection, but also causing metabolic complications. Given the essential role of host cholesterol in advancing the infection, restricting the pathogen-cholesterol interaction is an attractive treatment strategy to fight not only infections themselves but a range of their metabolic complications.

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Key points

- Pathogens of different taxa interfere with host cholesterol metabolism
- Objectives of this interference are to impair host immune response and procure cholesterol for building entry and assembly sites or protective membranes
- Infected cells secrete factors affecting cholesterol metabolism in uninfected bystander cells and systemically
- Cholesterol metabolism is an attractive strategy for therapeutic interventions targeting infections and their metabolic complications