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Review

Targeting of the Hydrophobic Metabolome by Pathogens

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Abstract

The hydrophobic molecules of the metabolome – also named the lipidome – constitute a major part of the entire metabolome. Novel technologies show the existence of a staggering number of individual lipid species, the biological functions of which are, with the exception of only a few lipid species, unknown. Much can be learned from pathogens that have evolved to take advantage of the complexity of the lipidome to escape the immune system of the host organism and to allow their survival and replication. Different types of pathogens target different lipids as shown in interaction maps, allowing visualization of differences between different types of pathogens. Bacterial and viral pathogens target predominantly structural and signaling lipids to alter the cellular phenotype of the host cell. Fungal and parasitic pathogens have complex lipidomes themselves and target predominantly the release of polyunsaturated fatty acids from the host cell lipidome, resulting in the generation of eicosanoids by either the host cell or the pathogen. Thus, whereas viruses and bacteria induce predominantly alterations in lipid metabolites at the host cell level, eukaryotic pathogens focus on interference with lipid metabolites affecting systemic inflammatory reactions that are part of the immune system. A better understanding of the interplay between host–pathogen interactions will not only help elucidate the fundamental role of lipid species in cellular physiology, but will also aid in the generation of novel therapeutic drugs.

Keywords bacteria, fungi, host–pathogen interactions, lipidome, lipids, metabolome, parasites, viruses

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The metabolome encompasses all small molecules that are present in a biological system (Figure 1). Unlike genes and proteins, the functions of which are subject to epigenetic regulation and post-translational modifications, respectively, metabolites serve as direct signatures of biochemical activity and tightly correlate with phenotype (1). These properties make the cellular metabolome an attractive target for pathogens in order to introduce phenotypic perturbations that allow their survival and replication.

With recent developments in instrumentation (mass spectroscopy), bioinformatics and software, our knowledge on the identification and quantification of metabolites, as well as on the metabolic pathways and metabolite fluxes is rapidly expanding. Metabolites are loosely defined as just about any small molecule with a molecular weight ~2000 Da that is metabolized by an organism (2). The METLIN metabolite database (http://metlin.scripps.edu/) is one of the most comprehensive freely accessible

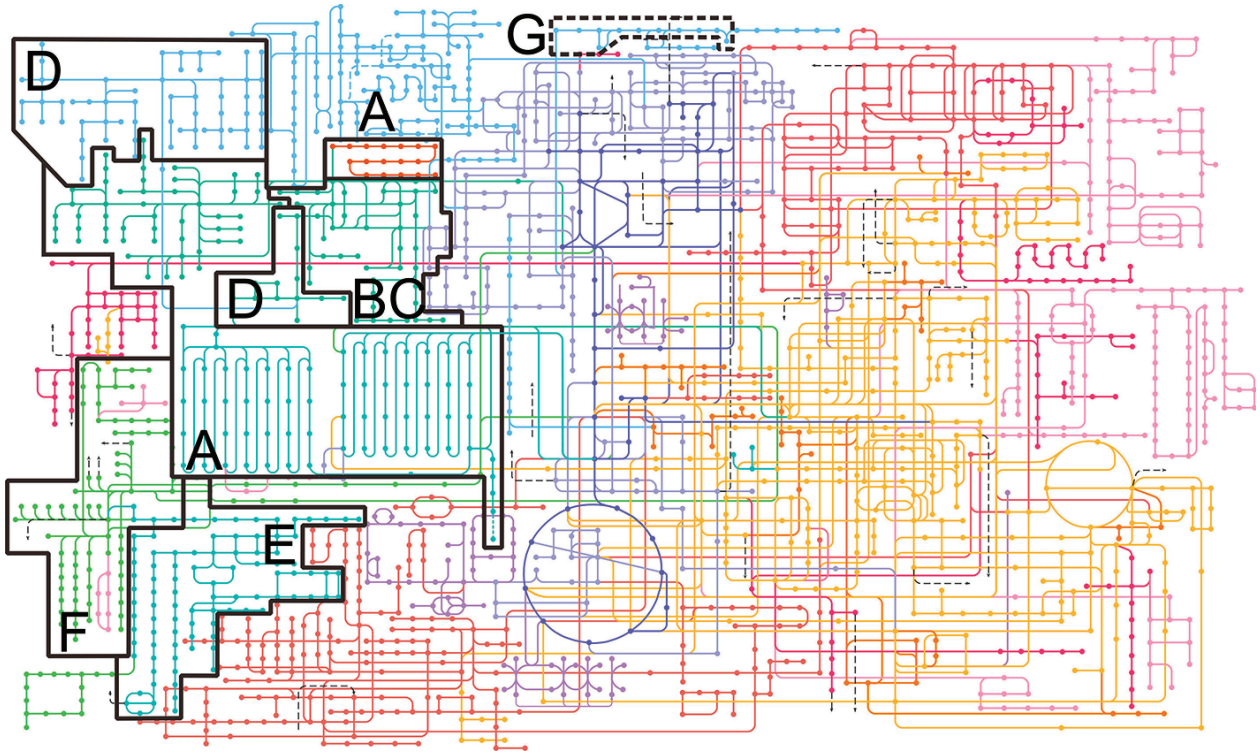

Figure 1: Contribution of lipid metabolic pathways to the KEGG map of metabolism. The metabolic map was constructed based on the KEGG (Kyoto Encyclopedia of Genes and Genomes) database (http://www.kegg.jp/) (245). The graphical presentation is based on the Genome-Linked Application for Metabolic Maps (glamm.lbl.gov) (246) with a minor modification that allows visualization of elongation and desaturation of palmitic- to stearic- and oleic acid, respectively. Lipid classification into eight main categories (A–H) is according to the 2005 convention on lipid nomenclature (19): A, fatty acids; B, glycerolipids; C, glycerophospholipids; D, sphingolipids; E, sterols; F, prenol lipids; G, saccharolipids. Polyketides (lipid category H) are not commonly found in mammalian hosts and are not depicted. Saccharolipids (lipid category G) are shown as a dotted line and not discussed in this review as they are not constituents of the mammalian lipidome. In this graphical pathway representation, cholesterol esters, lyso-phospholipids and bis(monoacylglycero)phosphate (BMP) species are lacking.

databases and currently contains more than 240 000 (possible) entries and approximately 60 000 different structures (3,4). The human metabolome database (http://www.hmdb.ca/) contains over 40 000 metabolite entries consisting of detected and expected metabolites (2). The metabolites in both databases include water-soluble and water-insoluble or lipid metabolites. The analysis of lipid metabolites by mass spectrometry poses additional requirements and constraints to the experiments due to their inherent hydrophobic nature. Lipids must first be extracted using a procedure that involves phase separation into a hydrophobic and a hydrophilic phase. In addition, mass spectrometry analyses require that the hydrophobic lipids must be charged prior to MS analysis. This only became routine with the advent of electrospray-mass spectrometry in the late 1980s (5,6). Hence, metabolomic analyses often refer to the water-soluble metabolome whereas lipidomic analyses refer (by definition) to water-insoluble analyses. Despite these additional experimental requirements and constraints, the lipidomic field is now rapidly expanding, providing a glimpse of its contribution to the metabolome (6–15). The LIPID MAPS Structure Database (http://www.lipidmaps.org/), the largest public lipid-only database, contains over 37 500 unique structures of biologically relevant lipids (16,17). Current estimates suggest that the entire lipidome may encompass approximately 180 000 different lipid species (18). Thus, of all the molecules contained in

the metabolome, the lipids constitute the largest subset, including tens of thousands of distinct lipid molecular species existing in cells and tissues (12).

Hydrophobic Metabolome

Each dot of the KEGG-based metabolic map (Figure 1) represents a single metabolite with its own unique chemical structure that is connected by line(s) indicating the metabolic pathway(s) each metabolite is involved in. The metabolic pathways involving lipid metabolites are outlined on the metabolic map. Recently, lipids have been divided into eight categories containing distinct classes and subclasses based on their chemical structure (19,20) and the presence of these categories within the metabolome is indicated by individual panels. In this overview of the metabolome, the contribution of lipids may appear under-represented relative to their abundance with the metabolome. This is mainly due to the fact that in this pathway representation, generic lipid classes are shown without sufficient fatty acid (side) chain information (relevant for all panels) and without carbohydrate head group variations (relevant for panel G). With these variations in fatty acid and glycolipid head group composition, an estimated number of 180 000 lipids has been predicted to exist (18) and this number does not even include the vast number of possible (per)oxidized lipids, that can be generated spontaneously during radical formation (e.g. stress) or by enzymatic reactions (21).

The enormous structural diversity of lipids requires complex regulation at multiple spatial and temporal scales and mainly due to innovations in lipidomic techniques we are only beginning to understand the biological role of lipids in health and disease. We are long past the dogma that lipids have an essential role as component of the lipid bilayer of biomembranes and in energy storage utilizing cellular lipid droplets and plasma lipoproteins. Research over the last decades has identified an additional role of lipids in cellular signaling, a structural role in membrane microdomain organization and dynamics, and a regulatory role in membrane trafficking. The importance of lipids as part of the metabolome is also evident from the numerous lipid-related pathologies including lipid storage diseases such as fatty liver, obesity, and atherosclerosis, neurodegenerative diseases such as Alzheimer's disease, cancer, inflammation, and infectious diseases.

Pathogens and Lipids

Pathogenic micro-organisms have evolved many strategies to circumvent host defenses and exploit the host cellular machinery. Specific virulence factors disable or subvert vesicular trafficking pathways to and from the host cell surface, which promotes pathogen entry, replication or escape (22–25). The direct link of the metabolome with the cellular phenotype as well as the abundance of hydrophobic metabolites within the metabolome (hydrophobic metabolome or lipidome) makes lipids an attractive target for pathogens to modulate host cell processes (26–30). In many instances, this results in altered intracellular trafficking of pathogens after entry into host cells, resulting in escape from the default pathway toward lysosomes (for reviews, see e.g. 22, 31–33).

Microbial pathogens can be classified into viral, bacterial, fungal and parasitic microbes. Obviously, these different types of pathogens have very different types of interactions with host cells and this is reflected in their usage of host cell lipids. An overview of the targeting of host cell lipids by pathogens is shown in Figure 2. Of note, we have excluded references to lipid rafts (discussed elsewhere e.g. 34–36) as in most instances it is not clear whether this is due to cholesterol, sphingolipids or indirect effects because of destabilization of lipid raft structures. Comparison of host cell lipid usage by viral (Figure 2A), bacterial (Figure 2B), fungal (Figure 2C) and parasitic (Figure 2D) pathogens shows that they each have a remarkable distinct and different preference for individual lipid categories in order to modulate host cell responses.

Viruses have no intrinsic lipid metabolism and by definition affect host cell lipids to modulate virus replication, host cell responses and/or to acquire lipids for their viral envelope. There is a strong focus on signaling lipids such as phosphoinositides (37–45) and phosphatidylserine (PS) (46–50) (Figure 2A). In addition, many viruses target cholesterol (51–58), a structural membrane lipid specific for host cells that allows the virus to modulate the physical properties of intracellular membranes. During the

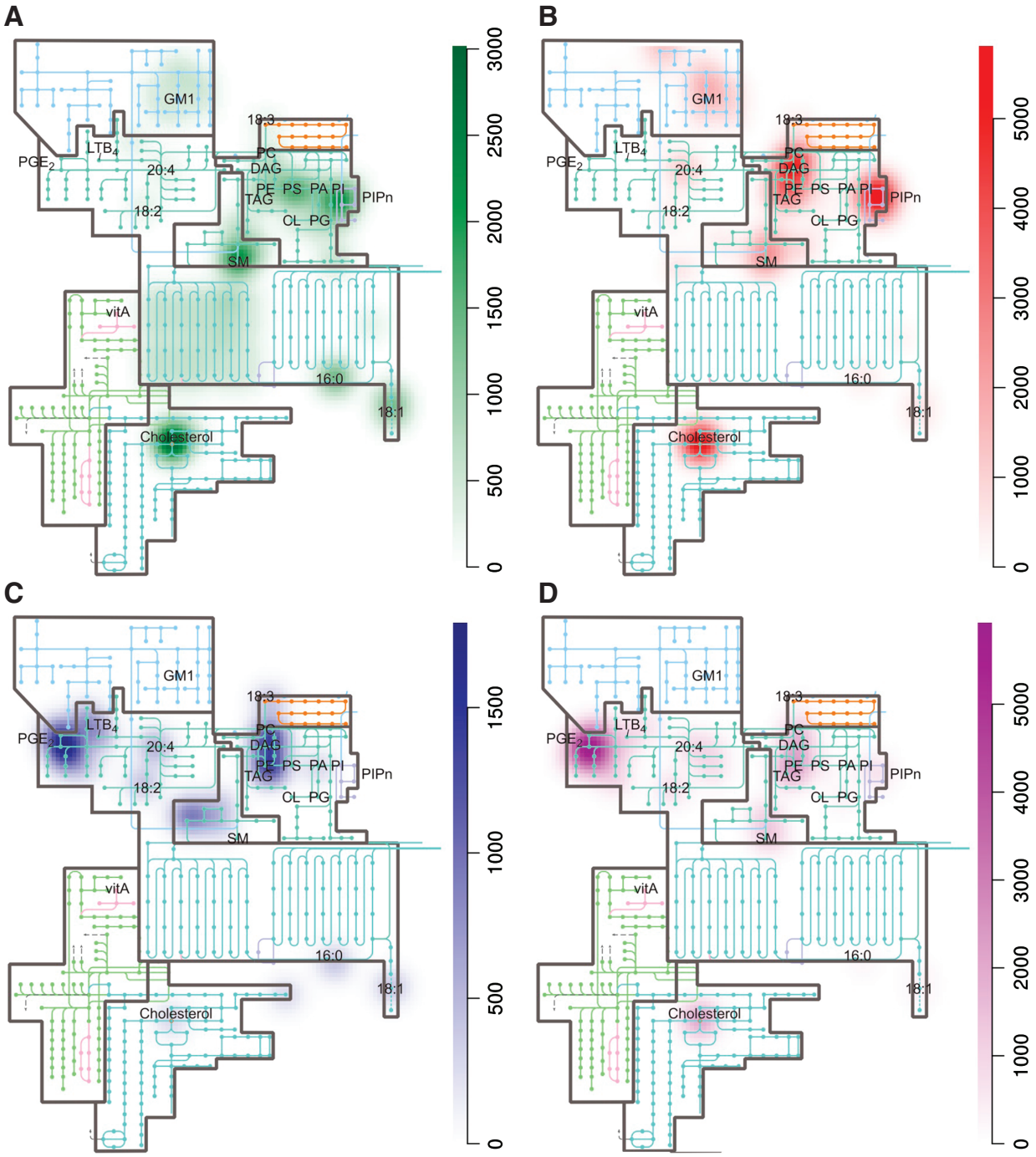

Figure 2: The involvement of lipids in host–pathogen interactions. Heat maps were generated for different types of pathogens (panels A–D) based on the weighted involvements of lipids in host–pathogen interactions (the list of pathogens and their lipid targets and weight factor is described in Table S1, Supporting Information). Heat maps show the frequency of involvements of specific host cell lipid (sub)classes (e.g. phosphatidylserine) and/or species (e.g. cholesterol) for viruses (A), bacteria (B), fungi (C), and parasites (D). Increased coloring indicates increased frequency. The heat maps were constructed with an algorithm using the R-package for spatial statistics (spatstat) (247).

genome replication stage, there are marked differences in the virus–host lipidome interaction even between viruses from the same family (40,59,60), whereas unrelated viruses might use similar strategies to usurp the host lipidome [e.g. the requirement for phosphatidylinositol-4-phosphate (PI(4)P) and cholesterol appears to be widespread] (37,40,45,60–63). Finally, viral activation of fatty acid synthase (FAS) for the production of new membrane compounds is frequently observed (59,64–70).

For the other types of pathogens, bacteria, parasites and fungi, the situation is more complex. Prokaryotic or eukaryotic micro-organisms not only target host cells to modulate host cell responses directly, but they can also produce lipids themselves, or acquire specific lipids from the host and/or convert these lipids, necessary for microbe growth or to influence host cell responses (26). This is highly relevant – but beyond the scope of this review – as it not only may provide important insights into the development of new therapeutic strategies, but also because the outcome of these lipid interactions may either lead to commensalism or to host damage/disease (26).

The interaction map of bacteria with host cell lipids (Figure 2B) shows that bacteria preferentially target phosphoinositides (71–78), cholesterol (79–83), sphingomyelin (SM) (79,84–86) and neutral lipids (87–90). Most bacteria are not capable of synthesizing these specific lipid classes. For example, the major phospholipids in *Escherichia coli* are phosphatidylethanolamine (PE, 70%), phosphatidylglycerol (20%) and cardiolipin (5%) (91). It is tempting to speculate that by targeting these host-cell specific lipids, bacteria are not in danger of affecting their own metabolism. Indeed, bacteria hardly target host cell PS, a minor lipid in bacteria, but needed for the synthesis of PE, whereas viruses do (compare Figure 2A and B).

The interaction map of fungi with host cell lipids is very different from that of viruses and bacteria and these pathogens appear to focus on structural phospholipids (PC and PE) (92,93), sphingolipids (94–96) and eicosanoids (97–99) (Figure 2C). The targeting of neutral lipids is possibly related to the generation of precursors for phospholipid biosynthesis or eicosanoids to induce inflammatory responses.

Parasites are in many aspects not comparable to other pathogens. In general, in accordance with their parasitic way of life, parasites have discarded pathways of *de novo* lipid synthesis but have selectively retained several biosynthetic pathways that modify host lipids (100,101). Although lipids such as fatty acids, phospholipids and sterols are obtained from their host or are synthesized from building blocks obtained from the host, less abundant lipids that are more difficult to acquire (e.g. specific unsaturated fatty acids, eicosanoids, ecdysteroids and quinones) are synthesized by the parasite, often by modification of more abundant substrates (102–104). Comparison of the four different panels shows that viruses, bacteria and parasites target glycolipids whereas fungi do not. Many viruses and bacteria use glyco(sphingo)lipids as receptors, but whether these lipids are indeed crucial for infection has been addressed in only a few cases. For more details about carbohydrates as virus (co)receptors, we refer to other reviews (85,105,106).

Viruses

Viruses constitute a highly diverse group of pathogens that are mainly classified by phenotypic characteristics, such as host organisms, the diseases they cause, their structure (e.g. presence or absence of a lipid bilayer, the 'envelope'), and the nucleic acid type of the viral genome, which is either single- or double-stranded DNA or RNA. Single-stranded genomes are then designated as positive-strand (+RNA), i.e. containing directly translatable information like mRNA, or negative-strand (−RNA). Viruses are obligate intracellular pathogens and require host cells in order to replicate. A viral replication cycle basically comprises the following steps: receptor binding (attachment to the host cell), cell entry (often via endocytosis), uncoating (release of the viral genome into the cell), genome replication, virion assembly (packaging of new genomes into virus particles), and virus release (by budding or cell lysis). Viruses can interact with the host lipidome in two ways, namely by exploiting pre-existing molecules or by actively altering host lipid metabolism. The role of lipids in (i) vital entry, (ii) genome replication, (iii) budding and (iv) innate immune response will be briefly addressed.

Viral entry

During entry, viruses usually specifically exploit one of the cellular endocytic routes and the lipids functioning in these pathways, but do not actively modulate the lipidome yet. The pathways and lipids exploited by viruses span the entire cellular repertoire. Despite this large degree of variation, cholesterol (category E) appears to be important for the entry of many different viruses (see e.g. 22, 107). The most straightforward explanation is the fundamental importance of cholesterol for the organization of membranes and the functioning of endocytic pathways.

Viral genome replication

To support the replication of their genome, viruses can actively modulate the host lipidome. Most DNA viruses (e.g. herpes viruses) replicate their genomes inside the nucleus, but some [e.g. vaccinia virus (VACV)] assemble structures in the cytoplasm to complete their replication cycles (reviewed in 108, 109). All +RNA viruses [e.g. poliovirus (PV), hepatitis C virus (HCV), dengue virus (DENV), West-Nile virus (WNV) and SARS- and MERS-coronavirus] reorganize host cell membranes into membranous structures in the cytoplasm that serve as a scaffold for viral RNA synthesis/replication (referred to as 'viral factories', 'membranous web' or 'replication organelles'). While all +RNA viruses generate replication organelles, the morphology of these organelles varies greatly among virus families. Each virus family hijacks membranes from a different cellular organelle (e.g. Golgi, ER, mitochondria, endosomes or lysosomes), exploits a distinct set of host factors, and modulates specific lipid metabolic pathways to build replication organelles with a unique protein and lipid composition (reviewed in 110, 111).

Fatty acids (FAs, category A) have been implicated in the replication of many different viruses. VACV was reported to rely on the synthesis and mitochondrial import of FAs and on β-oxidation for ATP production (69). Many +RNA viruses use FAs to synthesize lipids to build their replication organelles. PV was reported to enhance uptake and prevent routing of FAs to lipid droplets (64), whereas DENV recruited FAS to its replication organelles and increased the activity of the enzyme to ensure high amounts of local FA synthesis (66). Also other viruses, e.g. WNV, require FAS activity, as their replication is inhibited by FAS inhibitors (59). Furthermore, the cellular energy regulator AMPK, which is an inhibitor of FAS, restricted infection of a number of unrelated viruses including the -RNA virus Rift Valley Fever Virus (68) and HCV. At least HCV actively counteracts this restrictive mechanism by inactivating AMPK (112). Finally, not only the amount of FAs may be important, but also chain length and saturation. PV specifically enhances the uptake of long chain FAs (64) and the replication of HCV and the integrity of its membranous web depend on the enzyme stearoyl-CoA desaturase 1, which converts the saturated FA stearate into the mono-unsaturated FA oleate (113).

Recently, PI(4)P (category C) and the PI(4)P-synthesizing enzymes PI4KIIIα and PI4KIIIβ have been shown to play a pivotal role in +RNA virus replication. HCV utilizes predominantly PI4KIIIα to generate large pools of PI(4)P in its membranous web that are essential for viral RNA replication (38,39,41–43,114,115). PI4KIIIα activity was shown to be important for the integrity of the membranous web and the PI(4)P levels affect the phosphorylation status of one of the viral proteins (NS5A), thereby influencing the process of viral RNA replication (40,44). Enteroviruses (e.g. PV, Coxsackievirus B3 and most probably also the other enteroviruses) on the other hand rely on PI4KIIIβ for a PI(4)P-rich environment in their replication organelles (37,116,117). It has been suggested that the PI(4)P-rich environment attracts the viral polymerase to the replication organelles to replicate the viral RNA (37). A new role of PI(4)P in infection was recently uncovered for both HCV and enteroviruses, being the recruitment of oxysterol-binding protein (OSBP) to the replication organelles (60,63) (see below). Also the replication organelles of the -RNA virus Junin virus were reported to contain PI(4)P, but the significance of this finding is still unclear (118). Recent research into the importance of phospholipids for virus replication has focussed on PI(4)P, but there is emerging evidence that also other phospholipids play a role. In DENV-infected mosquito cells, PE (primarily lysoPE16:0) and PA are upregulated, but the role of these lipids in replication remains to be established (65). Most strikingly, influenza A virus (IAV), a -RNA virus that replicates in the nucleus, upregulates the synthesis of ether-phosphatidylcholine (ether-PC) species in peroxisomes, which appears to be important

for replication, although the role of the ether-PCs is unknown (119).

For virus genome replication, the importance of sphingolipids (category D) has only been covered by a few studies. It was noted that two Ceramide species (Cer18:1/16:0 and Cer18:0/16:0) are specifically enriched on replication organelles in DENV-infected mosquito cells, but the role of these lipids remains to be shown (65). During HCV infection, the SM synthases SMS1 and SMS2 are upregulated and inhibition of SMS activity impairs replication. A number of specific SM and Cer species, in particular SM18:1/16:0 and SM18:1/24:0, are enriched on the membranous web, where they interact with and increase the activity of NS5B, the viral RNA-dependent RNA-polymerase (120).

As mentioned above, HCV and enteroviruses were reported to use PI(4)P to recruit OSBP to replication organelles. OSBP is an important regulator of cellular lipid homeostasis that shuttles cholesterol from ER to Golgi (121). It is suggested that in infected cells OSBP is important for the accumulation of cholesterol (category E) on the replication organelles (60,63). To accommodate the requirements for cholesterol, HCV upregulates the synthesis of cholesterol (and FAs) via SREBP activation (122), whereas enteroviruses, which shut down host protein synthesis, acquire cholesterol by increasing uptake of the lipid and possibly by rerouting cholesterol from lipid droplets (61,62). The roles of cholesterol in virus replication have only begun to be unravelled. For HCV, OSBP and cholesterol appear to be important for the integrity of the membranous web (60). Enteroviruses were proposed to require cholesterol for optimal proteolytic processing of viral proteins by a mechanism that has yet to be elucidated (61), although a role in replication organelle organization similar to HCV remains possible. Other viruses also require cholesterol or modulate its synthesis for efficient replication (e.g. DENV, Norwalk virus; 51,58), although the role of cholesterol in the replication of these viruses is still under investigation. Interestingly, hepatitis B and C viruses, which are in distinct virus families, accumulate the cholesterol biosynthetic intermediates 7-dehydrocholesterol and desmosterol respectively (123,124). The importance of these lipids for infection is not known, but their function may extend beyond that of mere biosynthetic intermediates.

Viral budding

During budding, many – but not all – enveloped viruses acquire specific lipids, leading to an envelope with a lipid composition different from the donor membrane (reviewed in e.g. 125). These lipids are needed for efficient budding and release, optimal stability of the viral particle and entry. Viruses may obtain envelopes with a specific lipid composition by modulating host lipid metabolism and/or by budding from membrane microdomains (rafts) with a specific lipid composition. For example, the human immunodeficiency virus (HIV) obtains a raft-like envelope rich in sphingolipids (category D) presumably by budding from lipid rafts modulated by the viral protein Nef (126,127). Many other viruses (e.g. IAV and WNV) also have envelopes enriched in SM and ceramide species (119,128). Vaccinia virus has a PS-rich envelope (category C), which makes it resemble apoptotic bodies and provides an entry route via PS-dependent macropinocytosis (46). PS-dependent entry may be a widespread mechanism used by many different viruses, such as DENV virus and the −RNA ebola virus (EBOV) (reviewed in 107).

Innate antiviral response

Finally, cells can alter their lipidome to mediate antiviral defense mechanisms. When cells sense a viral infection, they produce and secrete interferons as danger signals. In response to interferons, a collection of interferon-stimulated genes (ISGs) is upregulated to combat the viral infection at several levels. Cholesterol-25-hydroxylase, which synthesizes the cholesterol derivative 25-hydroxycholesterol (25HC) (category E), was found to be such an ISG (129) and 25HC levels were highly elevated upon infection (130). 25HC was suggested to alter the properties of host and virus membranes (e.g. IAV, HIV and EBOV) and reduce their permissiveness for fusion (129). Additionally, 25HC inhibits the synthesis of a wide variety of lipids and thus may restrict viruses that require lipid synthesis. Another ISG, IFITM3, was reported to disrupt OSBP function and alter cellular cholesterol homeostasis, which inhibited infection of at least two different enveloped viruses (131). However, viruses in turn have developed mechanisms to neutralize the innate defense mechanism.

For example, WNV was reported to redistribute cellular cholesterol not only to enhance replication, but also to disrupt the cholesterol- and raft-dependent functioning of interferon signaling thereby reducing the innate immune response (132).

Pathogenic Bacteria

Intracellular bacterial pathogens induce a variety of metabolic changes in the affected host cells to promote their own survival and replication (133–136). By secreting virulence factors termed effectors, bacteria trigger uptake (invasion), intracellular replication and interfere with inflammation processes (23,137,138). Modulation of lipid metabolism by virulent bacteria is a common approach in their strategy to invade and propagate in the host cell (28). Thus, lipids are not only used as a nutrient source but also to influence the host cell metabolism, physiology and membrane trafficking, enabling pathogen survival and replication. While the targeting of plasma membrane lipid rafts and the modulation of phosphoinositides seems characteristic for influencing their invasion, targeting of host cell cholesterol (esters), triacylglycerols and phosphoinositides facilitates the intracellular survival of a number of pathogens. FAs are the predominant target for interference with inflammation. The role of lipids in (i) bacterial uptake, (ii) replication and (iii) inflammation will be briefly addressed.

Bacterial invasion

Pathogenic bacteria evolved different strategies to invade their host. For example, *Streptococcus*, *Salmonella* and *Coxiella* induce their uptake in nonphagocytic cells by triggering receptor-mediated endocytosis (139), by actin rearrangements (140,141) or by targeting lipid raft microdomains at the plasma membrane (142). Interference with the mechanism of uptake was shown to decrease the virulence of these pathogens suggesting that the entry mechanism is tightly linked to the intracellular survival of the bacteria. Cholesterol is considered a crucial factor in the uptake of host cells by *Salmonella* (143–145), *Helicobacter* (146), *Vibrio cholera* (147,148), *Shigella flexneri* (79) and *Listeria* (149).

Another target for intracellular bacteria to affect their invasion and subsequent diversion of host membrane trafficking pathways is the manipulation of phosphoinositides (71,74,150,151). All different phosphoinositide species are targeted during the bacterial-host interplay. Pathogens such as *Salmonella* and *Mycobacteria* e.g. directly interfere with the PI(3)P levels of the plasma membrane during entry by secreting effector molecules. The phosphatase SopB secreted by *Salmonella* increases the PI(3)P levels at the site of engulfment to recruit the host Rab 5 and PI(3)P kinase Vps34 to the newly formed *Salmonella*-containing vacuole (152,153). By contrast, *Mycobacteria* decreases PI(3)P levels to interfere with the intracellular maturation (154). Similar seemingly contrasting phenomena are observed for other phosphoinositides. For the benefit of *Shigella*, PI(4,5)P_2 levels are decreased in an bacterial effector driven way to produce PI(4)P and PI(5)P (155), but successful *Yersinia* invasion requires transient production of PI(4,5)P_2 at the site of bacterial entry (73). It will require a better understanding of the entire (hydrophobic) metabolome to understand how opposing regulation of phosphoinositide metabolites can both favor pathogen survival.

Bacterial replication

Once inside the host cell, bacterial pathogens use different strategies to subvert the host-cell trafficking pathways in order to resist intracellular killing (156). Interfering with the host cell lipid metabolism is a powerful mechanism used by a number of intracellular bacteria to create a replicative niche and to inhibit autophagosomal induction, vacuole acidification and apoptosis from inside the pathogenic vacuole (28).

Many bacteria interfere with phosphoinositide metabolism not only to promote host cell entry but also to facilitate survival (74,150). During invasion, targeting of host cell phosphoinositide metabolism is aimed at interference with the signal transduction pathways and cytoskeletal architecture. During intracellular survival, the role of phosphoinositides in the host cell membrane dynamics is targeted (157). Phosphoinositides contribute to organelle identity by recruitment of specific effector proteins (75,158). To subvert vesicular trafficking of infected host cells, *Legionella* was shown to secret effector proteins that are anchored to the *Legionella*-containing vacuole in a PI(4)P-dependent manner (159). Bacteria that reside in a bacterial containing vacuole for successful

replication like *Salmonella* (160–162), *Shigella* (163) and *Mycobacteria* (164), continuously manipulate phosphoinositide metabolism from within the vacuole by secreting phosphatases (SopB, IpgD and SapM, respectively).

Many intracellular pathogens also interfere with cholesterol metabolism by acquisition of host cell cholesterol. Accumulation of cholesterol on the vacuole of *Coxiella* (165,166), *Salmonella* (81,145,167), *Chlamydia* (80) and *Mycobacteria* (82) was shown to be essential for intracellular survival. The *Salmonella*-containing vacuole for example contains up to 30% of the cellular cholesterol pool (81) by redirecting exocytic vesicles from the Golgi complex rich in cholesterol and sphingolipids (168). A similar strategy is used by *Chlamydia* (33). Although the function of this recruitment is not clear, a role in membrane-trafficking pathways has been suggested (169). A role as a nutritional source can also not be excluded, similar to *Mycobacterial* cholesterol acquisition (170). *Coxiella*, a pathogen that persists for 4–5 days in the infected host cell, causes an increase of cellular cholesterol levels by up to 70% (166). It is not clear whether this is a pathogen driven process or a response by the host cell to maintain cholesterol homeostasis. Nevertheless, it is an evident example of pathogen-induced (de)regulation of host lipid metabolism.

Several intracellular bacteria also interfere with neutral lipid metabolism, either directly (e.g. secretion of lipases) or indirectly by interference with lipid droplet homeostasis. Besides their role in energy (TAG) and cholesterol ester storage, lipid droplets are involved in host cell lipid transport and metabolism, membrane trafficking, intracellular signaling, and production of inflammatory mediators (171,172). Although interference with lipid droplet biogenesis and turnover is a strategy used by many bacteria, the exact role of this interference is not well understood in most cases. This is illustrated by *Salmonella*, which actively interferes with host cell lipid droplets by secreting SSeJ and SseL effector molecules, however with opposing effects. SseJ mediates the esterification of cholesterol in cell membranes which results in enhanced lipid droplet biogenesis (173). SseL prevents the accumulation of lipid droplets via its deubiquitinase activity (87). Other bacteria like *Mycobacteria* and *Chlamydia* induce a massive increase of (TAG) containing lipid droplets in the infected macrophages and in both cases lipid droplet accumulation during infection was shown to be crucial for bacterial survival (174). *Mycobacteria* utilize lipid droplets as a nutritional source (88) and hijack lipid droplets as part of their strategy in acquiring host cell iron (175). *Chlamydia* targets lipid droplets to interfere with inflammation by replacing the lipid droplet core protein ADRP with bacterial derived effector molecules (89,90).

Bacterial inflammation

Inflammation is the body's immediate response in attempt to prevent the spread and infection of microbial pathogens (176,177). Lipid mediators, such as prostaglandins and leukotrienes (lipid category A) are key players in inducing inflammation (178). They are synthesized from phospholipid-derived polyunsaturated FAs (PUFAs) like arachidonic acid (ω6) and ω3 fatty acids (177). Both Gram-negative and Gram-positive bacteria are able to induce their synthesis via triggering signal transduction pathways that enhance phospholipase activities and/or cyclooxygenase COX-2 expression levels in target cells (179). *Salmonella* alters host cell signaling in the intestinal epithelial cells by delivering the effector protein SpiC to the cytosol of infected macrophages. This action promotes an immunosuppressive phenotype which impairs bacterial killing (180). *Escherichia coli*, *Vibrio cholera*, *Mycobacteria*, *Streptococcus* and *Pseudomonas* use similar mechanisms to induce the COX-2 expression and promote prostaglandin production for their own benefits (179). Bacterial pathogens also interfere with the biosynthesis of oxidized FAs that act as anti-inflammatory molecules. *Pseudomonas aeruginosa* secretes a lipo-oxygenase that converts host arachidonic acid for local 15-HETE production (181). In this way, the host-immune defense can be subverted by generating local 'stop signals' (182).

Fungi

Of the 1.5 million species of fungi, there are only around 300 known to cause pathology in humans (183,184). Pathogenic species such as the relatively common *Trichophyton* (causing athlete's foot), *Crytococcus neoformans* (causing meningoencephalitis) and *Aspergillus* spp. (causing infections of ear, eye and nails) are often opportunistic and systemic infections normally only occur in

immunocompromised individuals (185). Thus, fungi do not typically enter the host cell but affect host lipid metabolism by extracellular secretion of factors. Indeed, fungi are rich sources for molecules that interact with the lipid metabolism of mammals. Particularly, well studied are molecules that interfere with various steps in the synthesis of sphingolipids because of their applicability in fundamental research and cancer therapy (186,187). Sphingolipids are key molecules in protein trafficking, lipid homeostasis and cell differentiation and their balanced occurrence is essential. Serine palmitoyltransferase (SPT) catalyzes the first, committing- and rate limiting step in sphingolipid de novo synthesis. Sphingofungins, lipoxamycin and myriocin are fungal structural analogs of the SPT intermediate- or end products with potent and highly selective inhibitory activities (188,189). Also subsequent steps in the synthesis of the sphingolipid backbone are efficiently inhibited by fungal metabolites: ceramide synthase is sensitive to Fumonisins (isolated from *Fusarium verticillioides*), AAL-toxin (*Alternaria alternata*) and Australifungins (nonpathogenic *Sporormiella australis*) (190–192). It is interesting to note that all these fungi-derived molecules interfere with early steps in sphingolipid synthesis, i.e. prior to the synthesis of sphingomyelin in host cells (Figure 2C). This is probably related to the fact that after the synthesis of (dihydro-)ceramide, the fungal- and mammalian anabolic metabolism of phosphosphingolipids diverge. Whereas mammals synthesize SM, fungi use inositol as an headgroup, leading to inositol phosphorylceramide (IPC), which plays a crucial role in pathogenesis of *Cryptococcus neoformans* (193,194). Therefore, these inhibitors are also potent antifungals and it has been suggested that these inhibitors are used to gain advantage over fungi competing for the same resources (185).

Most pathogenic fungi also secrete phospholipases to facilitate adhesion, cell entry, and lysis (92). Phospholipases are hydrolytical enzymes that degrade membrane phospholipids, leading to membrane dysfunction or even disruption of the cell. In this case, targeting of the most abundant host cell membrane phospholipids, PC and PE, is effective in interference with membrane integrity (Figure 2C). The action of phospholipases also results in the generation of bioactive signaling molecules. In the case of phospholipase C action, diacylglycerol is generated which leads to activation of protein kinase C and tilts the survival/death balance toward survival and proliferation. In the case of phospholipase A or B, FAs are released that can be consumed by fungi and/or oxidized to generate potent signaling molecules with a profound impact on the immune system. These oxidation products are derived from PUFAs in the host cell. Arachidonic acid is used as a precursor in the generation of eicosanoids, a family of oxygenated C20 fatty acids that include prostaglandins, leukotrienes and thromboxanes (195) (Figure 2D). Enzymatic oxidation of arachidonic acid is achieved by the actions of either lipo-oxygenases, cyclooxigenases or CYP enzymes, but also nonenzymatic reactions (lipid peroxidation) can lead to the formation of bioactive arachidonic acid metabolites known as isoprostanes (196). Similarly, other PUFAs such as eicosapentaenoic acid (20:5) or docosahexaenoic acid (22:6) can serve as precursors for bioactive oxidation products in mammalian hosts. Analysis of the genomes of numerous fungi suggests the ubiquitous presence of enzymes forming oxidized FAs (197). This makes oxidized FAs ideal candidates for host–pathogen interaction and there are indeed numerous reports of fungal derived oxidized FAs interacting with the immune system of the host (198). For instance, the major pathogens *Cryptococcus neoformans*, *Candida albicans* and *Aspergillus fumigatus*, all synthesize and secrete anti-inflammatory prostaglandins PGE2 en PGD2 (97,98). Linked to decreased pulmonary function are PGF2a, TXB2, 6-keto PGF1a and isoprostanes, which are released by the respiratory pathogen *Aspergillus fumigatus* (97,99,199). It has been suggested that the immunosuppressive molecules secreted by fungi are necessary to establish a sustainable population of (nonpathogenic) yeast in e.g. the bowel and that fungal dysbiosis leads to disease (200).

As with the fungal-derived molecules that interfere with sphingolipid metabolism in both host cells and in fungi, oxidized FAs can also act both on host cells and on fungi. Fungi use oxidized FAs for regulation of fungal cell growth and differentiation, but these processes are still poorly understood. For instance, PGE2 and TXB2 induce germ tube formation in *C. albicans* and there is strong evidence that other oxidized FAs are involved in the development of the sexual stage in this and other yeasts (201). Also the formation of biofilms, conglomerates of fungi protected by a

mucuous layer, is directed by prostaglandins (202). Thus, fungal derived oxidized FAs modulate the host's immune system, while the same molecules influence normal fungal form and function. Here we see a typical example of signaling by oxidized FAs that is well conserved across biological kingdoms and that is optimally exploited as inter-kingdom signaling molecules (198). Whereas virulence factors from bacteria, viruses and parasites have evolved to optimally exploit the resources of the host, it seems that fungal effectors establish a stable commensalism based on complex bi-directional fungi–host interactions mediated by e.g. oxidized FAs, which may run out-of-control in the case of pathogenic fungi.

Parasites

Two completely different types of parasites exist: unicellular parasitic protozoa and parasitic helminths (worms). For the purpose of this review, parasitic protozoa can be divided in (i) protozoa that live inside cells of their host (e.g. erythrocytes or macrophages) and (ii) those that live outside the cells of the host, e.g. parasitizing the digestive and urogenital tract or the bloodstream of the host (see e.g. Table 1). Interactions with the lipid metabolism of the host can be strikingly different in these different niches. Parasitic helminths, however, for obvious reasons of magnitude never live inside cells of the host, but are always extracellular. However, with respect to metabolic interactions with their host a clear distinction can be made between helminths that live in, e.g. the digestive tract of the host, compared with helminths that live truly inside the body of their host (in, e.g. the lymphatic system or bloodstream). These differences in niche between the various types of parasites, protozoa as well as helminths, result in differences in the ways parasites interact with the lipid metabolism of their hosts.

In general, most parasites affect the host FA metabolism (lipid category A) by catabolism of host lipids. Subsequently, the parasites often take up the lipid degradation products, including FAs, from their host (100,203–207). Some parasites even lost the ability to synthesize FAs themselves *de novo*, such as the blood-dwelling helminths *Schistosoma* spp. (208,209), and thus depend entirely on FA uptake from the host. After uptake by the parasite these FAs are often remodeled, for instance, by chain elongation or by alteration of the desaturation of the FA moiety (104,203,210). Many parasites take up PUFAs, such as arachidonic acid, to produce eicosanoids that

Table 1: Protozoa versus helminths: Different niches of unicellular and multicellular parasites

Parasite type	Intra- or extra -cellular	Example (parasite group)	Example (species)	Intracellular location[a]	Extracellular location[a]
Protozoa	Intracellular	Apicomplexa	*Plasmodium* spp.	Erythrocytes	
			Toxoplasma gondii	Nucleated cells	
		Trypanosomatidae	*Leishmania* spp.	Macrophages	
			Trypanosoma cruzi	(Heart) Muscle cells	
		Microsporida	*Enterocytozoon* spp.	Mucosal cells	
	Extracellular	Diplomonadida	*Giardia lamblia*		Digestive tract
		Amoeba	*Entamoeba histolytica*		Digestive tract
		Parabasalia	*Trichomonas vaginalis*		Urogenital tract
		Trypanosomatidae	*Trypanosoma brucei*		Bloodstream
Helminths	Intracellular	None	None	–	
	Extracellular	Nematodes (roundworms)	*Ascaris lumbricoides*		Digestive tract
			Wuchereria bancrofti		Lymphatics / bloodstream
		Cestodes (tapeworms)	*Taenia saginata*		Digestive tract[b]
			Echinococcus granulosus		Digestive tract[c]
		Trematodes (flukes)	*Fasciola hepatica*		Bile duct
			Schistosoma mansoni		Bloodstream

[a]In final host.

[b]+ cysts in muscle tissue in mammalian host (cattle).

[c]+ cysts in liver and lungs of intermediate mammalian hosts.

subsequently affect the host immune reaction (211). For instance, prostaglandin PGE2 is synthesized by many parasites including parasitic protozoa (e.g. *Entamoeba histolytica*, *Toxoplasma gondii* and Trypanosoma spp.), as well as by nematode, cestodes and trematode helminth species (212). Prostaglandins produced by the parasite affect the host in many processes including vascular tone, hemostasis, chemotaxis, activation and skewing of various types of immune cells (212,213).

Similarly, parasites do not take up intact TAGs from the host and they tend to use phospholipases (affecting lipids in category C) to be able to take up free FAs and lyso compounds as building blocks for their own complex lipid biosynthesis. TAG metabolism (lipid category B) and trafficking has been shown to be essential for parasite development and proliferation in *Plasmodium*-infected erythrocytes (214,215). Accumulation of TAG in lipid droplets in *P. falciparum*-infected erythrocytes was shown to be strikingly pronounced during intraerythrocytic proliferation from trophozoite to the schizont stage, whereas TAG degradation became active from schizont to the segmented schizont stage. Presumably, TAG is not essential as a source of energy for the parasite, because the capacity for FA oxidation is very limited. Possibly TAG provides a source of FA groups for the glycerophospholipid biosynthesis that is required for membrane biosynthesis for merozoite release (215). Glycerophospholipids (lipid category C) of the host cell play a role in the invasion process of various intracellular protozoan parasites, as surface associated phospholipase enzymes of *Toxoplasma*, *Cryptosporidium*, *Entamoeba*, *Plasmodium* and *Trypanosoma cruzi* are supposed to be involved in their invasion of the host cells by creating pores in the host cell membrane, or by altering the host membrane fluidity (207). Phospholipase activity has also been shown to play a role in differentiation and intracellular development of these protozoan pathogens.

A biphasic generation of ceramide (lipid category D) is triggered in macrophages by the protozoan parasite *Leishmania* (216,217). First, attachment of the parasite to the macrophage membrane activates acid sphingomyelinase, which catalyzes the formation of ceramide from SM. Inhibition of acid sphingomyelinase resulted in reduced uptake and infection with the parasite, which shows that ceramides are important for entry into the host cell. Subsequently, *de novo* synthesis generates ceramide that will probably reduce the cellular cholesterol level and displace the cholesterol from the membrane, leading to enhanced membrane fluidity, disruption of rafts, and impaired antigen-presentation to the T cells. SM is likely to be an important lipid in *Toxoplasma*, as the SM levels in *Toxoplasma* infected cells are increased. *Toxoplasma* salvages sphingolipids from the host Golgi through the rerouting of selected Rab vesicles to the parasitophorous vacuole (218).

Parasites do not synthesize sterols (lipid category E) themselves and instead sterols are usually taken up from the host (204). In mammalian cells infected with *Toxoplasma gondii*, the uptake of low-density lipoproteins (LDL) is upregulated and its cargo is subsequently diverted such that LDL-derived cholesterol is not first transferred to the plasma membrane of the host cell but directly to the parasitophorous vacuole (219–221). In addition, in *Toxoplasma* infected cells cholesterol synthesis is suggested to be uncoupled from LDL uptake, such that the normally negative feedback on HMG-CoA reductase, the enzyme that controls the biosynthetic flux to cholesterol, is dysregulated (204,222).

Cholesterol from the host is not only required for parasite replication, it is also important in host cell invasion by *Toxoplasma*, because cholesterol depletion in the host cell plasma membrane blocks parasite internalization (223). Although cholesterol-enriched parasite apical organelles termed rhoptries discharge lipids during cell entry and contribute to the parasitophorous vacuolar membrane (PVM) formation, rhoptry cholesterol appeared not to be essential for this process. However, host plasma membrane cholesterol was shown to be incorporated into the forming PVM during invasion, through a caveolae-independent mechanism, which suggests that host cholesterol controls entry of an intracellular pathogen (27,223). Similar results were obtained for entry of the parasitic protozoan *Leishmania donovani* into macrophages and *Trypanosoma cruzi* into HeLa cells, as cholesterol depletion from the plasma membrane inhibited entry of the parasite (224–226).

Relevance to Membrane Trafficking

Research on the involvement of lipids in host–pathogen interactions has significantly contributed to our molecular understanding of intracellular membrane trafficking and dynamics in eukaryotic cells. A few examples will be given for each type of pathogen.

Notable contributions to the membrane trafficking field come from lipid related research on protein toxins internalization, yielding insight in retrograde transport from the plasma membrane to the endoplasmic reticulum. Shiga and cholera toxin are internalized into the host cell in a cholesterol-sphingolipid dependent manner (79). Retrograde transport was known to operate between PM and TGN, but these studies showed that it continued through Golgi cisternae to the ER (227–229). The targeting and interconversion of various phosphoinositides by pathogen kinases and phosphatases contributed to our understanding of the importance of phosphoinositide signatures to subcellular organelle identity (71,230).

In the 1980s, fumonisins were isolated from the fungus Fusarium moniliforme (231). The usability in biochemical research of these analogs of intermediates in sphingolipid biosynthesis was quickly recognized and fumonisins (together with other fungal sphingolipid analogs such as myriocin discussed above) have been widely used in the elucidation of the role of sphingolipids in the trafficking of proteins and lipids (232,233).

Viruses have evolved to utilize a wide variety of cellular molecules and pathways. The finding by Helenius and colleagues that Semliki Forest virus (SFV), an enveloped virus, fused in a prelysosomal compartment (234) was critical to the discovery and characterization of the organelles that we now know as 'endosomes' (235). The dependence of SFV on luminal acidification and cholesterol (236) suggested two important properties of endosomes. Since those pioneering studies, viruses have been indispensable tools for the elucidation of endocytic pathways and many other aspects of membrane and lipid biology (22,237).

During the obligate intracellular liver stage, *Plasmodium berghei* parasites are surrounded by vesicles from the host late endocytic pathway allowing transport of material toward the parasite interior (238). The *Plasmodium* parasitophorous vacuole (PV) membrane displays long tubular extensions that pervade the host cytoplasm, which increases the surface of exchange between the host cell and the PV. Although *Plasmodium* is unable to synthesize sterols, it does contain cholesterol that must be diverted from host cell compartments and properly delivered to the PV. Interestingly, the PV membrane forms tight associations with the host endoplasmic reticulum (ER) shortly after invasion and during schizogony (239). The gathering of host ER to the PV membrane offers an attractive mechanism to situate the host lipid biosynthetic machinery in close proximity to the PV and may be reminiscent of the currently intensely investigated organellar contact sites that allow rapid transport and/or exchange of lipids.

These examples from the various types of pathogens exemplify the relevance of lipid targeting by pathogens to affect host cell membrane trafficking. Due to the lack of experimental resolution, most of these studies address the effect of lipid classes. In only a very few cases, the role of a specific lipid species in membrane dynamics could be identified. Notable examples are the role of the ganglioside GM1 as the receptor of cholera toxin (although in this case the importance of the fatty acid composition is not known)(240), and a highly specific interaction of a single sphingomyelin species, SM 18, with the transmembrane domain the COPI machinery protein p24 (241). Lipidomic and/or metabolomic studies on host–pathogen interactions bear great potential to contribute to advancement of intracellular (lipid) trafficking pathways in eukaryotic cells. First of all, systematic lipidomic analysis of lipids allows the simultaneous screening of virtually all lipids in one assay. Second, using mass spectrometry, the analysis can be performed with much higher sensitivity, allowing the identification of minor (signaling) components. Third, the new generation of mass spectrometers has a much higher resolution, allowing precise annotation of molecular species.

Conclusions and Outlook

The hydrophobic metabolome encompasses an unprecedented number of lipid species and deserve more attention

as being a significant – if not largest – part of the entire metabolome. Even current estimates are probably conservative as there are almost unlimited possibilities with spontaneous and enzymatically catalyzed lipid oxidation products. It is becoming increasingly evident that even these oxidized lipids can have important cellular functions by interacting with lipid-binding proteins (242). In addition, there are numerous pathogen-specific lipids such as lipopolysaccharides containing a lipid A moiety in Gram-negative bacteria (243) and unique lyso-PS species (244) that are not considered in this review but that further increase the complexity of the entire lipidome. Yet, the function of the individual lipid species is largely unknown and only in a few cases we start seeing a glimpse of their biological function.

During evolution, microbial pathogens have exploited the potential of the hydrophobic metabolome and now take full advantage of the complexity of the lipidome to influence the host cell phenotype (28). The different types of microbial pathogens do so in a very different way. Simple (unicellular and prokaryotic) microbial pathogens such as bacteria target host cell lipids that are generally not synthesized by bacteria. These include structural membrane lipids such as cholesterol and phosphatidylcholine as well as signaling lipids such as phosphoinositides and sphingomyelin. In addition, they target neutral lipids for fatty acid production for a variety of functions. In broad outlines, viruses and bacteria target the same group of lipids (compare Figure 2A and B) with one notable exception: whereas several viruses target PS in the host cells, this is only sporadically reported for bacteria. The complex eukaryotic microbial pathogens, fungi and parasites, interact with the host cell lipidome in a very different way as compared to bacteria and viruses (compare Figure 2C and D with Figure 2A and B). The most notable differences between 'simple' and 'complex' microbial pathogens are (i) the lack of cholesterol and signaling lipid (phosphoinositides and sphingomyelin) targeting by fungi and parasites; and (ii) the abundant targeting of the eicosanoid pathways in the host cells by fungi and parasites, often dealing with systemic inflammations in the host organism.

All pathogens target the PC, PE, diacylglycerol and TAG area of the metabolic map (Figure 2). These lipids are located in close proximity for obvious reasons, i.e. having DAG as a shared precursor. The hydrolysis of these lipids can, however, yield very different fatty acids. TAG species generally contain saturated and mono/di unsaturated fatty acids with an average chain length of 16–18 carbon atoms. In contrast, PC and PE will contain mostly long chain (C20–C24) PUFAs at the *sn*-2 position. Hence, it is expected that complex pathogens predominantly target the phospholipids in this metabolic area to generate arachidonic acid, a central precursor for eicosanoid synthesis. Bacteria and viruses also target this metabolic area, but for other reasons, e.g. the generation of fatty acids needed for membrane formation.

Here we have presented one of the first visualizations of the lipid-based interaction of pathogens with host cells. Based on available data in the literature, we have categorized approximately 500 interactions using the cellular metabolome as a template. At this relatively low resolution, hotspots for the involvement of host–pathogen interactions can already be identified. Novel lipidomic technologies are rapidly being created and implemented such as Imaging mass spectrometry and single cell metabolomics/lipidomics. High-resolution mass spectrometry will allow precise annotation of lipid species and combined with automated high-throughput analysis and novel bioinformatics tools, we will soon witness the generation of enormous amounts of high density data allowing spatiotemporal resolution of the involvement of lipids in host–pathogen interactions. Therefore, we expect the resolution of the interaction maps to increase dramatically in the near future, allowing the identification of novel hotspots for the involvement of lipids in host–pathogen interactions with potential applications in fundamental and applied research.

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GLOSSARY

25HC : 25-hydroxycholesterol
AMPK : AMP-activated protein kinase
DENV : dengue virus
EBOV : Ebola virus
FAS : fatty acid synthase
FAs : fatty acids
HCV : hepatitis C virus
HIV : human immunodeficiency virus
IAV : influenza A virus
ISG : interferon-stimulated gene
OSBP : oxysterol-binding protein
PA : phosphatidic acid
PC : phosphatidylcholine
PE : phosphatidylethanolamine
PI(4)P : phosphatidylinositol-4-phosphate
PS : phosphatidylserine
PUFA : polyunsaturated fatty acid
PV : poliovirus
PVM : parasitophorous vacuolar membrane
SFV : Semliki Forest virus
SM : sphingomyelin
SPT : serine palmitoyltransferase
TAG : triacylglycerol
VACV : vaccinia virus
WNV : West-Nile virus

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: List of lipid-based interactions between host cells and pathogens that was used for the generation of Figure 2. A weighting of less than one was assigned if one specific interaction can be located at different nodes in the metabolic pathway. For example, phospholipase A2 activity of pathogens increases host levels of unesterified polyunsaturated fatty acids (18:2, 18:3, 20:4), commonly found at the *sn*-2 position of phospholipase A2 substrates. In this case, the three fatty acids will be assigned a weighting factor of 0.33. Similarly, distinct interactions of a pathogen that target the same lipid in the host will result in weighting factors larger than 1. For example, *Listeria* has been described to affect a lipase and a phospholipase C, both resulting in increased levels of DAG.

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