Lipids as regulators of inflammation and tissue regeneration

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8.1 Introduction

Inflammation is a homeostatic defensive reprogramming in response to harmful stimuli such as pathogens or tissue insults causing cell damage or death. *When tissue injury is caused by* trauma, ischemia-reperfusion or chemical agents in the absence of infection, or the implantation of a sterile medical device or biomaterial, the inflammatory response is called *sterile inflammation* [1]. In addition to its role in mitigating infections, inflammation is important for clearing damaged cells and initiating tissue repair. Inflammatory mechanisms are evolutionary conserved and function not only in mammals but also in lower organisms [2]. Inflammation has to be balanced as insufficient inflammation is associated with unresolved tissue destruction, whereas chronic unresolved inflammation can lead to a variety of pathologies, including cancer [3] and fibrosis [4]. Modulation of the inflammatory response requires an understanding of the signaling molecules and initiators involved in the process.

A variety of damage-associated molecular patterns (DAMPS) including oxidized lipids and lipoproteins or pathogen-associated molecular patterns (PAMPs), e.g., uncapped viral RNA, are recognized by pattern recognition receptors (PRRs) that act as sentinels and initiate an appropriate response by triggering a number of transcriptions factors (e.g., NF-κβ) followed by the expression of a series of cytokines [5]. Consequently, expression of endothelial adhesion molecules (VCAM-1) and chemokines (such as MCP-1) induce recruitment and activation/polarization of circulating immune cells particularly neutrophils and monocytes differentiating into macrophages [6].

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Our understanding of the role that lipids play in cell biology has changed and they are no longer considered only as structural constituents of cell membranes and efficient sources of energy but also as signaling molecules with important roles in immune regulation, inflammation, and maintenance of tissue homeostasis [7–9]. Lipids and their modified forms, including lipid mediators, are important regulators of all phases of inflammation, including cessation of the inflammatory process. Four major classes of bioactive lipids orchestrate the inflammatory response: (i) eicosanoids, (ii) specialized pro-resolving mediators (SPMs), (iii) lysoglycerophospho-lipids/sphingolipids, and (iv) endocannabinoids (eCBs). The majority of these lipids are produced from and/or contain ω-6 or ω-3 polyunsaturated fatty acids (PUFA) precursors, and their activity is mediated by binding/activation of specific G protein-coupled receptors (GPRs) [10–15]. In addition to biosynthetic mechanisms, the balance of pro-/anti-inflammatory lipids and their activity is controlled by either the hydrolytic reactions of membrane lipids or, vice versa, re-esterification back into membrane (phospho)lipids [1].

In recent years, the role of circulating extracellular vesicles (EV) in regulation of inflammation, tissue repair and immune responses has been the focus of extensive research [16–18]. These vesicles can be released by all types of cells and classified according to size, their biogenesis, or their function, among other criteria [19–22]. It has been demonstrated that EV are essential for the regenerative response of injured tissues [23]. Interestingly, PMN-derived EV have anti-inflammatory and immunosuppressive effects, mainly on dendritic cells and macrophages [24, 25]. Released at the site of inflammation, EV enhance PMN antimicrobial activity via expression of antimicrobial proteins, including myeloperoxidase [26, 27]. Macrophage-derived EV can exert pro-inflammatory effects, directed toward dendritic cells, macrophages, PMNs, and T lymphocytes [28, 29]. Both PMN- and macrophage-derived EV also carry enzymes essential for leukotriene B4 (LTB_4) biosynthesis, which in turn stimulates PMN chemotaxis [30, 31]. In addition to their pro-inflammatory actions, EV are also implicated in resolution of inflammatory response and tissue regeneration. Recently, the presence of EV embedded within the extracellular matrix, appropriately named matrix-bound nanovesicles (MBV), was described [32]. In contrast to liquid phase EV (exosomes), MBV are secreted by tissue-resident cells and integrated into the fibrillar matrix (Fig. 8.1). It has been shown that MBV enhance proliferation and differentiation of stem and progenitor cells, and promote activation of the anti-inflammatory and pro-resolving macrophage phenotype, both of which are hallmarks of constructive tissue remodeling [33, 34]. The potential utility of EV and bioactive lipids in modulation of the immune response to biomaterials has been largely unexplored. The potential role of EV as modulators of the immune response through various lipid signaling molecules is discussed later in this chapter.

8.2 LC-MS based approaches to analyze lipids and their oxidation products

Lipids can be categorized into two major groups—polar and nonpolar—with several major classes in each of them: glycerophospholipids, sphingophospholipids,

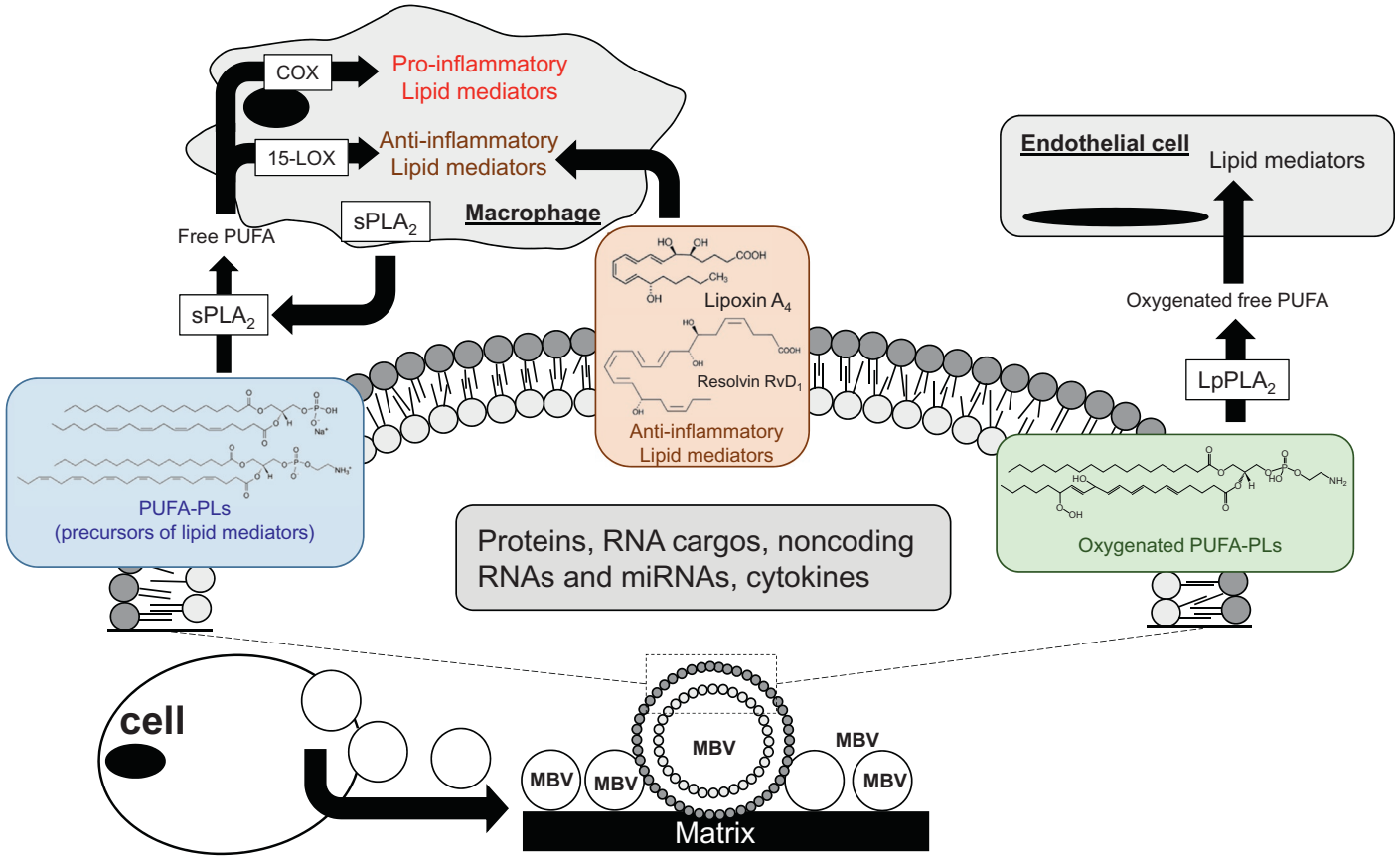

Fig. 8.1 MBV oxygenated phospholipids represent a potential reservoir of lipid mediators esterified into different phospholipids species. MBV polyunsaturated phospholipids can be hydrolyzed by $sPLA_2$ to release free PUFA for oxidation by COX and 15-LOX to form lipid mediators. MBV oxygenated phospholipids can be hydrolyzed by lipoprotein lipases A_2 to release anti-inflammatory mediators such as LXA_4 and resolvin D1 (RvD1) that are associated with M2 macrophage polarization and tissue repair.

glycosphingo-phospholipids, fatty acids, glycerolipids, sterols. As there are several subclasses in each class, lipids are highly diversified [35]. Lipids can undergo oxidation via the addition of oxygen to polyunsaturated fatty acid (PUFA) residues thus producing oxygenated derivatives which are involved in multiple signaling pathways [36–41]. Oxygenation of PUFA (eicosanoic, docosapentaenoic, docosahexaenoic fatty acids) induces the production of a variety of physiological regulators such as leukotrienes, prostaglandins, thromboxanes, resolvins [42].

In spite of the huge diversity, the advances in liquid chromatography-mass spectrometry (LC-MS) have made possible their accurate identification and quantitative analytical characterization [39, 43–50]. Analysis of oxidized lipids and interpretation of the MS/MS spectra without prior lipid separation appears to be very challenging due to their low abundance, ion suppression and a large number of isomeric species. However, LC-electrospray ionization (ESI) MS/MS strategies have been developed and optimized for the selective analysis of multiple oxygenated species of polar and non-polar lipids using normal-phase (NP) and reversed-phase chromatography (RP). Both techniques have their advantages and disadvantages. NPLC-MS allows separation of various lipid classes dependent on the character of the polar head group, although both oxidized and non-oxidized species may overlap and the signals for the low abundant (oxidized) species may be suppressed. To improve lipid separation a 2D-NPLC approach has been utilized whereby lipids are separated by class in the first dimension with further separation of oxidized and non-oxidized lipid species by RPLC-MS in the second dimension [51–53]. While RPLC-MS separation using C5, C8 and C18 columns allows to separate individual molecular species, multiple lipid classes may overlap. Moreover, acidic phospholipids (phosphatidylserine, phosphatidic acid, and their hydrolysis products lyso-phosphatidylserine, lyso-phosphatidic acid) often elute as broad peaks which leads to poor separation and quantification, and severely restricts the analytical power technique. There are several approaches to achieve better separation and identification of lipid mixtures, containing acid phospholipids and oxidized glycerolipids, for example by using protocols with improved columns such as HILIC NPLC-MS and C30 RPLC-MS [45, 46, 54–59]. In addition, several studies describe the utility of supercritical fluid chromatography/tandem mass spectrometry to detect oxygenated phospholipids [41, 60].

Identification and quantification of oxidized lipids can be achieved successfully by a newly developed approach—oxidative (or redox) lipidomics. Lipidomics can be performed in targeted or untargeted LC-MS techniques. Untargeted LC-MS protocols can be performed via data-dependent or data-independent acquisition. Protocols for LC-MS based targeted lipidomics include precursor ion scanning, neutral loss scanning, selected reaction monitoring (SRM) or multiple reaction monitoring (MRM). Targeted LC-based protocols can detect the chosen compounds with high selectivity and sensitivity. Identification of targeted ions includes optimized ionization efficiency, known fragmentation pattern, using appropriate standards and requires knowledge of phospholipid structures. For example, MRM transitions for oxidized fatty acids, have been established based on over a hundred of commercially available standards [42]. LC-MS SRM approaches have been used extensively to quantify fatty acid

aldehydes and aldehydes derived from PUFA oxidation without and with derivatization [50, 59, 61–64].

The structure of the oxidized phospholipids can be established on the basis of information related to the product ions derived from the head group and the oxidized acyl chain fatty acids. The appearance of oxygen-containing functional groups (hydroperoxy, hydroxy-, epoxy-, keto-) in acyl chains of oxidized lipids becomes more polar and elute earlier in comparison to their unmodified equivalents, in RPLC conditions. In addition to these major types of peroxidation products, oxidatively truncated molecular species [65, 66] as well as conjugates of electrophilic aminophospholipid products have been detected [67, 68]. Some groups have utilized oxidized phospholipid standards that were prepared by in vitro oxidation, as they are not commercially available and the applications of targeted methods are limited and less reported [69]. Given that the diversity of phospholipid oxidation products is 2–3 orders of magnitude greater than that of oxygenated free PUFA, enzymatic hydrolysis of oxidized phospholipids by phospholipase A_2 has been utilized which significantly reduces the diversification and simplifies the initial analysis [70, 71]. Considerable amounts of oxygenated neutral lipids: triacylglycerols and cholesteryl esters were detected in cells and tissues of tumor-bearing animals and cancer patients. Oxygenated TAGs were represented by a wide spectrum of truncated molecular species containing mostly 9-oxo-nonanoic acid [72, 73].

A new era in identification and quantitative characterization of low abundance oxidized lipids was associated with the development of high resolution MS orbitrap instruments such as Thermo's QExactive and Fusion Lumos. Unlimited fragmentation capacities in the ion-trap part of the Fusion Lumos spectrometer combined with the high mass accuracy of its Orbitrap platform, increased speed of spectral acquisition coupled with reverse phase liquid chromatography. These features permit detection, unequivocal identification and quantitative characterization of oxidized lipids (by high accuracy MS^1, MS^n fragmentation, position of specific fragments and retention time) in cells as well as in tissues in vivo [40, 73–77]. Combination of NPLC and RPLC separation with high-resolution, and higher energy dissociation provides another improvement in the detection of oxidized lipids [50, 58].

Given the potential therapeutic significance of EV and various species of lipid mediators, the employment of LC-MS-based lipidomics and redox lipidomics protocols to conduct their structural characterization provides a tool to design and manufacture immunomodulatory biomaterials.

8.3 Free PUFA and their oxidation products as signals for immunomodulation and tissue regeneration

Neutrophils and macrophages are central players in orchestrating inflammatory response and are therefore closely linked to tissue repair and regeneration [78–82]. Initiation and progression of inflammation, and its resolution and tissue repair [83] are strongly influenced by metabolites of arachidonic acid, eicosanoids, docosahexaenoic and eicosapentaenoic acids [84]. The early stage of inflammation is

characterized by production of pro-inflammatory arachidonic acid derived lipid mediators such as prostaglandins, thromboxanes and leukotriens [85, 86]. During later stages of the inflammatory response, a switch to the production of lipid mediators with anti-inflammatory properties occurs. Such lipids include lipoxins, resolvins and maresins, which suppress inflammation and promote resolution phase [87, 88].

One of the major sources of lipid mediators is polyunsaturated phospholipids localized in membranes. The conventional biosynthesis of these polyunsaturated phospholipids is initiated by a hydrolytic reaction catalyzed by phospholipases A_2 (PLA_2) [89] with subsequent enzymatic oxygenation of released polyunsaturated fatty acids by cyclooxygenases (COX) or lipoxygenases (LOX) [70]. A number of PLA_2 can release polyunsaturated fatty acids from phospholipids [86]. Secreted PLA_2 ($sPLA_2$) and cytosolic calcium-dependent PLA_2 ($cPLA_2$) effectively hydrolyze phospholipids and release arachidonic and docosahexaenoic acids [90] that can be metabolized into eicosanoids and pro-resolving mediators, respectively. Both $sPLA_2$ and $cPLA_2$ are expressed in macrophages. Pro-resolving lipid mediators are usually produced by alternatively activated M2-like human and murine macrophages [90], and released in response to a number of immune stimuli [91, 92].

Several lipoxygenases (5-, 12/15- and 15-LOXs) and cyclooxygenase (COX-1 and COX-2) are involved in the generation of lipid mediators. While 5-LOX play a central role in the formation of detrimental pro-inflammatory mediators, 12/15- and 15-LOXs are responsible for biosynthesis of anti-inflammatory lipid mediators that reduce inflammation and promote tissue repair [93–95]. Leukotriene B_4 (LTB_4) and hepoxilin A_3 (HXA_3) are two major metabolites of arachidonic acid consequently formed in the reaction catalyzed by 5-LOX mainly in neutrophils and 12-LOX in epithelial and endothelial cells during the early stage of inflammation [96–98]. Their key role is to recruit inflammatory cells to the site of tissue injury and prevent infection [96]. In addition, in the damaged tissue, neutrophil-originated leukotriene A_4 (LTA_4) can be metabolized by platelets to form cysteinyl leukotrienes [99], which can stimulate the recruitment of eosinophils that in time, produce molecules involved in tissue repair and remodeling [100]. During the first 24 h after tissue injury, COX in thrombocytes generates thromboxan A_2 that serves as a critical signal for tissue repair response [101]. Another COX metabolite, prostaglandin E_2 (PGE_2), is a key eicosanoid in physiological tissue repair [101]. Macrophages recruited to the site of inflammation produce PGE_2 that causes myofibroblasts activation and stimulation of wound reduction and closure [102, 103].

Resolution stage of inflammation is coordinated by pro-resolving lipid mediators such as lipoxins, resolvins and maresins [8, 86, 104, 105]. These lipid mediators may be prime candidates for use in conjunction with biomaterials to modulate the host default response to the implantation of such materials. Arachidonic acid derived lipoxin A_4 (LXA_4) is formed by the combined actions of 2 lipoxygenases: 5-LOX and 12/15-LOX [106] and belongs to a group of lipid mediators generated later in the course of inflammatory response, and contributing to resolution of inflammation. Due to its ability to reduce inflammation, LXA_4 has been implicated in tissue regeneration. Several studies demonstrated that LXA_4 could promote re-epithelialization and wound healing [94, 107]. Lipid mediators derived from docosahexaenoic acid

(D series resolvins and maresins) and eicosapentaenoic acid (E series resolvins) are generated during the resolution stage of inflammation [108]. The effect of these metabolites includes modulation of the immune response, assisting to resolve inflammation, and promoting wound healing and tissue regeneration. Similar to LXA_4, 15-LOX and 5-LOX contribute to resolvins biosynthesis [109]. 17-Hydroperoxydocosahexaenoic acid generated by epithelial or endothelial 15-LOXes, is taken up by neutrophils where it is metabolized by 5-LOX to form D-series resolvins (RvD_1, RvD_2) [109, 110]. The action of acetylated COX-2 or cytochrome P450 monooxygenases on eicosapentaenoic acid results in the formation of 18-hydroperoxyeicosapentaenoic acid that is converted by 5-LOX into resolvins RvE_1 or RvE_2 [8]. Maresins (MaR_1, MsR_2 and MaR_3) are synthetized in macrophages [111] from docosahexaenoic acid via reaction catalyzed by 12-LOX and have a potent pro-resolving and tissue regenerative actions [105] associated with the switch from M1 to M2 macrophage phenotypes [112] that is associated with reparative and anti-inflammatory macrophage functions [8, 113].

8.4 Oxidized phospholipids as modulators of the inflammatory response

In addition to lipid mediators biosynthesized from polyunsaturated fatty acids, oxygenated phospholipids may act as important signals that regulate inflammatory response [114, 115]. For example, oxygenated cardiolipin, particularly its species containing oxygenated linoleic acid [116], generated in mitochondria during early stage of apoptosis facilitate release of cytochrome c into cytoplasm [117]. These pro-apoptotic cardiolipin oxidation products are pro-resolving, as they culminate in the accumulation of apoptotic cells with their anti-inflammatory signals. Oxidation of polyunsaturated phosphatidylserine in plasma membrane results to its externalization on the cell surface [118]. Consequently, oxygenated phosphatidylserine species serve as recognition signals for engulfment and phagocytosis of apoptotic cells [118, 119] therefore initiating a resolution phase of inflammation [119, 120]. Another example is the production of oxygenated species of arachidonoyl-phosphatidylethanolamine, 15-hydroperoxy-arachidonoyl-phosphatidyl-ethaniolamines (15HpETE-PE), generated by the complex of 15-LOX with PEBP1 in conditions when activity of glutathione peroxidase 4, capable of reducing 15-hydroperoxy-arachidonoyl-phosphatidylethaniolamines, is suppressed in cells. Accumulating 15HpETE-PE acts as a ferroptotic signals and triggers ferroptosis with pro-inflammatory (necro-inflammatory) consequences [40, 75]. Furthermore, a number of LDL-associated oxidized phosphatidylcholine species are generated in blood and plasma at the sites of chronic inflammation as well as in damaged tissues inducing various pro-inflammatory events [121, 122].

In addition to these direct effects of peroxidized phospholipids on the inflammatory response, oxygenated phospholipids can serve as precursors of lipid mediators [50, 71, 123]. This occurs via non-conventional mechanisms of generation of lipid mediators that begins with the enzymatic oxygenation of phospholipids followed by the hydrolysis of peroxidation products by specialized PLA_2 with catalytic competence towards

oxidized phospholipids [71, 123]. Several specialized phospholipases A_2 of this type have been described, including lipoprotein lipase A_2 or PAF hydrolase [118], calcium independent iPLA$_2\gamma$ [124] and iPLA$_2\beta$ [70, 71]. These enzymes preferentially hydrolyze peroxy-phospholipids at the *sn-2* position thus liberating oxygenated fatty acids to yield a diversified series of pro-inflammatory and pro-resolving lipid mediators [71, 123]. Indeed, hydrolysis of oxygenated cardiolipins by iPLA$_2\gamma$ [8, 20] and oxidized phosphatidylcholins [29] and phosphatidylserines [26, 28] by lipoprotein lipase A_2 is associated with the accumulation of pro-inflammatory oxygenated octadecanoids and eicosanoids.

8.5 Phospholipid signatures of EV

EV are generally classified according to their size and biogenesis [125]. Exosomes represent one of the most studied types of EV with typical exosome-associated proteins such as endosomal proteins, as well as rich and diverse RNA cargos [126]. Engineered exosomes have been utilized as delivery systems for a plethora of different molecules, such as drugs, microRNAs and proteins [127]. Lipids are an important component of EV [128], where they play not only a structural role of forming the membrane bilayer but they are essential for EV formation and release to extracellular environment [128, 129]. The lipid composition of EV originated from different cells have been investigated [130–133]. Compared to their cellular sources, EV are enriched in sphingolipids [132, 133], cholesterol [134], and phospholipids, including phosphatidylserine and phosphatidylethanolamine [129, 133, 135]. LC/MS analysis of EV reveals the presence of phospholipids containing polyunsaturated fatty acid residues (Fig. 8.2), including those with arachidonic and docosahexaenoic acids [133]. Thus, EV phospholipids can be a source of arachidonic and docosahexaenoic acids that can be released upon hydrolysis by phospholipases [86]. In addition, EV are a highly potent source of prostaglandins [136] and leukotrienes [133] due to the presence in them of enzymes, involved in biosynthesis of lipid mediators, such as COX 1 and 12-LOX [136, 137].

A specific new type of extracellular vesicles, matrix bound vesicles (MBV), has been discovered with highly promising anti-inflammatory, immunomodulatory properties [32]. MBV carry a variety of protein and RNA cargos, including noncoding RNAs and miRNAs that facilitate the effective cell growth [138, 139]. Similar to all EV, lipids are used as building blocks for the construction of the MBV membrane. While lipid bilayer represents the structural carcass of MBV, emerging evidence ascribes an important signaling role to the lipid constituents of the membrane, particularly to their polyunsaturated species (Fig. 8.1). However, our knowledge about the lipid composition and the function of lipids in these vesicles is limited. A recent study identified MBV as a rich reservoir of polyunsaturated phospholipids and revealed significant differences in the molecular speciation as well as relative contents of these phospholipids between exosomes and MBVs [133]. The phospholipidome of MBV is highly diversified. Nine major phospholipid classes (including phosphatidylcholine, phosphatidylethanolamine, phosphatidyl-inositol,

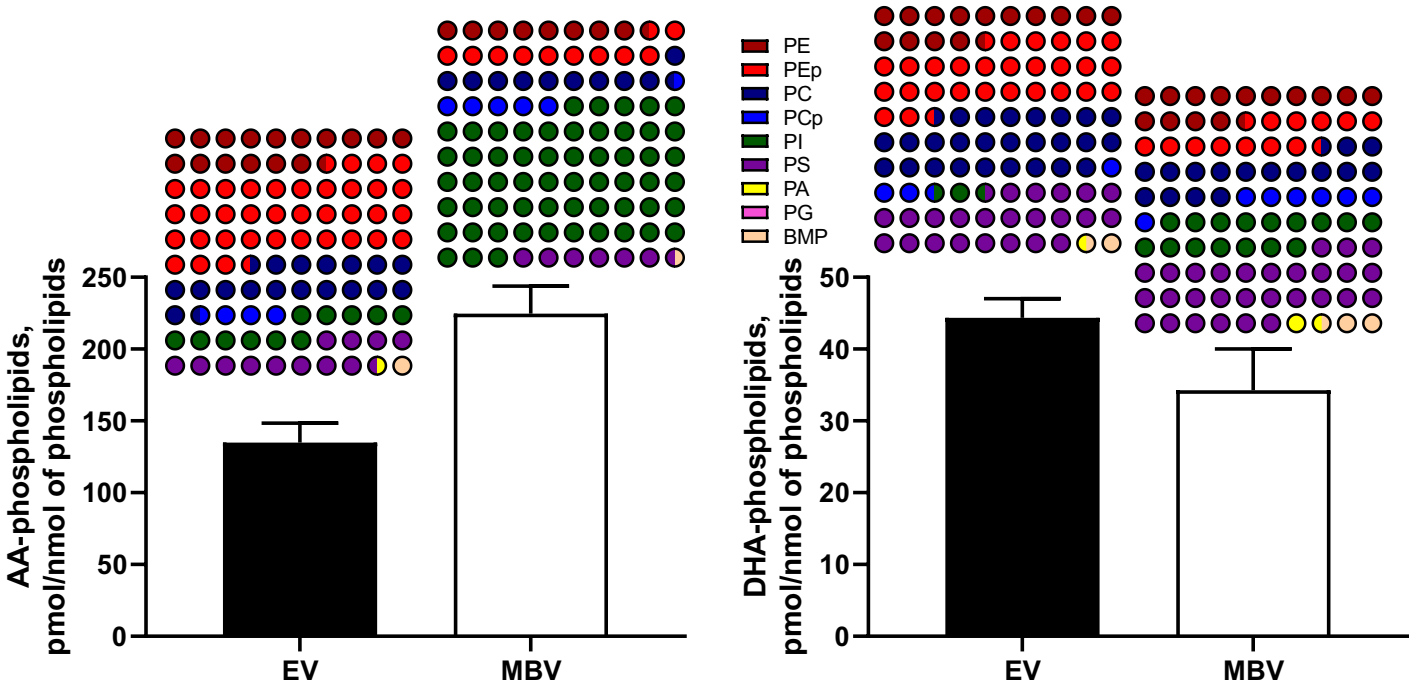

Fig. 8.2 Content of arachidonic acid (AA) *(left panel)* and docosahexaenoic (DHA) *(right panel)* acid containing phospholipids in extracellular vesicles (EV) and matrix bound vesicles (MBV) originated from 3T3 mouse fibroblasts. Inserts: distribution of AA- and DHA-phospholipids are presented as a percentage plots.

phosphatidylserine, bis-monoacylglycerophosphate, phosphatidic acid, phosphatidylglycerol, sphingomyelin and cardiolipin) with constitutive 536 individual molecular species have been detected and identified by lipidomics analysis. Compared to their cellular sources and EV originated from the same cells, MBV phospholipids are predominantly represented by highly polyunsaturated molecular species [133] (Fig. 8.1). This feature of molecular speciation of MBV phospholipids makes them a potentially important source of precursors of biologically active lipid signaling molecules—pro- and anti-inflammatory lipid mediators.

8.6 Hydrolysis of MBV derived oxygenated lipids and their possible role in inflammation and tissue regeneration

Functionally, MBV are viewed as signaling extracellular structures that instruct professional phagocytes, particularly macrophages, to perform context-specific transition from a pro-inflammatory to an anti-inflammatory pro-resolving phenotype, which has been associated with tissue repair [140]. The nature of these commands is not sufficiently characterized, particularly with regards to possible participation of the lipid components of MBV. Notably, lipid mediators, oxygenated derivatives of free polyunsaturated fatty acids, are among the most potent regulators of macrophages transition from conventional activated to alternatively activated state [141]. It has been established that macrophages exposed to EV of different origins express predominantly M2-like phenotype [142] and this effect is recapitulated by co-incubations with MBV [140]. In this sense, the lipid bilayer of MBV, particularly polyunsaturated molecular species of its phospholipids, may act as direct signaling entities or represent precursors of a diversified group of oxygenated lipid mediators with established pro- and anti-inflammatory features [143]. Recently, oxygenated products generated from the major free polyunsaturated fatty acids—arachidonic and docosahexaenoic acids in exosomes and MBV originated from mouse fibroblasts were characterized [133] (Fig. 8.3). It has been demonstrated that fibroblast-derived MBV have lower levels of free arachidonic acid metabolites such as 12-HETE, 15-HETE, LXA_4 compared to exosomes (Fig. 8.3). In contrast, higher levels of esterified metabolites were detected in MBV (Fig. 8.4). Among these species, singly-, doubly- and triply-oxygenated phospholipids were detected [133]. Thus, in contrast to exosomes enriched with "ready to act" lipid mediators, arachidonic acid oxygenated metabolites, MBV are enriched with their polyunsaturated fatty acids precursors. Furthermore, MBV but not exosomes, are enriched in oxygenated phospholipids and therefore represent a potential reservoir of lipid mediators esterified into different PL species. These oxygenated phospholipids can be hydrolyzed by lipoprotein lipases A_2 to release anti-inflammatory mediators such as LXA_4 and resolvin D1 (RvD_1) that are associated with M2 macrophage polarization and tissue repair (Fig. 8.1). In the context of tissue repair [94, 107, 113, 144], anti-inflammatory lipid mediators, LXA_4 and D-series resolvin D_1 (RvD_1)—produced by 12/15-LOX from arachidonic and docosahexaenoic acids—stimulate macrophage polarization to M2-like type [145, 146]. Exposure of murine bone-marrow derived macrophages to MBV results in the

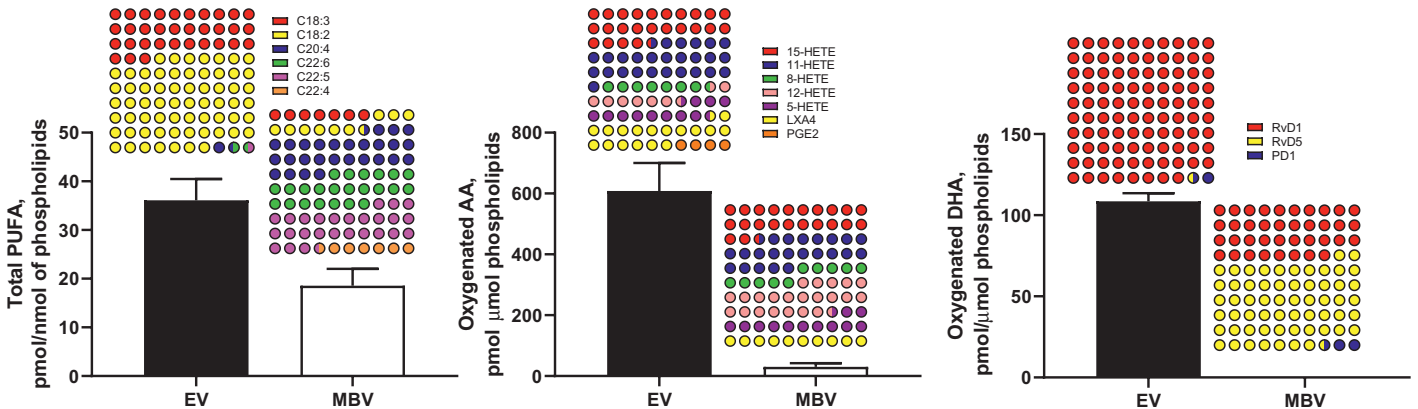

Fig. 8.3 Content of free polyunsaturated fatty acids *(left panel)*, free oxygenated arachidonic acid (AA) (middle panel) and free oxygenated docosahexaenoic (DHA) *(right panel)* acid in extracellular vesicles (EV) and matrix bound vesicles (MBV) originated from 3T3 mouse fibroblasts. Inserts: distribution of fatty acids is presented as a percentage plots.

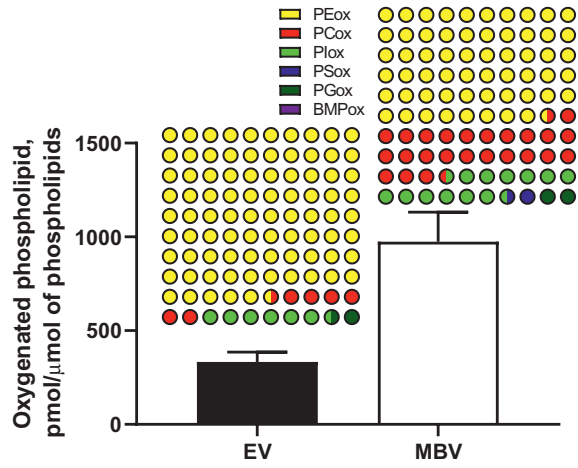

Fig. 8.4 Content of oxygenated phospholipids in extracellular vesicles (EV) and matrix bound vesicles (MBV) originated from 3T3 mouse fibroblasts. Inserts: distribution of oxygenated phospholipids is presented as a percentage plots.

expression of M2-like markers, Fizz1 and Arg1, which are associated with a reconstructive macrophage phenotype [140]. Thus, MBV, a specific new type of extracellular vesicles, have highly promising propensities for successful application in the field of tissue reconstruction and immunomodulation.

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