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Inflammatory Biomarkers for Cardiovascular Risk Stratification in Familial Hypercholesterolemia

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Contents

Abstract Familial hypercholesterolemia (FH) is a frequent autosomal genetic disease characterized by elevated concentrations of low-density lipoprotein cholesterol (LDL) from birth with increased risk of premature atherosclerotic complications. Accumulating evidence has shown enhanced inflammation in patients with FH. In vessels, the deposition of modified cholesterol lipoproteins triggers local inflammation. Then, inflammation facilitates fatty streak formation by activating the endothelium to produce chemokines and adhesion molecules. This process eventually results in the uptake of vascular oxidized LDL (OxLDL) by scavenger receptors in monocyte-derived macrophages and formation of foam cells. Further leukocyte recruitment into the sub-endothelial space leads to plaque progression and activation of smooth muscle cells proliferation. Several inflammatory biomarkers have been reported in this setting which can be directly synthetized by activated inflammatory/vascular cells or can be indirectly produced by organs other than vessels, e.g., liver. Of note, inflammation is boosted in FH patients. Inflammatory biomarkers might improve the risk stratification for coronary heart disease and predict atherosclerotic events in FH patients. This review aims at summarizing the current knowledge about the role of inflammation in FH and the potential application of inflammatory biomarkers for cardiovascular risk estimation in these patients.

Keywords Cardiovascular risk · CRP · Familial hypercholesterolemia, inflammation · Markers · Oxidized LDL · TNF-α

Abbreviations

ALCAM	Activated leukocyte cell adhesion molecule
apoB	Apolipoprotein B
BAFF	B cell activating factor receptor
baPWV	Brachial-ankle pulse wave velocity

CAC	Coronary artery calcifications
CHD	Coronary heart disease
CV	Cardiovascular
CVD	CV disease
CYS	Cholesterol-year score
ELAM-1	Endothelial-leukocyte adhesion molecule-1
FCH	Combined familiar hypercholesterolemia
FFAs	Free fatty acids
FH	Familial hypercholesterolemia
GTP	Guanosine triphosphate
HDL	High-density lipoprotein cholesterol
He	Heterozygous
Ho	Homozygous
hs-CRP	High sensitivity C-reactive protein levels
IFN-γ	Interferon gamma
IL	Interleukin
IL-RA	IL-1 receptor antagonist
IMT	Intima-media thickness
LDL	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LOX-1	Lectin-like oxidized low-density lipoprotein receptor-1
Lp	Lipoprotein
Lp-PLA2	Lipoprotein-associated phospholipase A2
MCP-1	Monocyte chemoattractive protein
M-CSF	Macrophage colony stimulating factor
MI	Myocardial infarction
MIP	Macrophage inflammatory protein
MMPs	Metalloproteinases
MPV	Mean platelet volume
OxLDL	Oxidized LDL
PAI-1	Plasminogen activatorinhibitor-1
PBMCs	Peripheral blood mononuclear cells
PON1	Paraoxonase type 1
PPAR	Peroxisome proliferator-activated receptor
PWV	Pulse wave velocity
RANK	Receptor activator of NF-κB
ROS	Reactive oxygen species
RUC	Related unaffected relatives
sICAM − 1	Soluble intercellular adhesion molecule-1
sVCAM − 1	Soluble vascular adhesion molecule-1
Th	T helper cells
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TNFRSF	TNF receptor superfamily

TNFSF	TNF superfamily
TRAIL	TNF-related apoptosis-inducing ligand
XO	Xanthine oxidase

1 Introduction

Familial hypercholesterolemia (FH) is a common autosomal inherited disorder of lipoprotein metabolism characterized by high levels of total and low-density lipoprotein cholesterol (LDL) from birth, increased risk for early onset cardiovascular (CV) diseases (CVDs) and pathologic cholesterol accumulations often found in tendons (i.e., xanthomas), eyelids (i.e., xanthelasmas), and corneas (i.e., corneal arcus). In FH, defects in LDL receptor (LDLR) functionality or metabolism affect the uptake/handling of LDL by the liver resulting in increased circulating cholesterol levels (McNeely et al. 2001). Familial hypercholesterolemia is further defined based on the number of mutated alleles and severity of the disease as (1) heterozygous (HeFH), the common milder form with nearly two-fold elevation in LDL levels (Goldstein and Brown 2009) or (2) homozygous (HoFH) a rare more severe pattern with LDL levels above 500 mg/dL and as high as 1,000 mg/dL. FH is a silent disease which becomes clinically evident only after the early development of its cardiovascular complications (i.e., coronary heart disease) (Soutar and Naoumova 2007; Gidding et al. 2015; Benn et al. 2012; Reiner 2015). In the case FH would remain untreated, 85% of men and 50% of women are thought to suffer a premature coronary event (Civeira 2004). Accordingly, about 5% of the patients with HeFH suffer from myocardial infarction (MI) before the age of 60 years (Goldstein and Brown 2009). Although CV risk is increased in all FH patients, the onset of clinically manifested CVD may vary among patients even when they carry identical mutation (Jansen et al. 2002; Ferrieres et al. 1995). Traditional risk factors account only for a part (~20%) of this variability (Ferrieres et al. 1995; Moorjani et al. 1993). Accordingly, it has been hypothesized that other factors such as levels of inflammation may influence the susceptibility of FH patients to cardiac disease and explain the variability in phenotypic expression (Sharifi et al. 2016).

Atherosclerosis is a multi-step process characterized by both accumulation and retention of atherogenic lipoproteins into the sub-endothelial space and chronic arterial wall inflammation with activation of resident cells and recruitment of circulating leukocytes (Montecucco et al. 2017; Mawhin 2017; Hansson et al. 2015; Hansson and Libby 2006; Iwata and Nagai 2012). Recently, clinical trials targeting inflammation confirmed the causative role of this process in atherosclerosis by showing reduced rate of secondary CV events in post-myocardial infarction patients (Ridker et al. 2017; Tardif et al. 2019). Several lines of evidence suggest enhanced chronic low-grade inflammation in patients with FH (Narverud et al. 2011a; Real et al. 2010a) and this is thought to account for part of their increased CV risk (Cheng et al. 2007a; Kastelein et al. 2003).

Given that atherosclerotic complications are major causes of morbidity in individuals diagnosed with FH, the improvement in risk stratification assessment in those patients who are at higher CV risk is important, since they could benefit from earlier and more intensive treatment. In view of the above mentioned, this review aims at dissecting the interplay between hyperlipidemia and inflammation in the determination of CV risk in FH population and analyzing the potential application of inflammatory biomarkers in the CV risk estimation of these patients.

2 Lipids and Inflammation: A Deadly Combination in FH Patients

Both lipids (either modified or in their canonical isoform) and inflammation are deeply involved in the regulation of early atherogenesis (Libby 2002). Specifically, hypercholesterolemia induces the expression of leukocyte adhesion molecules by arterial endothelium while LDL penetrates and is selectively retained at susceptible sites where it undergoes oxidative modification to OxLDL (Bergheanu et al. 2017). Circulating leukocytes invade the vessel wall driven by high levels of chemotactic factors, such as OxLDL and monocyte chemoattractive protein (MCP-1) (Montecucco et al. 2017; Bonaventura et al. 2018; Liberale et al. 2017). Besides enhancing monocyte recruitment, OxLDL also triggers their differentiation into macrophages and the expression of scavenger receptors which mediate lipids internalization and foam cell formation (Tekin et al. 2013). This sets a vicious circle since macrophages can oxidize LDL and OxLDL can directly and indirectly stimulate monocyte recruitment. Accordingly, different clinical studies report hypercholesterolemia, oxidative stress, and inflammation to be closely related (Karbiner et al. 2013; Narverud et al. 2014; Real et al. 2010b). Of interest, biomarkers of such deleterious processes are upregulated in patients with FH (Van Tits et al. 2003; Rahman et al. 2017).

Not only lipids and inflammatory molecules collaborate to initiate atherosclerotic lesions in FH (Fig. 1), these mediators are also promoters of plaque progression and culprit mediators of sudden atherosclerotic complications, including myocardial infarction. Indeed, fibrous cap fissuring and formation of thrombi are closely associated with inflammatory products that are released from endothelial cells, monocytes, and neutrophils such as tissue factor, adhesion molecules, cytokines [e.g., IL-1β, tumor necrosis factor (TNF)-α], and metalloproteinases (MMPs) (Mawhin 2017; Hansson et al. 2015). Furthermore, OxLDL increases the production of prothrombotic plasminogen activator inhibitor-1 (PAI-1) while suppressing the secretion of tissue plasminogen activator, thus reducing the fibrinolytic activity in endothelial cells (Kugiyama et al. 1993). As a result, OxLDL level predicts both carotid plaque progression and major adverse cardiovascular events in different populations (Wallenfeldt et al. 2004; Tsimikas et al. 2012; Johnston et al. 2006; Lee et al. 2005). Specific contributions of each inflammatory mediator to

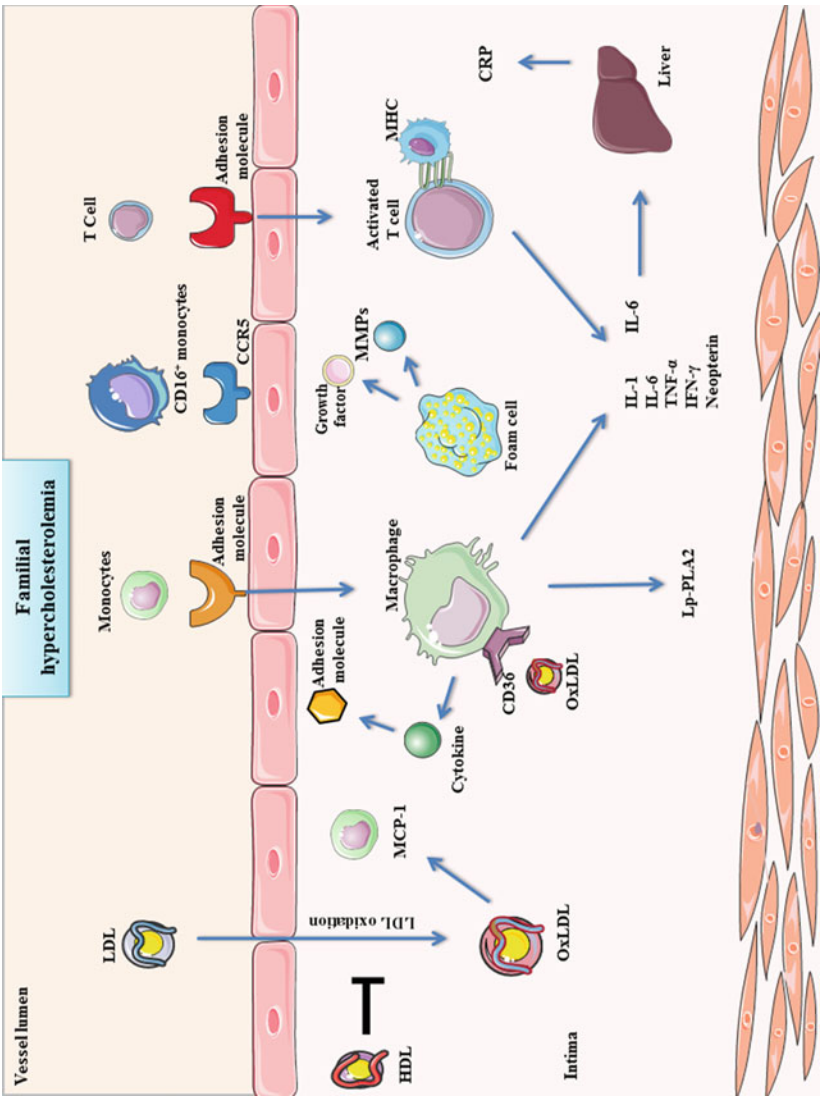

Fig. 1 Inflammation influences atherogenesis in familial hypercholesterolemia. *CCR5* C-C chemokine receptor type 5, *CRP* C-reactive protein, *ICAM-1* intercellular adhesion molecule-1, *IFN-γ* interferon gamma, *IL* interleukin, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *MCP-1* monocyte chemo-attractant protein 1, *Lp-PLA2* lipoprotein-associated phospholipase A2, *MMPs* matrix metalloproteinases, *OxLDL* oxidized LDL, *TNF-α* tumor necrosis factor-alpha

atherosclerosis in FH setting and their potential role as predictor of CV risk in these patients will be dissected in the following paragraphs.

3 Inflammatory Biomarkers in FH

Biomarkers obtained from blood, plasma, and urine specimens can offer valuable details on inflammatory phenomena (Kinlay and Selwyn 2003; Packard and Libby 2008). Inflammatory biomarkers in atherosclerotic patients can be generated either directly due to activation of inflammatory/vascular cells in the plaque or indirectly in other organs, e.g., the liver (Table 1). Also, we should consider that inflammation is a non-specific phenomenon and other processes such as infection, autoimmune diseases, and traumas can induce the expression of a broad spectrum of inflammatory biomarkers and lead to misinterpretation of results in cardiovascular studies.

4 C-Reactive Protein (CRP)

High sensitivity-CRP (hs-CRP) is widely used as a biomarker of systemic inflammation in different settings (Tabatabaeizadeh et al. 2017; Zannad et al. 2012). Together with routine lipid screening test, levels of hs-CRP were shown to predict the presence of subclinical atherosclerosis in healthy men (Ridker et al. 1997). Hs-CRP is increased in adults with FH (Real et al. 2010a; Toutouzas et al. 2018). El Messal et al. assessed hs-CRP levels in FH patients with homozygous (HoFH) or heterozygous disease never treated with any lipid-lowering drug and compared to those with controls without FH (El Messal et al. 2006). Of interest, HoFH and HeFH patients had higher mean hs-CRP levels when compared to controls (five- and two-fold, respectively). Furthermore, in patients with HoFH direct relationships were reported between hs-CRP and total cholesterol, apoB and IL-18 (El Messal et al. 2006). Altogether, never-treated HoFH and HeFH patients had increased hs-CRP and higher risk for coronary heart disease (CHD) (El Messal et al. 2006). Similarly, plasma levels of hs-CRP were reported to directly correlate to those of NF-κB—a transcription factor modulating the synthesis of several inflammatory mediators—and to those of xanthine oxidase [(XO), an enzyme involved in production of reactive oxygen species (ROS)] in both FH patients and controls (Real et al. 2010a). Of interest, it has been recently reported that lectin-like oxidized low-density lipoprotein receptor-1 [LOX-1, initially identified as the major receptor for oxidized LDL (OxLDL)] also mediates CRP signaling, thus further evidencing the close interplay between inflammation and modified lipids in the setting of atherogenesis (Pothineni et al. 2017; Xu et al. 2013). Cheng et al. further analyzed the association between atherogenesis, arterial stiffness, and circulating CRP in patient with HeFH. In another study, cholesterol-year score (CYS) was used to assess the exposure to high cholesterol and brachial-ankle pulse wave velocity (baPWV) was used to

Table 1 Inflammatory biomarkers in familial hypercholesterolemia and suggested pathogenic mechanisms

Biomarker	Main mechanism	References
CRP	Negatively influences the atherogenesis at endothelium level directly by stimulating MCP-1 secretion and indirectly by enhancing the uptake of OxLDL via macrophages	Pasceri et al. (2000, 2001)
ICAM-1	Allows adhesion of monocytes/lymphocytes to the activated endothelium Participates to transendothelial migration	Santos et al. (2018)
E-selectin	Facilitates adherence of leucocytes to vascular endothelium and stimulates the cascade of pathogenic events	Rahman et al. (2017); Ley (2002)
TNF-α	Promotes the attachment of leucocytes to endothelium by stimulating adhesion molecule expression, facilitates foam cell formation and T-lymphocyte and monocyte/macrophage activation	Enayati et al. (2015)
IL-10	Prevents atherogenesis through inhibition of macrophage activation and decreases the expression of MMPs, cytokines, and cyclooxygenase-2	Hansson (2001)
CD40/CD40L	Induces the expression of different pro-atherogenic substances, such as adhesion molecules, cytokines, chemokines, growth factors, and MMPs	Gissler et al. (2016); Yuan et al. (2015)
NF-Kb	Regulates gene involved in endothelial cell activation as well as transcription of different chemokines, adhesion molecules, and other inflammatory mediators	Zernecke and Weber (2009); Monaco et al. (2004)
MCP-1	Is responsible for the recruitment of monocytes within the atherosclerotic lesion	França et al. (2017)
OxLDL	Is internalized by macrophage via the scavenger receptors, causing foam cell formation LDL oxidation process within vascular wall induces cascades of immunogenic and pro-inflammatory consequences which initiate atherogenesis	Linton and Fazio (2001); Navab et al. (2004)
Lp-PLA2	Has pro-inflammatory and pro-oxidant properties By hydrolyzing oxidized phospholipids, it produces bioactive fat compounds including lysophosphatidylcholine and oxidized non-esterified FFAs which stimulate inflammation, oxidative stress, and atherogenesis Induces in endothelial dysfunction, aortic wall inflammation, and injury	Stafforini (2009); Caslake et al. (2000); Yang et al. (2006); Weintraub (2008); Tsimikas et al. (2007)

(continued)

Table 1 (continued)

Biomarker	Main mechanism	References
$CD16^{+}$monocytes	Shows increased phagocytosis and higher tendency to adhere to the endothelium in response to native LDL/OxLDL Expresses and generates inflammatory mediators which are involved in atherosclerotic process	Belge et al. (2002); Mosig et al. (2009); Ancuta et al. (2003); Tacke et al. (2007)
MPV	High volume characterizes excessively reactive platelets with more metabolic, enzymatic, and coagulation potential Reactive platelets are associated with prothrombotic molecules, such as thromboxane	Kamath et al. (2001); Park et al. (2002); Vizioli et al. (2009)
Neopterin	Inflammatory mediator General marker of boosted cellular immunity Reflects activation of monocyte in response to IFN-γ	Murr et al. (2002)

CRP C-reactive protein, *FFAs* free fatty acids, *ICAM-1* intercellular adhesion molecule-1, *IL* interleukin, *MCP-1* monocyte chemo-attractant protein 1, *Lp-PLA2* lipoprotein-associated phospholipase A2, *MMPs* matrix metalloproteinases, *MPV* mean platelet volume, *OxLDL* oxidized LDL, *Th* T helper cell, *TNF-α* tumor necrosis factor-alpha, *NF-κB* transcription nuclear factor-kappa B

estimate arterial stiffness in FH patients (Cheng et al. 2007b). HeFH patients showed increased value of total cholesterol, LDL, as well as carotid intima-media thickness (IMT) as compared to controls. Interestingly, in patients with HeFH carotid IMT and baPWV were higher in those with long-time cholesterol exposure and in those with modestly increased hs-CRP level (>1 mg/L) (Cheng et al. 2007b). Furthermore, a multivariate regression analysis indicated both CYS and hs-CRP as strong independent predictors of IMT and baPWV in HeFH patients (Cheng et al. 2007b). This evidence implies that the pro-inflammatory vascular state is not only linked with atherosclerosis, but it also plays an important role in the progression of arterial stiffness in FH (Cheng et al. 2007b). Interestingly, in another recent report, serum concentrations of hs-CRP were significantly elevated in patients with combined familiar hypercholesterolemia (FCH) and with HeFH with respect to controls, while mean hs-CRP levels did not differ between HeFH and FCH patients (Toutouzas et al. 2018). Of importance, this is among the few studies assessing vascular inflammation in patients with FH by the mean of fluorodeoxyglucose-positron emission tomography (FDG-PET), showing a directly correlation between vascular inflammatory activity and circulating levels of hs-CRP in this population (Toutouzas et al. 2018; Iosif et al. 2017). On the other hand, another study showed no differences in CRP values between FH adult patients ($n = 89$, diagnosis based on clinical criteria with no genetic confirmation) and normal healthy controls ($n = 31$) (Martinez et al. 2008). In addition, no correlation was reported between CRP levels and atherosclerosis imaging variables, such as coronary artery calcifications (CAC) and carotid-femoral pulse wave velocity (PWV). On the other hand, a modest association between CRP levels and carotid IMT was demonstrated (Martinez et al. 2008). These results are in partial contrast with previous studies, showing

associations between CRP and IMT or CAC in the general population (Lakoski et al. 2007; Khera et al. 2005).

Although many data are available from FH adults, evidence from children is still limited and discordant. Among different studies assessing hs-CRP circulating levels in children with FH, only four articles showed significantly increased hs-CRP concentrations in FH children versus normal matched controls (Ueland et al. 2006; Ryu et al. 2011; Guardamagna et al. 2009), while five reported no difference (Narverud et al. 2011a, 2013a, 2013b; Stübiger et al. 2012; Charakida et al. 2009; Holven et al. 2006). Altogether these reports suggest that hs-CRP might be a less reliable indicator of endothelial activation and atherosclerotic progression in FH children than in adults. Of interest, Uelend et al. also demonstrated that 2-year pravastatin treatment did not affect hs-CRP levels in children with HeFH concluding that the anti-inflammatory impact of statins might be less important in children with FH than in adults (Ueland et al. 2006).

5 Soluble Adhesion Molecules

The results of several studies have supported a pivotal role of endothelial activation in atherogenesis, showing robust associations between circulating levels of adhesion molecules [i.e., E-selectin, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular adhesion molecule-1 (sVCAM-1), and activated leukocyte cell adhesion molecule (ALCAM)] and atherosclerosis (Blankenberg et al. 2003; Galkina and Ley 2007). Indeed, the activated endothelium releases soluble adhesion molecules and thus, quantification of these molecules might be a potential indicator of endothelial dysfunction (Galkina and Ley 2007). Of interest, inflammatory molecules (i.e., CRP) can induce endothelial dysfunction and are associated with expression of different adhesion molecules (Pasceri et al. 2000; Hein et al. 2009). ICAM-1 is a transmembrane protein synthesized by leucocytes and endothelial cells which mediates adhesion of monocytes and lymphocytes to activated endothelium and participates to their transendothelial migration (Santos et al. 2018). E-selectin [also known as endothelial-leukocyte adhesion molecule-1 (ELAM-1)] is a carbohydrate-binding protein found on endothelial surface which facilitates adherence of leucocytes to the endothelium and is again implicated in the regulation of leukocyte migration (Rahman et al. 2017; Ley 2002). Much of the recent findings concerning adhesion molecules in FH derive from a case-control study on FH patients and their unaffected family members, which however based FH diagnosis only on clinical criteria without genetic confirmation thus requiring particular caution in interpretation of data (Rahman et al. 2017). In this study, both sICAM-1 and E-selectin were higher in FH patients when compared to healthy controls, while only sICAM-1 concentration was higher in unaffected family members with respect to controls. Van Haelst et al. confirmed higher ICAM-1 plasma levels in FH individuals (van Haelst et al. 2003). These results have been further confirmed in children with clinically diagnosed FH, thus suggesting an important role for

leukocyte-endothelial cell interactions also at early stages of endothelial dysfunction and atherogenesis (Charakida et al. 2009).

6 Cytokines

Cytokines are central players of cell–cell communication deeply regulating immune system function in both positive and negative fashions. Increasing evidence supports the contribution of major pro-inflammatory cytokines, namely IL-1, IL-6, and TNF-α in atherogenesis (Tousoulis et al. 2016). TNF-α is a multifunctional circulating cytokine which is nowadays accepted to be one of the main mediators of atherogenesis through promotion of leucocytes adhesion to the endothelium, foam cell formation, T-lymphocytes, and monocyte/macrophages activation (Enayati et al. 2015). TNF-α is produced by macrophages, mast cells, endothelial and smooth muscle cells and is found in vulnerable sites of atherosclerotic plaques (e.g., plaque shoulder) (Soeki and Sata 2016; Pasterkamp et al. 1999). In addition to TNF-α, other important members of the TNF superfamily (TNFSF) and TNF receptor superfamily (TNFRSF) are involved in atherosclerosis pathophysiology including Tκα, OX40 (CD134)/TNFRSF4 and its ligand (OX40L)/TNFSF4, CD40/TNFRSF5 and its ligand (CD40L,CD154)/TNFSF5, TNF-related apoptosis-inducing ligand (TRAIL or Apo2L)/TNFSF10, as well as receptor activator of NF-κB (RANK)/TNFRSF11A and its ligand (RANKL)/TNFSF11A (Dostert et al. 2018). In addition, two other pro-inflammatory pleiotropic cytokines, IL-1 and IL-6, have many humoral and cellular immune properties connecting them to inflammation and enhanced atherosclerosis as also outlined by the recent CANTOS trial (Ridker et al. 2017, 2018; Tousoulis et al. 2016). Also, CD40 and its counterpart ligand (CD40L) collaborate to enhance atherosclerosis, thromboembolism, and inflammation by inducing the expression of different pro-atherogenic substances such as adhesion molecules, cytokines, chemokines, growth factors, and MMPs in different cell types (Gissler et al. 2016; Yuan et al. 2015). ECs and smooth muscle cells amplify MCP-1 (also known as CCL2) in response to different cytokines and to OxLDL (Deshmane et al. 2009). Circulating levels of both CCL2 and its receptor CCR2 have been directly associated with enhanced atherogenesis and increased CV risk due to higher macrophage infiltration (França et al. 2017). Oppositely anti-inflammatory cytokines, such as IL-10, negatively modulate atherogenesis by favoring resolution of inflammation and are downregulated in patients with atherosclerosis and at higher risk of CV events (Mallat et al. 1999; Han and Boisvert 2015). TNFα/IL-10 ratio is emerging as an interesting marker to estimate the imbalance between pro- and anti-inflammatory cytokines and assess the CV risk (Goswami et al. 2009; Kumari et al. 2018; Narverud et al. 2011b).

Supporting the role of inflammatory cytokines in FH patients, the expression of the inflammatory gene-regulating transcription factor NF-kB in mononuclear cells of FH patients was significantly associated with plasma levels of OxLDL, xanthine oxidase, hs-CPR, apoB, and LDL (Real et al. 2010a). Increased TNF-α levels and

TNF-α/sTNFRs ratio have been reported in FH children, while no difference was reported in adults with and without FH (Narverud et al. 2011a). Of interest, FH children had lower circulating levels of IL-10 resulting in increased TNF-α/IL-10 ratios (Narverud et al. 2011a). In another similar investigation, mRNA transcription levels of TNFSF/TNFRSF genes in peripheral blood mononuclear cells (PBMCs) of children and young people with FH before and after statin therapy were measured (Narverud et al. 2013a). Baseline expression of OX40L, B cell activating factor receptor (BAFF) receptor, and TRAILR1 were significantly increased, while TRAIL and TRAILR3 were considerably reduced in FH patients when compared to controls (Narverud et al. 2013a). After statin administration, expression levels of OX40L and TRAILR1 decreased while BAFF, TRAIL, and TRAILR3 increased (Narverud et al. 2013a). Altogether these findings suggest FH children to have an impaired balance between anti- and pro-inflammatory signaling which may play an important role in the increased CV risk of these patients. In adults, the evidence is less clear, a study reported increased level of TNF-α in patients with HoFH as compared to normocholesterolemic controls (Gokalp et al. 2009). Oppositely, in the general FH population under optimal therapy no difference in terms of circulating inflammatory markers such as TNF-α, IL-1β, IL-1 receptor antagonist (IL-RA), IL-6, IL-10, and MCP-1 has been reported when compared to healthy controls (Real et al. 2010a; Hovland et al. 2010). In contrast, both HoFH and HeFH patients who were never treated with lipid-lowering agents have high or very high CHD risk and increased levels of MMP-9, TIMP-1, and IL-18 (El Messal et al. 2006). At the cellular level, monocytes from FH patients show a pro-inflammatory phenotype characterized by increased expression of CCR2, resulting in enhanced migratory capacity—a feature strongly associated with atherosclerosis development (Bernelot Moens et al. 2017). Accordingly, PBMCs from FH patients release a substantial amount of macrophage inflammatory protein (MIP)-1α, −1β, and IL-8 as compared to controls (Holven et al.2003, 2006). In young FH patients, main inflammatory mediators might differ as PBMCs from HeFH children have increased transcription of RANTES/CCL5, but not MIP-1α (Holven et al. 2006). Suggesting that during the early inflammatory phase of atherosclerosis, the crucial mediator might be leukocyte-derived RANTES (Holven et al. 2006). Lipid-lowering drugs have been hypothesized to impact inflammatory biomarkers in FH patients. A study by Semb et al demonstrated that FH patients have increased serum levels of sCD40L (about 27-folds) as compared to normal controls, while 2-year-long statin treatment reduced sCD40 levels by 40% (Semb et al. 2003). In another study, PBMCs obtained from FH patients and treated with statins for a long time (median 17 years) displayed higher expression levels of 4-1BB (CD137), CD40, TNFR1, TNFR2, and TRAIL when compared with control subjects (Holven et al. 2014). However, serum concentrations of CD40L and CD137 were similar between FH patients and controls (Holven et al. 2014). This is in accordance with a previous report from a cohort of FH children in which serum sCD40L levels were comparable to those of healthy siblings and pravastatin treatment did not modify them (Ueland et al. 2006). Also, Hovland et al. reported no significant alterations in inflammatory state among statin-treated FH patients and healthy controls (Hovland et al. 2010). Considering the pathophysiological

involvement of TNF-related molecules in FH, the use of novel anti-inflammatory treatments on top of lipid-lowering agents in highest tolerable doses in FH patients could be also suggested. For instance, the use of PCSK9 monoclonal antibodies in FH patients did not only affect plasma values of LDL, but significantly reduced the expression of CCR2 mRNA in PBMCs, monocyte migratory ability, and intracellular lipid content (Bernelot Moens et al. 2017; Pecin et al. 2017; Reiner 2018). These data suggest a pro-inflammatory role for LDL on peripheral monocytes in FH patients, which can be reversed by cholesterol-lowering therapies.

7 OxLDL

OxLDL particles are produced by lipid peroxidation due to the action of oxygen-derived free radicals on native LDL. OxLDL are thought to be key mediators in the context of atherosclerosis as previously discussed. Previous studies showed that FH patients have higher OxLDL levels when compared to those without FH (Real et al. 2010a). Increased OxLDL levels were also observed in FH children when compared to non-FH children. Of interest, OxLDL values are significantly correlated with the expression of OX40L, TRAILR1, and BAFF-receptor, deeply involved in inflammation (Narverud et al. 2013a; Jehlička et al. 2009). In PBMCs from FH patients, OxLDL induces gene expression of TRAILR1, TRAILR4, and BAFF-receptor (Narverud et al. 2013a). Moreover, in vitro experiments revealed that OX40L promotes OxLDL-induced expression of MMP-9 in human monocytes (Narverud et al. 2013a). Furthermore, higher OxLDL have been reported in patients with HeFH particularly when showing Achilles tendon xanthoma (Nielsen et al. 2015). In this population, regression analysis demonstrated that OxLDL is a strong predictor of MMP levels and regulates monocyte expression of pro-atherosclerotic and pro-inflammatory genes by interaction with its scavenger receptor CD36 (Nielsen et al. 2015). Modified LDL epitopes including OxLDL are found within macrophages of FH patients with tendon xanthoma (Sugiyama et al. 1992). Interestingly, macrophages of FH patients with Achilles tendon xanthoma have greater intracellular cholesterol ester pooling and a unique gene expression pattern as compared to those of patients without tendon lesion (Sugiyama et al. 1992). Accordingly, the occurrence of xanthomas in FH patients could be explained by distinctive gene expression profile (including several pro-inflammatory chemokines), which enhances the transformation of macrophages into foam cells (Artieda et al. 2005).

OxLDL is associated with and predicts acute CVD events in apparently healthy subjects and is thought to be a promising risk marker for CV events (Holvoet et al. 2004; Tsimikas et al. 2003; Nordin Fredrikson et al. 2003; Meisinger et al. 2005; Gao and Liu 2017). This evidence still needs specific validation in FH patients. Being modified self-lipoprotein, OxLDLs can trigger an adaptive immune response eventually leading to formation of anti-OxLDL autoantibodies (Zhang et al. 2015). Based on the existing evidence, IgG autoantibodies might be directly associated with CVD events, while IgM autoantibodies seem to have a protective profile (Shoenfeld

et al. 2004; Karvonen et al. 2003). Of interest, when compared to unaffected siblings, FH children are characterized by elevated levels of total immune complex per apoB and malondialdehyde-LDL autoantibodies (Rodenburg et al. 2006). Lipid-lowering therapy was able to reduce circulating autoantibodies in the same cohort (Rodenburg et al. 2006). Interference due to lipid-lowering therapy might account for some apparent discordant findings in this field (Barros et al. 2006). Further investigations are needed to confirm the role of autoantibodies against modified LDL in atherosclerosis and dissect their potential function as CV risk biomarkers in the specific FH setting.

Paraoxonase type 1 (PON1) is a HDL-related enzyme capable of hydrolyzing different substrates among which are oxidative pro-oxidant species (van den Berg et al. 2019). For this reason, PON1 was hypothesized to protect against atherosclerosis. Despite this, in FH patients no association was found between peripheral concentration of PON1 and carotid IMT, levels of OxLDL and hs-CRP (van Himbergen et al. 2005). More recently, PON1 esterase activity was found to be reduced in FH patients as compared to healthy relatives (Idrees et al. 2018). These results are still very preliminary and should be interpreted with caution; more evidence is needed to assess the potential role of PON1 in FH-related atherosclerosis.

8 Lipoprotein-Associated Phospholipase A2

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a calcium-independent catalytic enzyme predominantly synthetized in macrophages (De Stefano et al. 2019). Lp-PLA2 is thought to hold pro-atherogenic function by its pro-inflammatory and pro-oxidant activity (Stafforini 2009). Through hydrolysis of oxidized phos pholipid molecules, Lp-PLA2 produces bioactive substances including lysophosphatidylcholine and oxidized non-esterified free fatty acids (FFAs) and modifies OxLDL (Caslake et al. 2000). Also, Lp-PLA2 participates in endothelial dysfunction (Yang et al. 2006), aortic wall inflammation and affects vulnerability of plaques with thin caps (Weintraub 2008; Tsimikas et al. 2007). Lp-PLA2 circulates together with Lp(a) and apoB-100 containing lipoproteins, mainly LDL (~80%) and HDL (~20%) (Tsimikas et al. 2007; Saougos et al. 2007; Blencowe et al. 1995). A considerable amount of evidence supports the idea that increased concentrations of Lp-PLA2 are associated with higher risk of coronary heart disease, stroke, and general vascular morbidity and mortality (Collaboration L-PS 2010; Wallentin et al. 2016; Tibuakuu et al. 2018; Garg et al. 2015, 2016).

It has been reported that hypercholesterolemic patients without FH have lower Lp-PLA2 activity when compared with patients with clinically confirmed FH diagnosis independently of circulating lipoprotein values (Mattina et al. 2018). The increased Lp-PLA2 activity might account for the enhanced arterial inflammation as reported in FH patients and participate in premature onset of CV events (Mattina et al. 2018). In children with FH, Lp-PLA2 mass and activity were also considerably

higher in comparison with unaffected siblings, but Lp(a) levels and carotid IMT were not (Ryu et al. 2011). In addition, after 2 years of statin therapy Lp-PLA2 mass and activity were significantly decreased and net-changes in Lp-PLA2 activity positively correlated with the changes in LDL-C levels (Ryu et al. 2011). Summarizing, the predictive role of Lp-PLA2 on CV events in FH patients still requires further investigations.

HDL particles have several athero- and vasculo-protective features such as reverse cholesterol transport, anti-oxidant and anti-inflammatory properties (Ganjali et al. 2017, 2018; Chapman et al. 2011). A specific sub-fraction, HDL3 particles in normolipidemic subjects effectively prevent vascular injury caused by LDL. In FH patients, anti-oxidative and anti-inflammation properties of HDL3, which prevent deposition of OxLDL in vessels, are decreased by up to three-fold (Hussein et al. 2016). Moreover, surface lipids of HDL are decreased, while the amount of core lipids is increased in FH. This ratio is directly associated with the anti-oxidant and anti-inflammatory characteristics of HDL which are suboptimal in FH patients (Hussein et al. 2016).

9 $CD16^{+}$Monocytes

Peripheral monocytes are heterogeneous and two main subsets have been described according to surface expression of CD14 and CD16 (Ghattas et al. 2013; Ziegler-Heitbrock 1996). It is well known that in early reversible stage of atherosclerotic process, inflammatory lesions are mainly consisting of monocyte-derived macrophages with high CD16 and low CD14 expression (Häkkinen et al. 2000). At this stage, the activation of $CD16^{pos}$ monocytes by the Toll-like receptor (TLR)-4/-2 ligands leads to increased TNF-α and decreased IL-10 mRNA transcription levels. Thus, $CD16^{pos}$ monocytes are generally thought to be pro-inflammatory cells (Belge et al. 2002). Also, $CD16^{pos}$ monocytes have elevated phagocytosis capability and higher tendency to adhere to the endothelium as a result of LDL and OxLDL infiltration (Mosig et al. 2009). $CD16^{pos}$ monocytes express and generate inflammatory mediators and chemokine receptors, which are involved in atherosclerotic process (Ancuta et al. 2003; Tacke et al. 2007). Uptake of OxLDL via CD36 in monocytes results in over-expression of this scavenger receptor via induction of transcription factors NF-κB and peroxisome proliferator-activated receptor (PPAR)-γ. As a result of this vicious circle, macrophages undergo phenotypic alteration and become atherogenic foam cells (Gurnell 2003; Tak and Firestein 2001). Yet, all monocyte subsets have been described in advanced atherosclerotic plaques (Hansson 2005).

FH patients have increased amount of intermediate $CD14^{++}CD16^{+}$ monocytes (Nielsen et al. 2015). Additionally, their transcription of pro-atherosclerotic and pro-inflammatory genes in response to OxLDL–CD36 interaction is significantly elevated, particularly in patients with Achilles tendon xanthoma (Nielsen et al. 2015). Also, $CD16^{pos}$ monocytes from FH patients show an increased uptake of

OxLDL-C via the scavenger receptor CD36, while $CD16^{neg}$ monocytes from FH subjects preferentially uptake native LDL particles (Mosig et al. 2009). $CD16^{pos}$ monocytes of FH patients are more mature as compared to $CD16^{pos}$ of healthy persons. It has been speculated that $CD16^{pos}$ monocytes evolve and more quickly transform into macrophages as a reaction to OxLDL which also stimulates cell apoptosis (Wintergerst et al. 2000; Kashiwakura et al. 2004). The potential role of monocyte and their subset as predictive markers of CV disease in the setting of FH still requires further investigations.

10 Mean Platelet Volume

Platelets from clinically diagnosed FH patients are highly active, easy to activate, and show reduced circulating life (Blaha et al. 2004; Betteridge et al. 1994). Platelet activation plays an important role in both early and advanced atherogenesis in patients with FH (Heidari-Bakavoli et al. 2018). Among many platelet parameters, mean platelet volume (MPV) as a marker of platelet activity appears to be promising (Heidari-Bakavoli et al. 2018). Indeed, an increased MPV is associated with larger and excessive reactive platelets with more metabolic, enzymatic, and coagulation potential (Kamath et al. 2001; Park et al. 2002). Reactive platelets are associated with higher levels of prothrombotic substances, thromboxane, and glycoproteins which enhance their aggregability (Vizioli et al. 2009). Many data have demonstrated increased prothrombotic tendency and activity in platelets from dyslipidemia patients (Georgieva et al. 2004; Khemka and Kulkarni 2014). Also, it has been shown that FH patients have remarkably increased MPV levels, but lower platelet count when compared to controls (Icli et al. 2016). Of interest, MPV is independently correlated with total cholesterol in clinically diagnosed FH patients (Icli et al. 2016).

11 Neopterin

Activated blood-derived macrophages contribute throughout the whole atherogenesis process (Liberale et al. 2017; Ross 1999; Robbie and Libby 2001). Neopterin is produced in macrophages stimulated with interferon gamma (IFN-γ) as a result of guanosine triphosphate (GTP) catabolism. Accordingly, neopterin is an inflammation product considered to be a general marker of cellular immunity (Murr et al. 2002) as well as an indicator of activation of T helper cells (Th) type 1 (Wachter et al. 1989), whose main product is IFN-γ.

Two comparable studies reported increased levels of neopterin in HeFH children as compared to controls or unaffected siblings. Furthermore, BMI and HDL-C were independent predictors of neopterin in these subjects (Ueland et al. 2006; Holven et al. 2006). However, the first reports suggest such a difference not to be conserved

in adult HeFH patients (Holven et al. 2006). Although this observation may be due to the rather low number of adults enrolled, it may also indicate a unique pattern of macrophage activation in HeFH adults and children (Holven et al. 2006). Although IFN-γ activates the pathways responsible for elevation of neopterin concentrations in different pathologic states, no significant differences were found on IFN-γ expression in stimulated T-cells from children with HeFH and healthy controls (Holven et al. 2006). This observation might be explained by the fact that neopterin is not only regulated through IFN-γ (Holven et al. 2006). Indeed several cytokines such as IL-1, IL-6, and TNF-α modulate monocyte activation and thus might modulate neopterin levels, and some of these cytokines possibly have an important role in low-grade inflammation in FH children (Holven et al. 2006). Despite very preliminary, these findings might suggest the important role of chronic Th1-induced monocyte/macrophage over-activation in the early onset of atherosclerosis (Ueland et al. 2006; Holven et al. 2006).

12 CV Risk Assessment in Patients with FH

Differences in incidence of CV events remain a major unsolved issue for patients with FH and this is reflected by the availability of different CV risk scores. Different studies demonstrated that traditional CV risk factors are not totally overwhelmed by the high LDL levels in FH patients and they still hold important predictive value also in such a particular population (Kramer et al. 2006; et al. 2019). In the SAFEHEART-Risk Equation, CV risk in FH is estimated based on age, sex, BMI, levels of LDL and Lp(a), history of CV disease, hypertension, or smoking (et al. 2019; Mata and Alonso 2018). An expert consensus from the International Atherosclerosis Society (IAS) suggests to further define FH patients in severe and non-severe FH with the former being characterized by severely elevated levels of LDL (>400 mg/dL) or milder elevation of LDL (>310 mg/dL or>190 mg/dL) with respectively one or high-risk features (Santos et al. 2016). These supplementary risk factors include those listed for the SAFEHEART-Risk Equation while also taking into consideration low HDL levels or presence of diabetes mellitus, chronic kidney disease, and familial history of early CV afflictions (Santos et al. 2016). Interestingly, the IAS risk stratification also includes the diagnosis of advanced coronary disease as assessed by coronary artery calcium score or degree of obstruction at CT angiography. In this sense, CV imaging techniques are thought to provide crucial information to guide the prognostic assessment of patients with FH and are fundamental for providing an adequate CV assessment in studies investigating potential novel risk biomarkers. With particular reference to potential inflammatory risk biomarkers, FDG-PET may represent an important additional value providing direct evidence of inflammatory activity of the vessel/plaque and allowing direct correlation with circulating markers (Joshi et al. 2018; Duivenvoorden et al. 2013). None of the previously mentioned inflammatory biomarkers has so far provided enough sensitivity and specificity to be included in any CV risk prediction algorithms for

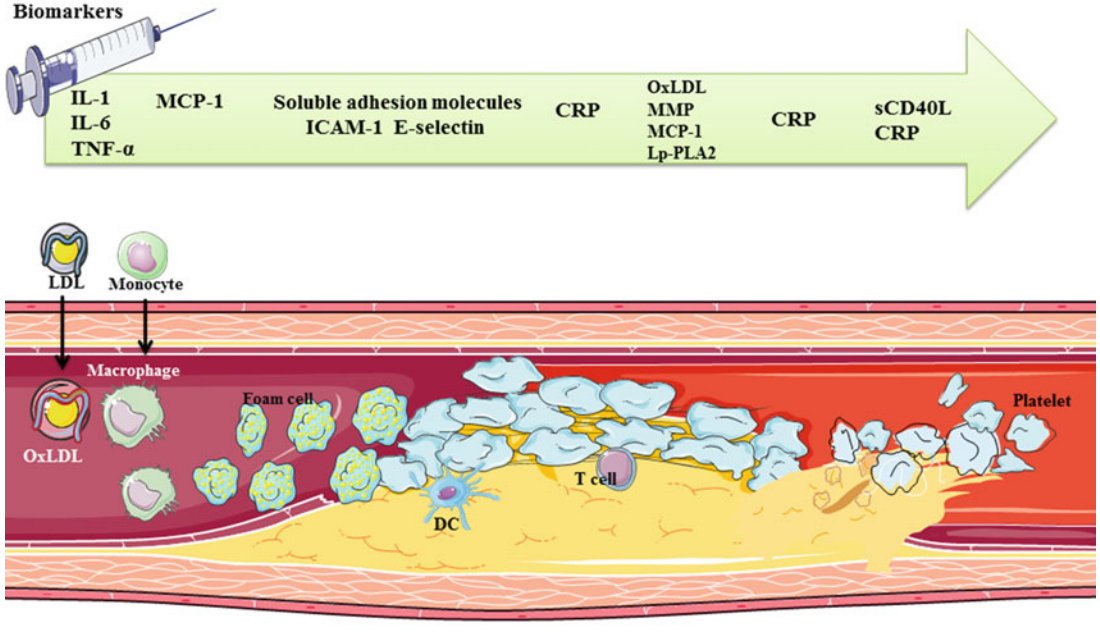

Fig. 2 Promising inflammatory biomarkers in familial hypercholesterolemia. *CRP* C-reactive protein, *DC* dendritic cell, *ICAM-1* intercellular adhesion molecule-1, *IL* interleukin, *MCP-1* monocyte chemo-attractant protein 1, *Lp-PLA2* Lipoprotein-associated phospholipase A2, *MMPs* matrix metalloproteinases, *OxLDL* oxidized LDL, *TNF-α* tumor necrosis factor-alpha

FH patients. This is likely due to many reasons including different limitations of studies so far investigating this hypothesis. Some of them enrolled heterogeneous cohorts of FH patients without genetic characterization which are likely to include patients with familial combined hyperlipidemia and metabolic syndrome. Also, patients with FH are often affected by metabolic syndrome which associates with increased levels of inflammatory biomarkers on its own thus adding even more variability to the literature. Solid large, longitudinal data from registry cohorts enrolling patients with definite disease diagnosis and optimal patient characterization—including comorbidities and imaging characterization of the coronary three—are needed to investigate whether inflammatory biomarkers might provide additional value to CV risk stratification in FH.

13 Conclusion

Atherosclerotic complications are leading causes of mortality in FH patients. In the last decades, our understanding of atherosclerosis pathophysiology revealed a previously unexpected pivotal role for inflammation in this process. Accordingly, inflammatory mediators became interesting markers of disease as well as therapeutic targets to counteract plaque initiation and progression. In FH patients, the enhanced inflammation may account for part of the increased CV risk and anti-inflammatory interventions on top of optimal lipid-lowering therapy may effectively reduce the incidence of major CV events. Yet, whether inflammatory biomarkers may be of help in stratifying the risk of this highly heterogenic population remains to be fully assessed (Fig. 2). Available evidence suggests that the predictive role of each inflammatory mediator may vary depending on the age of FH subjects and the stage of the atherosclerotic disease. Further prospective studies are needed to elucidate whether measurements of these inflammatory biomarkers, alone or in combination, will provide added value in the identification of those patients at higher CV risk who will benefit from more intense pharmacological interventions.

Conflict of Interest None.

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