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Highlighting Residual Atherosclerotic Cardiovascular Disease Risk

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Precision medicine is increasingly moving health care from a conventional “one-size-fits-all” approach towards a personalized medicine strategy. For example, patients with certain types of cancer can now make treatment choices based not only on the tumor’s histological type, but also on tissue expression of targeted proteins and specific gene mutations. Precision medicine has made less progress in atherosclerotic cardiovascular disease (ASCVD). What will be necessary for us to achieve effective precision medicine in patients with ASCVD? Since the landmark Scandinavian Simvastatin Survival Study (4S) demonstrated a beneficial effect of statin treatment on recurrent cardiovascular events in patients with overt hyperlipidemia,[1] many subsequent studies on primary and secondary prevention have demonstrated favorable effects of low-density lipoprotein cholesterol (LDL-C) lowering therapies on ASCVD outcomes.[2345] These beneficial effects of statins are now known to extend to patients without clear dyslipidemia or pre-existing cardiovascular disease. However, many statin-treated patients remain at a significantly elevated risk of having a major cardiovascular event that is unresolved despite statin treatment. This is commonly referred to as “residual risk.”

The American College of Cardiology and American Heart Association recently published the 2018 clinical practice guidelines for management of blood cholesterol.[6] The guidelines suggest that the more LDL-C is reduced, the greater will be the ASCVD risk reduction. The guidelines stratify patients based on LDL-C levels and other clinical risk factors (such as clinical ASCVD or diabetes) and risk-enhancing factors (such as metabolic syndrome or chronic inflammatory conditions) and recommend treatment options/intensity of treatment based on each stratum for primary and secondary ASCVD prevention. Even with more stringent treatment strategies going forward, there are several important questions to be

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addressed, including; 1) whether optimal LDL-C control varies from person to person rather than according to overall clinical subgroup; 2) whether residual ASCVD risk could be prevented by even more aggressive LDL-C lowering using more stringent statin regimens or additional LDL-C-lowering strategies such as inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9),[7] which has some effects distinct from those of statins on non-LDL-C risk factors;[89] and 3) to what extent non-LDL-C risk factors explain the residual risk.

Type 2 diabetes mellitus is associated with dyslipidemia characterized by a number of abnormalities that have collectively been referred to as the atherogenic dyslipidemia complex,[10] and are believed to contribute to residual risk in these patients. Thus, high prevalence of ASCVD can be observed in type 2 diabetic patients with elevated levels of plasma triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C), and levels of glycated hemoglobin outside the target range of 7%.[1112] A large study on more than 270,000 patients with type 2 diabetes included in the Swedish National Diabetes Register indicated that when glycated hemoglobin, LDL-C, albuminuria, blood pressure, and smoking are all within the target range, these patients have no residual risk of myocardial infarction (MI), as compared with the general population.[12] This suggests that well-controlled diabetes *per se* does not increase residual risk as long as LDL-C and the other assessed risk factors are well controlled.

Conversely, genome-wide association studies, Mendelian randomization studies, and studies on humans with loss-of-function mutations in identified genes have made it abundantly clear that variations in genes not only related to LDL-C (e.g. *PCSK9, SORT1, APOB*), but also related to triglycerides (e.g. *APOC3, LPL, ANGPTL3*), and inflammation (e.g. *CXCL12, IL6R*) associate with ASCVD risk.[1314] Residual risk is therefore likely to be higher in certain populations of patients with genetic risk and patients who for other reasons have elevated triglycerides, low HDL-C or increased inflammation.

In this *ATVB* Highlights article we will review recent articles published in *ATVB* related to residual risk in cardiovascular disease and put this research into a wider context. We will focus primarily on triglyceride-rich lipoproteins (TRLs) and their remnants, lipoprotein(a), HDL, and inflammation as residual risk factors. Increased understanding of the contributions of those residual risk factors in different patient populations will move the field closer towards more effective precision medicine approaches to prevent ASCVD events.

Triglyceride-rich lipoproteins (TRLs) and their remnants

Treatment strategies to improve triglyceride clearance or reduce production, especially in patients with type 2 diabetes, have become a central topic in the debate over residual risk of ASCVD. Blood concentrations of triglycerides are generally considered to reflect atherogenic lipoproteins, such as TRLs and their remnants. TRLs are converted into their remnants primarily by lipoprotein lipase (LPL), and subsequently, these smaller apoB-containing lipoprotein remnant particles can penetrate and accumulate in the subendothelial arterial space and induce local and systemic atherogenic responses. Thus, patients with familial dysbetalipoproteinemia (also known as type III hyperlipoproteinemia or remnant removal disease) exhibit markedly accelerated atherosclerosis despite LDL-C levels being in

the normal range.[15] These patients exhibit elevated remnants primarily because of mutations in the apolipoprotein E (*APOE*) gene, which prevent effective hepatic clearance of the apoE-containing TRLs. Furthermore, increased arterial inflammation, measured as increased arterial ^{18}F-fluorodeoxyglucose uptake, can be seen in patients with familial dysbetalipoproteinemia.[16] Increased ^{18}F-fluorodeoxyglucose uptake is closely associated with inflammatory activation of macrophages,[17] suggesting that remnants result in increased activation of lesional macrophages exposed to TRL remnants. The elevated remnant levels result in increased lipid accumulation in circulating monocytes and increased expression of adhesion molecules in these cells, as well as monocytosis,[15] which would all be predicted to increase macrophage accumulation in lesions of atherosclerosis. Thus, a marked increase in remnants results in atherogenic effects both systemically and locally.

In patients without known genetic conditions affecting TRL remnant clearance, the role of remnants in ASCVD is more difficult to assess, in part because remnants are poorly defined and are difficult to measure. One common method of assessing remnant levels is to subtract LDL-C and HDL-C from total cholesterol levels. This method is inexact, especially at high triglyceride levels. Measurements of plasma triglyceride levels, often used as a surrogate of TRLs and remnants, are also an approximation because fasting concentrations of plasma triglycerides correspond to the sum of triglyceride content in nascent VLDL and remnants. Nevertheless, fasting triglyceride levels can predict long-term and short-term cardiovascular risk in patients with acute coronary syndrome who are treated effectively with statins,[18] suggesting that elevated fasting triglycerides contribute to residual risk. Triglyceride content in plasma increases in the postprandial state due to the presence of triglyceride-rich chylomicrons and their remnants.[19] Non-fasting triglycerides are also associated with increased risk of ischemic heart disease and MI,[20] and with a stepwise higher risk of heart failure.[21] Therefore, in some patients it is recommended to assess both non-fasting and fasting lipid profiles.[22]

A recent article in *ATVB* highlights the importance of postprandial triglyceride clearance in atherosclerosis in humans. Kurihara and colleagues used optical coherence tomography to visualize high-risk atherosclerotic lesions, defined as thin-cap fibroatheroma, and the association with postprandial dyslipidemia after a meal tolerance test in 30 patients with stable coronary artery disease. They demonstrated that thin-cap fibroatheromas are associated with increased levels of remnants after the meal tolerance test, and with elevated baseline apolipoprotein C-III (apoC-III) levels,[23] suggesting baseline abnormalities in TRL clearance in patients with high-risk lesions. In another *ATVB* article, insulin treatment of diabetic mice was shown to reduce plasma triglycerides and cholesterol, and to increase LPL activity concomitant with a reduction in atherosclerosis.[24] LPL hydrolyzes triglycerides and promotes uptake of fatty acids into tissues, thereby lowering plasma triglyceride levels. Interestingly, blood glucose lowering by an SGLT2 inhibitor had no such effects, suggesting that in diabetes, lipids are more important than glucose in promoting atherosclerosis,[25] at least in this mouse model.

Do abnormalities in triglyceride metabolism causally associate with ASCVD? A number of clinical trials evaluating the effect of triglyceride lowering therapies on ASCVD have yielded variable results.[262728] The conflicting results between trials can be interpreted in

several ways; 1) niacin, fish oils and fibrates tested have multiple effects, including effects unrelated to triglyceride-lowering; 2) the dose-setting or formulations of triglyceride-lowering drugs might have been insufficient to show a beneficial effect on ASCVD; 3) the most relevant patient populations might not have been targeted by these clinical trials; and 4) plasma triglycerides are regulated by a number of different genes and mechanisms. The very recently published REDUCE-IT trial tested the effect of icosapent ethyl (a pure and stable eicosapentaenoic acid ethyl ester; EPA; 4 g daily dose) in statin-treated high-risk ASCVD patients with baseline fasting plasma triglycerides levels ranging from 135 to 499 mg/dl. After a median study period of 5 years, the results showed a 25% reduction in the primary composite end points including coronary revascularization or unstable angina, and a 26% reduction in the secondary end points composed of cardiovascular death, MI and stroke.[29] The icosapent ethyl treatment resulted in a 18% reduction in plasma triglycerides during the first year of the study. These results are similar to those of Japan EPA lipid intervention study (JELIS), which also demonstrated a beneficial effect of EPA on ASCVD events in statin-treated subjects.[30] To what extent the beneficial effects of EPA ethyl ester on ASCVD are due to triglyceride-lowering needs further study. Thus, it remains unclear whether triglyceride lowering is effective in preventing ASCVD in patients with residual risk. Several additional trials are under way that will aid our understanding of the roles of TLRs in ASCVD risk.[28]

On the other hand, recent Mendelian randomization studies strongly support the causal relationship between genes involved in triglyceride metabolism and coronary heart disease.[31] Genetic and genomic studies have revealed that genes involved in triglyceride clearance, including *APOC3*,[32][33][34] *APOA5*,[35] *ANGPTL3*,[36] and *LPL*[37] strongly associate with cardiovascular disease risk. Indeed, plasma apoC-III levels associate with high-risk coronary plaques[23] and the risk of ASCVD.[38] Consistently, the low risk of cardiovascular disease in patients with *APOC3* loss-of-function mutations is considered to be mainly mediated by the associated low remnant cholesterol and not by the low level of LDL-C.[34] Also, apoC-III is involved in the formation of small dense LDL,[39][40] another cardiovascular risk factor; therefore, its inhibition can potentially modify the pro-atherogenic properties of LDL in addition to increasing triglyceride clearance. New strategies such as inhibition of APOC3 or ANGPTL3 (which inhibits LPL) might prove to be effective therapeutic options to increase triglyceride clearance and reduce residual risk of ASCVD.[28]

Mechanisms whereby TRL remnants or genes that impair remnant removal promote major ASCVD events are still poorly understood, but are believed to include increased trapping of remnants in the artery wall, increased remnant uptake by lesional macrophages, inflammatory and proapoptotic effects on lesional cells, and procoagulant effects.[41]

High-density lipoprotein

Low levels of HDL cholesterol (HDL-C) are often associated with elevated triglycerides, and are a clinical hallmark in patients with metabolic syndrome or type 2 diabetes. Reduced levels of HDL-C can also be observed in other populations. For example, a recent publication in *ATVB* demonstrated that HDL-C levels are reduced by environmental factors, such as traffic-related pollution.[42] A large number of epidemiological studies have

consistently shown a strong inverse correlation between HDL-C and the incidence of cardiovascular events, therefore, therapies to increase the level of HDL-C have been extensively tested as a strategy to reduce cardiovascular events, particularly in patients with type 2 diabetes.[43]

HDL is a heterogeneous population of particles with sizes ranging from 7 nm to 14 nm that collectively contain >80 different proteins and can be divided into partly distinct subpopulations characterized by different protein composition, which may have different functions.[44] We know now that small HDL particles are most effective in removing cholesterol from cells through the cholesterol transport protein ABCA1,[45] whereas large HDL contains the most cholesterol.[43] A recent manuscript published in *ATVB* demonstrated that the function of both small HDL (preβ−1-HDL) and large HDL (α−1+α−2 HDL) are altered in patients with coronary artery disease.[46] Therefore, treatment strategies that increase levels of HDL-C would not necessarily be predicted to increase the atheroprotective cholesterol efflux capacity of HDL. Strategies to boost the atheroprotective function of HDL particles might prove to be more effective.

So far, the main strategy for increasing HDL has focused on increasing HDL-C levels by inhibition of cholesteryl ester transfer protein (CETP). Because CETP transfers triglycerides from VLDL and other lipoproteins to HDL in exchange for cholesteryl esters, its inhibition results in increased levels of cholesteryl esters in HDL in humans.[47] Consistently, a recent study published in *ATVB* used a new rabbit CETP knockout model to demonstrate that CETP-deficiency results in elevated HDL-C levels, increased cholesterol efflux capacity of apoB-depleted plasma, markedly reduced levels of VLDL, and protection against cholesterol diet-induced atherosclerosis.[48] Another study found that pharmacological inhibition of CETP activity reduces in-stent restenosis via inhibition of vascular smooth muscle cell proliferation,[49] suggesting that CETP inhibition may be a potential strategy to protect against ASCVD and related vascular damage. Whereas these animal models show beneficial effects of loss of CETP, human studies are less conclusive. Three clinical trials using different types of CETP inhibitors failed to demonstrate a beneficial effect on cardiovascular outcomes despite showing increased HDL-C levels.[50] A recent Mendelian randomization study[51] found that a common variation in the *CETP* gene reduced the risk of MI, however, this gene variant was also associated with a decreased level of LDL-C coupled with the increased level of HDL-C. Recently, the REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid modification) trial demonstrated that CETP inhibition by anacetrapib reduced coronary artery disease events, however, this agent not only increased the HDL-C level but also reduced the LDL-C level,[52] similarly to the findings observed in the above Mendelian randomization study. Taking these results together, we still cannot conclude that a low level of HDL-C is a causal risk factor of ASCVD because we are unable to exclude the effect of LDL-C lowering by CETP inhibition on the positive results.

Another approach to raise HDL-C is to increase levels of apolipoprotein A-I (apoA-I), the main structural protein of HDL.[53] So far, several interventional approaches targeting apoA-I have been developed[54, 55] and a few of them revealed beneficial effects against atherosclerosis in humans,[56] but none of these strategies have resulted in clinical use. A recent manuscript published in *ATVB* demonstrated that apoA-I vascular gene therapy

targeting endothelial cells shows a protective effect against atherosclerosis in hyperlipidemic rabbits,[57] suggesting that increased apoA-I expression in the endothelium is atheroprotective. In addition, apoA-I mimetic peptides have been continuously developed in parallel with the investigation of its functionality *in vivo*. [58]

Endothelial lipase (EL, gene name *LIPG*) determines HDL-C levels by hydrolyzing HDL phospholipids, and mice deficient in EL exhibit a marked increase in fasting HDL-C and increased numbers of HDL particles.[59] Consistently, *LIPG* gene variants have been shown to be associated with increased plasma HDL-C in humans.[6061] However, the effect of EL on atherogenesis is controversial.[6263] Recent studies published in *ATVB* examined rabbit and mice overexpressing human EL in the liver. In the rabbit model, HDL-C levels and atherosclerotic lesions were reduced by EL overexpression.[64] In the mouse model, HDL levels were similarly reduced, but reverse cholesterol transport was not dampened unless hepatic scavenger receptor class B type I was inhibited.[65] Furthermore, a Mendelian randomization study found that carriers of the *LIPG* 396Ser allele had higher HDL-C but similar levels of other lipid and non-lipid risk factors for MI compared with non-carriers; yet this allele was not associated with reduced risk of MI.[51]

Moreover, a recent *ATVB* article on the relationship between HDL-C and mortality has shown a U-shaped curve, suggesting that an extremely high level of HDL-C is not related to a favorable outcome, in contrast, showing increased mortality.[66] These results suggest that a strategy simply aimed at quantitatively increasing HDL-C levels does not improve cardiovascular outcomes. Taken together, the dogma that HDL-C is atheroprotective is not uniformly supported by human data.

In this context, there is a growing debate on HDL's functionality, rather than cholesterol content, in mediating HDL's atheroprotective effect.[43] Higher cholesterol efflux capacity of plasma HDL, measured as cholesterol mass efflux, was recently shown to be associated with lower risk of incident coronary heart disease events.[67] The correlation between plasma HDL's cholesterol mass efflux capacity and HDL-C in this study was modest. Furthermore, studies on the effect of exercise and weight loss have demonstrated that some measures of HDL function can be improved at least partly independently of HDL-C levels.[6869] The search for mechanisms that improve HDL function is therefore an intense topic of study. One such mechanism is related to sphingosine-1-phosphate (S1P), which appears to mediate some of the atheroprotective functions of HDL. Thus, Denimal *et al.* demonstrated that blunted activation of eNOS by HDL in patients with metabolic syndrome was mainly due to reduced levels of S1P in HDL.[70] Apolipoprotein M is the main carrier of S1P in plasma, and a subpopulation of HDL carries apoM and binds S1P. The relative level of S1P in HDL versus apoB-containing lipoproteins is modulated by CETP.[71] It has been shown that apoM-bound S1P is responsible for HDL's ability to suppress adhesion molecule expression in the endothelium.[72] These findings suggest that S1P is a mediator of at least some of the atheroprotective effects of HDL. Further studies on the functionality of HDL, and regulators of its functionality will be needed.

Furthermore, a series of studies have supported the idea that the concentration of HDL particles is a superior marker of ASCVD risk over HDL-C, and of residual risk after statin

treatment.[7374] Consistently, niacin and CETP inhibitors that raise HDL-C but did not show a beneficial effect on cardiovascular disease,[7550] had only weak effects on increasing the number of HDL particles.[76] Therapeutic strategies to increase HDL particle concentrations might be able to reduce the residual risk. Further investigation of the clinical significance of various HDL metrics and their effectiveness in preventing ASCVD risk is needed.

Lipoprotein(a)

Lipoprotein(a) [Lp(a); gene name *LPA*] is an apo-B100-containing LDL particle covalently attached to the protein apolipoprotein(a) [apo(a)]. Lp(a) levels are not generally lowered by statins, which makes Lp(a) a strong residual risk factor candidate. However, increased Lp(a) does not appear to explain the residual risk associated with diabetes.[10] Instead, a series of genetic studies including meta-analysis and Mendelian randomization studies have suggested that genetically elevated levels of Lp(a) causally associate with cardiovascular disease risk.[77] Plasma levels of Lp(a) vary more than 1000-fold between individuals and partly reflect acute or chronic inflammation; however, they are primarily determined by polymorphisms in the *LPA* gene. *LPA* variants associate with cardiovascular events in patients receiving statin therapy.[78] Moreover, progression of carotid atherosclerosis positively associates with the level of Lp(a) in patients treated with intensive lipid-lowering medication with the goal of LDL-C <70 mg/dl.[79] These findings support the notion that Lp(a) is a candidate component of residual risk in ASCVD in some patients. In addition to apo(a) synthesis in hepatocytes, catabolic pathways also impact plasma levels of Lp(a). A large-scale genetic study in humans found that differences in plasma Lp(a) levels are associated with *APOE* genotypes, suggesting that apoE can affect the catabolism of Lp(a), perhaps through competition for the hepatic clearance receptors LDLR and LRP1.[80]

Given that Lp(a) might be a promising therapeutic target in some patients with increased residual risk, we need to define its therapeutic threshold value. There have been continuous efforts to determine the therapeutic cutoff value in Lp(a).[81] A recent analysis estimating population impact of lowering the plasma Lp(a) level to < 50 mg/dl, based on data from a large prospective cohort study, suggested that reducing Lp(a) is expected to have a significant impact on the reduction of cardiovascular disease.[82] Niacin, [838485] PCSK9 inhibition,[986] apo(a) antisense oligonucleotides,[87] CETP inhibition by anacetrapib,[88] and the removal of Lp(a) by lipoprotein apheresis[89] might be candidates for therapeutic strategies to reduce Lp(a) levels. A recent chronic renal insufficiency cohort study showed that elevated Lp(a) is independently associated with MI and death among patients with chronic kidney disease;[90] therefore, therapeutic intervention to lower Lp(a) might provide benefits especially in high risk populations with prevalent chronic kidney disease.

The mechanisms whereby Lp(a) promotes atherothrombotic disease are not well understood, in part because rodents and rabbits, which are commonly used for mechanistic studies on atherogenesis, do not normally express Lp(a). Animals transgenic for Lp(a) suggest that Lp(a) promotes fatty streak formation and atherosclerotic lesion calcification, but better models are needed to understand the mechanisms.[91]

Inflammation

It is now well recognized that inflammation, orchestrated by various types of immune cells,[92] their subpopulations,[93] and cytokines[9495] in circulation or in the local milieu, associate with and participate in the development and progression of atherosclerosis. Moreover, interest in the relationships among inflammatory processes and ASCVD extends to the involvement of humoral immunity,[96] such as the classic pathway of complement activation,[97] IgM,[98] and IgE.[99] Conditions associated with an increased ASCVD risk, such as diabetes, are characterized by increased low-grade inflammation. In addition, it is interesting to note that ambient air pollution is associated with systemic inflammation,[100] which in turn might contribute to incident cardiovascular events.[101]

Although we have known for decades from mechanistic animal models that inflammatory processes are critically involved in atherosclerosis, whether inflammation itself can be a therapeutic target in prevention of ASCVD in humans has been a longstanding clinical question. The CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcome Study) recently offered an answer to this question by demonstrating that inhibition of the cytokine interleukin-1β (IL-1β) can prevent ASCVD events in subjects with a prior MI and elevated high-sensitive C-reactive protein (hs-CRP), highlighting inflammation as a non-lipid residual risk factor in these patients.[102] The results of this trial showed that targeting the IL-1β innate immunity pathway with canakinumab (a human IL-1β neutralizing monoclonal antibody) at a dose of 150 mg every 3 months led to a lower rate of recurrent cardiovascular events than did placebo treatment, independent of lipid-level lowering.[102] It is noteworthy that a majority of subjects included in the CANTOS trial were on statin therapy. Also, it is worth mentioning that this study proposed the concept of “residual inflammatory risk”,[103104] and suggested that inflammation is a major residual risk factor of ASCVD. The CANTOS trial concurrently demonstrated that IL-1β can contribute to cardiovascular events in humans. However, it is unknown if blocking IL-1β would be effective in the general population of patients with elevated ASCVD risk, including those who do not have increased C-reactive protein. The very recent CIRT (Cardiovascular Inflammation Reduction Trial) failed to demonstrate a beneficial effect of low-dose methotrexate as an anti-inflammatory agent in ASCVD patients with a median level of hs-CRP at randomization at 1.5 mg/l (compared to more than 4 mg/l in CANTOS).[105102] However, methotrexate did not reduce circulating levels of IL-1β, IL-6 or hs-CRP, suggesting that the treatment did not alter the key inflammatory pathway(s).

Many lines of evidence evoke IL-1β as especially important in ASCVD. Chai *et al.* identified *Il1b* as one of the upstream regulators of enriched gene sets when comparing the transcriptome of macrophages from symptomatic atherosclerotic lesions with that of macrophages from asymptomatic lesions.[106] Inflammasomes are essential for IL-1β secretion via activation of caspase-1.[107] Thus, the inactivation of inflammasomes might be a therapeutic option to prevent cardiovascular event.[108] Indeed, a recent study using apoE-deficient mice treated with a specific inhibitor of the most studied inflammasome component, NLRP3, showed attenuation of atherosclerosis development.[109] Conversely, physiological activators of inflammasomes include saturated fatty acids,[110] ceramide,[111] oxidized LDL,[112] and cholesterol crystals,[113114] which are present in atherosclerotic lesions.

These lipids or other inflammasome activators are therefore likely to accelerate inflammation and lesion progression.

Recently, clonal hematopoiesis of indeterminate potential (CHIP) has emerged as another non-lipid residual risk factor related to inflammation in older patients.[115] Deficiency of one of the most common genes responsible for CHIP in humans, TET2 (Tet Methylcytosine Dioxygenase 2), was shown to promote atherogenesis in mouse models through an IL-1β- and NLRP3 inflammasome- dependent mechanism.[115] Taken together, activation of the NLRP3 inflammasome, a mediator associated with both cell death and inflammation, can be a potential mechanism underlying the formation of the large necrotic cores with accumulation of inflammatory cells, which characterizes high-risk plaque.

Defective efferocytosis, the process by which dying cells are removed by phagocytes, also contributes to the expansion of necrotic cores in lesions of atherosclerosis. However, the mechanisms that determine the efficiency of efferocytosis have only partly been worked out. In an interesting study, Wang and colleagues recently demonstrated that mitochondrial fission in response to the initial uptake of apoptotic or dying cells is essential for continued efferocytosis.[116] This finding suggests that defective efferocytosis might be partly due to the failure of mitochondrial remodeling after uptake of a first-round of apoptotic cells. In agreement, Yu *et al.* demonstrated that human atherosclerotic plaques exhibit marked mitochondrial dysfunction, defined by increased mitochondrial DNA damage and reduced mitochondrial respiration, and that reducing mitochondrial DNA damage and increasing mitochondrial respiration led to attenuated necrotic core formation in mice.[117] Rinne and co-workers offered a solution to limit expansion of necrotic cores. By treating *Apoe*$^{-/-}$ mice with palmitoylethanolamide, an endogenous fatty acid mediator, they generated a pro-resolving environment, which reduced inflammation and enhanced efferocytosis, thus resulting in smaller necrotic cores.[118] These findings support the notion that inflammation and associated cell death and impaired efferocytosis in response to the lesion environment concertedly shape pathological traits of high-risk atherosclerotic plaques. However, inflammation cannot be characterized by the dualism of “good or bad” in the process of atherogenesis. Therefore, the development of additional strategies to target specific inflammatory processes relevant to ASCVD demands further research.

Summary

We are now in an era where it is becoming possible to integrate individual large-scale data on disease, genomics, and artificial intelligence,[119] which will likely allow us to redefine the meaning of “residual risk factor for ASCVD” to go beyond LDL-C control and statin treatment. That is, if more detailed understanding of residual risk factors of ASCVD could be achieved in parallel with mechanistic insights, we would be able to fine-tune treatment and prevention strategies. In this article, we focused on TRLs and their remnants, HDL, Lp(a), and inflammation as candidates of residual risk factors of ASCVD. Full understanding of residual risk in ASCVD might be a difficult task; however, with continuous research efforts in clinical and basic studies relevant to residual risk, it might not be long before precision medicine can be more efficiently applied in this area.

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