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Invited commentary

A new piece in the puzzling effect of n-3 fatty acids on atherosclerosis?

Wilfried Le Goff [a, b, c, *]

[a] INSERM UMR_S1166, Team 4: Integrative Biology of Atherosclerosis, F-75013 Paris, France
[b] Université Pierre et Marie Curie-Paris6, F-75005 Paris, France
[c] Institute of Cardiometabolism and Nutrition (ICAN), Pitié-Salpêtrière Hospital, F-75013 Paris, France

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ABSTRACT

Omega-3 fatty acids (n-3) FA are reported to be protective against cardiovascular disease (CVD), notably through their beneficial action on atherosclerosis development. In this context dietary intake of long-chain marine eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is recommended and randomised trials largely support that EPA and DHA intake is associated with a reduction of CVD. However, mechanisms governing the atheroprotective action of n-3 FA are still unclear and numerous studies using mouse models conducted so far do not allow to reach a precise view of the cellular and molecular effects of n-3 FA on atherosclerosis. In the current issue of *Atherosclerosis*, Chang et al. provide important new information on the anti-atherogenic properties of n-3 FA by analysing the incremental replacement of saturated FA by pure fish oil as a source of EPA and DHA in $Ldlr^{-/-}$ mice fed a high fat/high cholesterol diet.

Cardiovascular disease (CVD) is the leading causes of death in the world [1] and is frequently associated with atherosclerosis, a pathology characterised by the accumulation of lipids, mainly cholesterol in the arterial wall. Among major risk factors for CVD, circulating levels of lipids and more especially those originating from diets are closely linked to development of atherosclerosis. In this context, not only cholesterol, but also dietary fatty acids (FA) may appear particularly deleterious in regards to atherosclerosis and associated CVD [2]. However, although saturated fats are pro-atherogenic, omega-3 fatty acids (n-3 FA), and more especially long-chain marine eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert atheroprotective properties through several potential underlying mechanisms [3]. Therefore, the intake of EPA and DHA is recommended around the world and randomised trials with n-3 FA confirmed that EPA and DHA intake reduced risk for CVD events [4]. However benefits of n-3 FA intake were challenged by recent clinical trials that failed to replicate protective effects of EPA + DHA on CVD, raising the controversy on the healthy side of marine n-3 FA [5].

Animal models are commonly employed in order to decipher mechanisms by which n-3 FA exert their beneficial actions regarding lipid metabolism and atherosclerosis [6]. Since the last past 20 years, mouse models, and more especially genetically modified mouse models, became the reference model to evaluate the effects of dietary fatty acids, especially n-3 FA, on atherosclerosis development [7–20]. However, the use of different mouse models of atherosclerosis ($Apoe^{-/-}$, $Ldlr^{-/-}$, double $Apoe^{-/-}$ x $Ldlr^{-/-}$, $Ldlr^{-/-}$ x *hApoB* mice), as well as diet composition (chow, high cholesterol, high fat, high cholesterol/high fat), source of n-3 FA supplementation (fish oil, perilla seed oil, flaxseed, pure ALA, EPA or DHA), duration of the diet (from 4 to 32 weeks), size of atherosclerotic lesions in control animals (from 51 to 700.10^3 μm^2) in those studies led to heterogeneous results and therefore to a partial understanding of the effects of n-3 FA on atherosclerosis. For more clarity on the main findings obtained in mouse models, those studies are summarised in Table 1.

Contrary to what observed in $Apoe^{-/-}$ mice, dietary supplementation of $Ldlr^{-/-}$ mice with n-3 FA led to a reproducible reduction of aortic atherosclerosis, although to various degrees, confirming that $Ldlr^{-/-}$ mice constitute the most appropriate model for studying the atheroprotective effects of n-3 FA (Table 1). When evaluated, the decrease of atherosclerosis upon n-3 FA-rich diet was accompanied by a reduction in the macrophage content as well

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* INSERM UMR_S1166, Team 4: Integrative Biology of Atherosclerosis, Hôpital de la Pitié, Pavillon Benjamin Delessert, 83, boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Tel.: +33 1 42 17 79 75; fax: +33 1 45 82 81 98.
E-mail address: wilfried.le_goff@upmc.fr.

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Table 1
Impact of dietary enrichment in n-3 fatty acids on atherosclerosis development in mouse models.

Study		n-3 FA supplementation		Plasma			Atherosclerotic lesions				Major findings
		Diet	Weeks	TC	TG	HDL	Effect of n-3 FA enrichment	Size in control diet	MΦ content	Inflammation	
Brown AL. et al. [7]	6/8-week female Ldlr$^{-/-}$	10% palm oil/0.2% chol. + 10% palm oil, echium oil (botanical 18:4 n -3), fish oil	16	↘	nd	nd	↘ 40−70% (aortic roots)	~650.10^{3}μm^2 (Palm oil)	↘ 30−40% (CD68)	nd	↘ splenic/circulating Ly6Chi monocytosis, ↘ monocyte trafficking into the aortic root, ↘ splenic/circulating neutrophils
	6−8 weeks female Apoe$^{-/-}$	idem	12	↗	↗	nd	↔ (aortic roots)	~700.10^{3}μm^2 (palm oil)		nd	↔ monocyte trafficking, ↘ splenic/circulating neutrophils
Nakajima K. et al. [8]	6-week male Ldlr$^{-/-}$	8-weeks HF/HC (21% fat, 1.25% chol., 0.5% cholate) followed by normal diet +/− 5% EPA	4	↘	↔	↗	↘ 20.9% regression (↔ +IDO inhibitor)	538.10^{3}μm^2 (chow)	↘ 23% (MOMA-2)	↘ IFN-γ, IL-10, IL-12p40, TNFα, MMP-2, MMP-9, ICAM-1, ↗ TGF-β	↘ CD4+ T cells, mature DCs in atherosclerotic lesions, ↗ splenic immature DC (CD11c$^+$ CD80$^-$ CD86$^-$), ↗ splenic IDO DC, ↗ lesion α-SMA and collagen content
Winnik et al. [9]	8-week male Apoe$^{-/-}$	0.21% chol. + high (7.3%) vs low (0.03%) plant ALA content	16	↘	↔	nd	↘ 50% (thoraco-abdominal aortae)	125.10^{3}μm^2 (low ALA)	↔(CD68)	↘ TNFα, VCAM-1	↘ CD3+ T cells in atherosclerotic lesions, ↔ circulating monocytes and l ymphocytes, Shift prostaglandin and isoprostane formation towards 3-series compounds
Zhang et al. [10]	8-week male Apoe$^{-/-}$	5% fat + safflower oil (83% LA)/perilla seed oil (81% ALA) (n-6/n-3 ratio : 1.28, 5.03, 9.98, 68.25)	6	↔	↔	↘	↔	51.10^{3}μm^2 (control, no ALA)	nd	nd	↗ LCAT activity, ↘ hepatic apoA-I, LCAT, SR-B1, ABCA1, ABCG1, LXRα
Wang et al. [11]	8-week male Ldlr$^{-/-}$	20% fat, 0.2% chol. + ω-6 : EPA+DHA (no EPA+DHA, 20:1, 4:1, 1:1 ratio) (safflower oil : fish oil)	32	↘	↘	↔	↘ (whole aorta)	nd	↘ (MOMA-2)	nd	↘ plasma IL-6, ↘ peritoneal mΦ chol., MCP-1, TNFα, ABCA1, ↔ mΦ IL-6, CD36, SR-B1, MSR1, PPARα, β/δ, γ
Matsumoto et al. [12]	5-week male Apoe$^{-/-}$	0.15% chol, 15% butter +/− 5% EPA	13	↔	↗	↔	↘ 27%/73% (aortic root /whole aorta)	429.10^{3}μm^2 (no EPA)	↘ (F4/80)	nd	↗ lesion α-SMA and collagen content, ↘ peritoneal mΦ infiltration, ↘ aortic MMP-2, MMP-9, ↗ aortic lesion PPARα, ABCA1

(*continued on next page*)

Table 1 (*continued*)

Study		n-3 FA supplementation		Plasma			Atherosclerotic lesions				Major findings
		Diet	Weeks	TC	TG	HDL	Effect of n-3 FA enrichment	Size in control diet	MΦ content	Inflammation	
	4-week male Ldlr$^{-/-}$	idem	12	↘	nd	↘	↘ 93% (whole aorta)		nd	nd	
Dupasquier C. et al. [13]	5/7-week female Ldlr$^{-/-}$	Chow diet +/− 10% flaxseed vs 2% chol. Diet +/− 10%, 5%, 1% flaxseed or 5% coconut oil	24	↘	↔	nd	↘ 14% (aortic root/whole aorta)	nd	↘ mac-3	↘ IL-6, VCAM-1	↘ cell proliferation in aortic tissue, ↔ aortic tissue PPARγ
Saraswathi et al. [14]	8/12-week female Ldlr$^{-/-}$	39% fat, 0.5% chol. + 6% olive oil or fish oil (menhaden oil)	12	↘	↘	nd	↘ 37% (aortic root)	$100.10^3\mu m^2$ (olive oil)	nd	nd	↘ F_2-isoprostanes, ↗ F_3- and F_4-isoprostanes in heart, ↗ cholesterol storage in WAT, ↗ adiponectin secretion
Zampolli et al. [15]	5-week female Apoe$^{-/-}$	Chow diet +/− 1% fish (n-3) or corn oil (n-6)	20	↗	↗	↗	↔ (aortic root/whole aorta)	$260.10^3\mu m^2$ (no supplement)	nd	nd	
	8-week male Ldlr$^{-/-}$	23% fat + 0.045% chol. +/− 1% fish (n-3) or corn oil (n-6)	20	↘	↘	↔	↘ 42%/−40% (aortic root/whole aorta)	$120.10^3\mu m^2$ (no supplement)	nd	nd	↘ plasma lipid levels
Yamashita et al. [16]	6-week male Apoe$^{-/-}$ Ldlr$^{-/-}$	40% lipid, 40% carbohydrates, 20% protein, 0.05% chol. + safflower oil (76% n-6 FA) + flaxseed oil (55% n-3 FA) (n-6/n-3 : 0.29, 1.43, 5 and 8)	16	↔	↘	↗	↘ 40% (whole aorta)	nd	nd	nd	↘ thrombogenicity, ↘ atherogenic LDL/HDL ratio
Wang et al. [17]	10-week male Apoe$^{-/-}$	Control vs Fish oil vs corn oil	10	↔	↗	↔	↘ 68% (aortic root)	$40.10^3\mu m^2$ (corn oil)	nd	nd	↗ hepatic SOD and CAT antioxidant activities
Adan et al. [18]	7-week male Apoe$^{-/-}$	9% olive oil, 43.75% sucrose, 1% chol.+/− 1% DHA or safflower	8	↔	↗	↗	↔ (whole aorta)	nd	nd	nd	↗ liver EPA+DHA ↘ liver linoleic, eicosatrienoic, arachidonic acids
	7-week female Apoe$^{-/-}$	idem	8	↘	↔	↔	↔ (whole aorta)	nd	nd	nd	
Rudel et al. [19]	8-week 8/9-week male/female Ldlr$^{-/-}$/hApoB	10% fat, 0.005% chol +/− saturated (palm oil), cis/trans mono, n-3 (fish oil), n-6 (safflower oil) polyunsaturated FA	16	↘	↔	↘	↘ (whole aorta)	nd	nd	nd	↘ LDL size, ↗ LDL-TG, ↘ LDL-CE (n-3 poly FA-rich)
Renier G. et al. [20]	6-week C57BL/6J	Control +/− 10% menhaden oil or 10% palm oil + 2% chol.	15	nd	nd	nd	↘ 57% (aortic root)	nd	nd	nd	↘ TNFα and IL-1β secretion from peritoneal mΦ ↘ LPL secretion from peritoneal mΦ ↗ NO_2 from IFNγ-stimulated peritoneal mΦ ↘ PGE_2 secretion from LPS-stimulated peritoneal mΦ ↘ tumoricidal activity from LPS-stimulated peritoneal mΦ

EPA : eicosapentaenoic acid, DHA : docosahexaenoic acid, ALA : α-linoleic acid (flaxseed oil, precursor of EPA, DPA and DHA), LA : linoleic acid, mΦ : macrophage : not described,

as inflammation in aortic lesions highlighting the major impact of n-3 FA on monocyte recruitment and subsequent macrophage accumulation in the arterial wall. However, although supplementation with n-3 FA allows an efficacious lowering of plasma lipid levels in humans [5], studies in mouse models suggest that the anti-atherogenic action of n-3 FA is independent of any effects on plasma cholesterol or triglyceride levels [7]. However, that must be asserted with caution as lipid metabolism is quite different in mouse in comparison to humans, highlighting the need to study in the future the effects of n-3 FA on atherosclerosis in a mouse model exhibiting a more "humanized" lipid metabolism as achieved in hApoB/CETP mice.

In a previous issue of *Atherosclerosis*, Chang et al. [21] re-evaluate the impact of fish oil n-3 FA on atherosclerosis development by operating an incremental replacement of saturated fats (SAT) by n-3 FA (pure fish oil, EPA- and DHA-rich) in *Ldlr*$^{-/-}$ mice fed a high-fat (21%, w/w)/high-cholesterol (0.2%, w/w) diet for a 12-week period. This experimental approach is quite pertinent as dietary fat intake in developed countries, as in United States, derived mostly from saturated FA and is poor in n-3 FA. Then, using this strategy the authors were able to evaluate the potential beneficial effects of a supplementation with fish oil n-3 FA in a dietary context for which n-3 FA intake is relevant.

Here, Chang et al. demonstrated that the progressive increase of dietary intake of fish oil n-3 FA (EPA and DHA) abrogated the deleterious effects of a SAT diet, thereby suggesting that a dietary n-3 FA intake on a SAT background is potentially efficient to decrease CVD in humans. Indeed, replacement of SAT by fish oil n-3 FA markedly reduced plasma cholesterol and triglycerides levels and abolished diet-induced atherosclerosis mediated by SAT in *Ldlr*$^{-/-}$ mice. To note that in the present study, *Ldlr*$^{-/-}$ mice only developed small atherosclerosic lesions (~100.10^3 μm^2) after 12 weeks of diet with SAT.

As previously reported [7,13], decreased atherosclerotic lesions were accompanied by a reduced content of aortic macrophages and inflammation. Based on their previous works [22,23], the authors proposed that the reduction of atherosclerosis upon n-3 FA resulted from an impairment of cholesterol uptake by arterial macrophages consecutive to the decrease of Lipoprotein Lipase (LPL) expression in those cells. Indeed, beyond its lipolysis action on triglycerides, LPL was reported to promote lipid accumulation, in particular in macrophages, by binding to lipoproteins and cell surface proteoglycans and then acting as a bridging molecule that facilitates cellular lipid uptake. Coherent with this mechanism, macrophage LPL expression was reported to promote foam cell formation and atherosclerosis [24,25]. In the present study, replacement of SAT by n-3 FA both decreased expression and altered distribution of arterial LPL. Such a mechanism for n-3 FA (EPA and DHA) was proposed by this group in earlier studies [22,23] to favour reduction of arterial LDL-cholesterol. It is noteworthy that lipid rafts alter distribution of LPL at the cell surface and subsequently the LPL-dependent accumulation of lipids in macrophages and foam cell formation [26,27]. As incorporation of n-3 FA, such as DHA, into cell membrane phospholipids disrupts lipid rafts organisation [28], it cannot be exclude that reduction of lipid accumulation in arterial macrophages upon addition of n-3 FA results in part from an impairment of the localisation and of the anchoring function of LPL at the cell surface of macrophages. Indeed Chang et al. observed that progressive replacement of SAT by n-3 FA affected aortic FA composition leading to a pronounced increase of arterial EPA and DHA, then suggesting that content of n-3 FA in macrophage membrane may be equally altered. However, the implication of LPL in the atheroprotective effects of n-3 FA need to be validated using an appropriate mouse model for which LPL expression may be controlled.

Analysis of LPL and macrophages in aortic roots from mice fed the different diets indicated that LPL expression colocalized with macrophages, an observation in agreement with the idea that LPL in atherosclerotic lesions is mostly expressed by macrophages [29]. Incremental replacement of SAT by fish oil n-3 FA strongly attenuated both macrophage and LPL contents in lesion areas. However the diminished amount of aortic LPL did not only result from the reduced number of macrophages as *LPL* mRNA levels were found decreased in aortic macrophages isolated by Laser Capture Microdissection (LCM). This observation clearly indicate that dietary n-3 FA intake not only hamper monocyte trafficking into the aorta [7], but also repress LPL expression by aortic macrophages.

The inhibitory effect of n-3 FA on LPL expression by macrophages was previously observed [20] and was proposed to involve PPAR [30]. Because a decrease of PPARδ expression parallelled that of LPL in arterial macrophages extracted by LCM, the authors speculate that PPARδ might participate to the anti-atherogenic role of n-3 FA by regulation of LPL expression. Although such a mechanism still needs to be demonstrated, this hypothesis is not supported by a recent study indicating that activation of PPARδ in macrophages reduced LPL activity through activation of Angiopoietin-like 4 (ANGPTL4) expression without having any effect on *LPL* mRNA levels [31]. In addition, coherent with the role of LPL in macrophage lipid uptake, activation of PPARδ in this latter study inhibits foam formation. In some aspects, the reduction of aortic macrophage LPL expression by fish oil n-3 FA (EPA and DHA) observed by Chang et al. may appear surprising as EPA and DHA are natural ligands for PPARγ [32] which is a potent activator of LPL expression [33]. Taken together with the observation that lipolysis of triglyceride-rich lipoproteins (TRL) by LPL generates free FA (FFA) acting as PPAR ligands able to trigger an anti-inflammatory response [34], that suggests that beneficial effects of the replacement of SAT by n-3 FA dependent on LPL likely do not require PPARs.

Among the various mechanisms by which n-3 FA exert anti-inflammatory properties [3], EPA and DHA repressed inflammation by shutting down NF-κB activation in macrophages. Since expression of TLR-4 and NF-κB target genes, IL-6 and TNFα, in aorta from mice fed diets containing n-3 FA were decreased when compared to SAT, those results strongly support the contention that n-3 FA repress inflammation by inhibiting the TLR4/NF-κB signalling cascade likely through the macrophage n-3 FA receptor GPR120 [35].

Although further studies are needed to explore the complete spectrum of actions of n-3 FA on atherosclerosis development and CVD, this study provides important information that supports that n-3 FA intake is a pertinent strategy to reduce risk of CVD.

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