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REVIEW

Adipokines, adiposity, and atherosclerosis

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Abstract

Characterized by a surplus of whole-body adiposity, obesity is strongly associated with the prognosis of atherosclerosis, a hallmark of coronary artery disease (CAD) and the major contributor to cardiovascular disease (CVD) mortality. Adipose tissue serves a primary role as a lipid-storage organ, secreting cytokines known as adipokines that affect whole-body metabolism, inflammation, and endocrine functions. Emerging evidence suggests that adipokines can play important roles in atherosclerosis development, progression, as well as regression. Here, we review the versatile functions of various adipokines in atherosclerosis and divide these respective functions into three major groups: protective, deteriorative, and undefined. The protective adipokines represented here are adiponectin, fibroblast growth factor 21 (FGF-21), C1q tumor necrosis factor-related protein 9 (CTRP9), and progranulin, while the deteriorative adipokines listed include leptin, chemerin, resistin, Interleukin- 6 (IL-6), and more, with additional adipokines that have unclear roles denoted as undefined adipokines. Comprehensively categorizing adipokines in the context of atherosclerosis can help elucidate the various pathways involved and potentially pave novel therapeutic approaches to treat CVDs.

Keywords Cardiovascular diseases · Adipose tissue · Adiponectin · Leptin · Obesity

Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality, with approximately 17.9 million deaths reported in 2019 globally [1]. Coronary artery disease (CAD) is among the most common forms of CVDs. CAD is characterized by the formation of plaques along the arterial walls that are highly and chronically inflammatory, and this buildup is known as atherosclerosis [2]. Atherosclerosis is initiated by the retention of apolipoprotein-B containing lipoproteins in the subendothelial space of arteries that triggers an inflammatory response [3], promotes the migration and proliferation of smooth muscle cells, and forms a necrotic core [4]. Chronic inflammation has become an inevitable factor contributing to the formation of atherosclerotic plaque and participating in various stages of development. Inflammatory signaling in atherosclerosis coordinates the recruitment of monocyte-derived macrophages and T lymphocytes that heavily influence plaque stability, leading to rupture and thrombosis [5].

Obesity is one of the major risk factors for CVDs. Its primary co-morbidities, insulin resistance and type 2 diabetes (T2DM), increase the incidence and severity of atherosclerosis 2–4 folds. About 40% of deaths in T2DM patients are due to risk factors associated with CVDs [6]. Features in obesity, like adiposity, confer abnormalities in metabolism and are linked to CVDs and other metabolic diseases. Besides as the primary organ of energy storage, adipose tissue has been well recognized to produce adipokines that regulate metabolism, inflammation, and endocrine functions [7]. Moreover, the patterns associated with the secretion of adipokines can vary depending on the state of the adipose tissue. Adiposity in obesity can be classified into two key fates: hyperplasia, the de novo maturation of preadipocytes, and hypertrophy,

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an enlargement in adipocyte size. Hyperplasia obesity and hypertrophic obesity show distinct profiles in adipokine production, generally beneficial and detrimental, respectively [8]. Adipokines, such as adiponectin, FGF21, and CTRP9, can be protective in metabolic diseases like atherosclerosis, while other adipokines, such as leptin, chemerin, resistin, and pro-inflammatory cytokines that are secreted from hypertrophic adipose tissue, can further burden the progression of the disease.

In this review, we highlight the well-known and lesser known adipokines, extensively catalog the roles they play in atherosclerosis, and further explore adipokines as potential therapeutic targets for the treatment of atherosclerosis. Based on the rigorous assessments made, we labeled each adipokine into three major groups: protective, deteriorative, and undefined (Fig. 1 and Tables 1, 2, 3).

Protective adipokines in atherosclerosis

Adiponectin

Adiponectin (Acrp30, AdipoQ, apM1) was identified as an adipokine by several independent groups, and has been initially shown to regulate lipid metabolism and insulin sensitivity [9–11]. A number of clinical studies have indicated that adiponectin could possibly be anti-atherogenic. A case–control study of 101 patients with type 1 diabetes revealed an inverse association with plasma adiponectin levels and the progression of coronary artery calcification (CAC) [12]. In patients with coronary heart disease, adiponectin was found to be positively associated with circulating high density lipoprotein-cholesterol (HDL-C), but negatively associated with plasma triglycerides (TG) [13, 14]. In

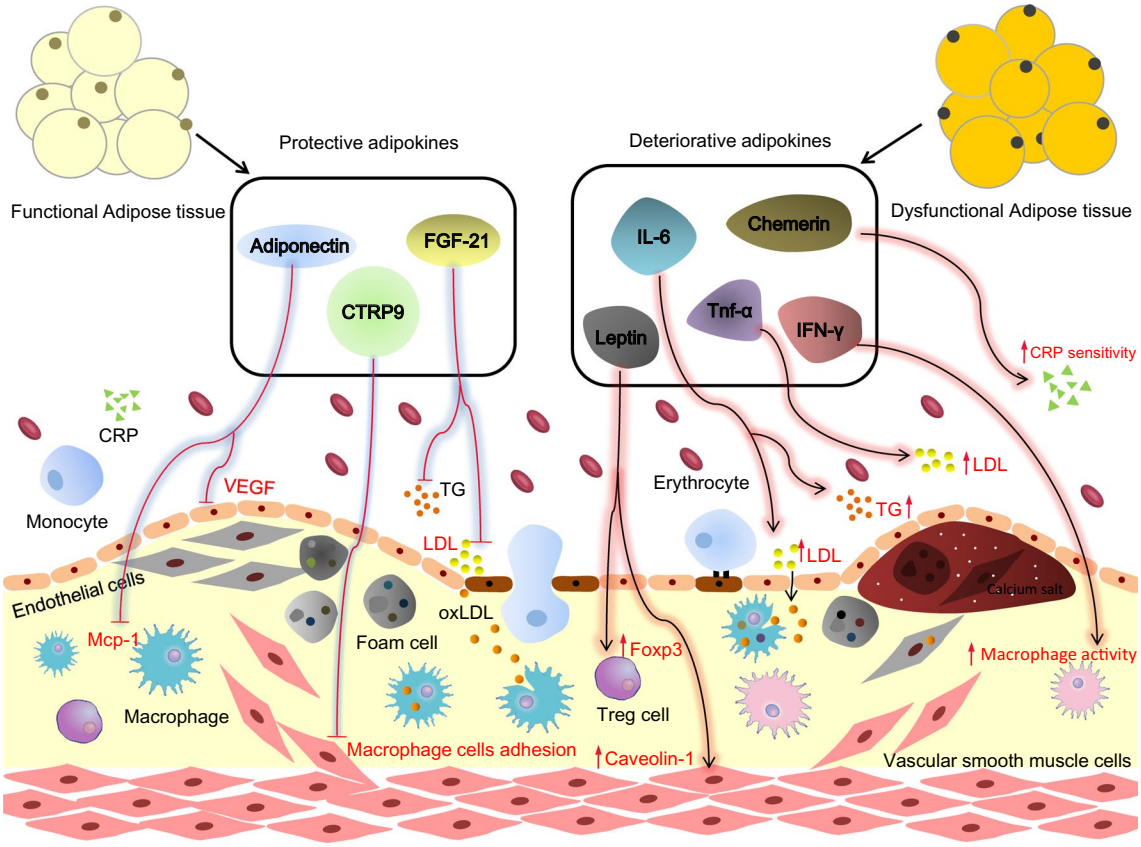

Fig. 1 Representative adipokines in regulating atherosclerosis. Atherosclerosis is a chronic inflammatory cardiovascular disease impacting the arterial walls with lipid-laden plaque. Obesity is a major risk factor for atherosclerosis. Adipokines have been shown to play a myriad of roles in the progression and regression of atherosclerosis, with the former being exacerbated in obesity. Key representative adipokines that regulate atherosclerosis are described here. Protective adipokines depicted are adiponectin, CTRP9, and FGF-21. Adiponectin inhibits macrophage and endothelial cell (EC) activation via the inhibition of monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF), respectively. FGF-21 decreases circulating triglycerides (TG) and low-density lipoproteins (LDL). CTRP9 prevents monocyte adhesion to the vascular wall. Deteriorative adipokines depicted are leptin, chemerin, IL-6, TNF-α, and IFN-γ. Leptin upregulates the expression of FoxP3 in regulatory T cells (Treg) and caveolin-1 in ECs. Chemerin upregulates pathogenic C-Reactive Protein (CRP) levels. IL-6 and TNF-α activate the inflammatory response and influence the lipid profile. IFN-γ also induces inflammation and promotes the transformation of macrophages into cholesterol-loaded foam cells

Table 1 Protective adipokines for atherosclerosis

Adipokines	Major function	Rank of evidence	References
Adiponectin	↓ cholesterol, lipid droplet MSR, VCAM-1, TNF-α, MCP-1 in macrophage, ↓ cAMP-PKA- TNF-α,IL-8, VEGF in ECs ↓adiponectin ∞ ↑CAC, TG, plaque volume, IMT, ∞ ↓ HDL-C	****	[12–23, 25]
FGF21	↑ insulin sensitivity and regulates lipid metabolism ↓the levels of plasma triglycerides, free fatty acids and cholesterol in genetically compromised diabetic and obese rodents ↓ the levels of TG and LDL,↑HDL ↑ ABCA1/ABCG1 expression at mRNA and protein level in macrophages ↑foam cells formation, macrophage migration, inflammatory response, and lipid metabolism in OxLDL-induced THP-1 macrophages ↓ proliferation and migration of smooth muscle cells ↓endothelial dysfunction ↓ conversion of macrophages to foam cells ↓oxidized LDL-C uptake by macrophages ↓sterol regulatory element-binding protein-2 ↓ apoptosis in cultured cardiac endothelial cells from male adult rats ↓∞ the cytotoxic and apoptotic effect of H_2O_2 in a dose-dependent manner	****	[26, 29–34, 192–202]
CTRP9	↓VSMCs' proliferation and phenotype switch and cell dysfunction ↓neointimal formation, endothelial cell senescence and dysfunction ↓pro-inflammatory cytokines in macrophages and THP-1 cell adhesion to VSMCs; ↑ the autophagy level in atherosclerosis lesions ↓ serum glucose level and VSMC cholesterol uptake; ↑the expression of cholesterol efflux-related molecules ↑carotid plaque stability ↓atherosclerosis through AMPK-NLRP3 inflammasome singling pathway, activating AMP-dependent kinase, PGC-1α/AMPK-mediated antioxidant enzyme induction, the AMPKα/ KLF4 signaling pathway, or AMPK/ mTOR pathway	******	[36–42, 203]
PGRN	↓inflammation and adhesion molecules, conversion of macrophages to foam cells and foam cell formation; PGRN degradation into GRNs ↑ inflammation; ↑endothelial nitric oxide synthase ↓cholesterol uptake ↓TNF-α	***	[45, 47, 49, 51]

Rank of evidence: Weak (*), moderate (**), strong (***), stronger (****), Strongest (*****)

another study, nondiabetic patients with low circulating adiponectin corresponded with intimal thickening, an increase in lipid-rich plaque, and elevated plasma lipoproteins [15]. Similar results were replicated in obese subjects in which adiponectin levels were inversely connected to intima-media thickness (IMT), serum triglycerides, fasting insulin, and insulin resistance using homeostasis model assessment-insulin resistance (HOMA-IR). Positive associations were found when evaluating large artery elasticity index (LAEI), small artery elasticity index (SAEI), and HDL-C [16]. Furthermore, a study in atherosclerotic patients suggested similar findings, as well as the discovery that adiponectin secretion from adipocytes was further dampened in patients who smoked [17]. Smoking has been identified as a risk factor for atherosclerosis. This study found adiponectin was decreased in smokers and proved that nicotine might reduce adiponectin expression via ATP-dependent potassium (KATP) channel in adipocytes.

In assessing inflammation, a clinical study in patients with CAD exhibited a decrease in adiponectin and an increase in IL-6, tumor necrosis factor-α (TNF-α), Toll-like receptor 4 (TLR4), and macrophage infiltration in epicardial adipose tissue [18]. Further strengthening the negative association between adiponectin and atherosclerosis, the Matsuzawa group at Osaka University uncovered a specific role for adiponectin that involves inhibiting the formation of foam cells by preventing lipid droplet accumulation and cholesterol loading in macrophages [19]. Mechanistically, this was achieved by inhibiting the expression and activity of the class A macrophage scavenger receptor (MSR) ligand [19]. An in vivo study from the same group showed a reduction in atherosclerotic lesion area in apolipoprotein E-deficient ($apoE^{-/-}$) mice upon treatment with a recombinant adenovirus expressing adiponectin. Adiponectin downregulated the expression of vascular cell adhesion molecule-1(VCAM-1), MSR, and TNF-α, with no changes in CD36 [20]. Luo et al. overexpressed adiponectin in macrophages, resulting in decreased secretion of pro-inflammatory cytokines, such as monocyte chemotactic protein-1 (MCP-1) and TNF-α, prevented macrophage foam cell formation, and improved

Table 2 Deteriorative adipokines for atherosclerosis

Adipokines	Major function	Rank of evidence	References
Leptin	↑piHDL, Lp(a) and apoB100 ↓T-cell helper type 1 response ↑FoxP3 expression and Treg cell function ↑caveolin-1, ERK1/2, eNOS in ECs ↑AngII, ROS, JNK, caveolin-1 in smooth cells ↑TSP-1	****	[53–59, 61, 204, 205]
Chemerin	↑chemerin ∞ ↑ high-sensitivity CRP, IL6, TNF-α, resistin, leptin, BMI, TG, hypertension, ∞ ↓ HDL-C ↑chemerin ∞ ↑ Gensini score ↓chemerin → ↓atherosclerosis, TNFα,IL1β in Apoe$^{-/-}$ mice	***	[67–70]
Resistin	↑ lipid profile,↑ insulin resistance, ↑TG ↑ macrophages polarization, ↑TNF-α, ↑IL-1β, ↑IL-6, ↑VCAM-1, ↑VSMCs, ↑MCP-1, ↑monocyte-endothelial adhesion	****	[71–78]
FABP4	∞ a cluster of metabolic and inflammatory risk factors ↓levels of the adipocyte fatty acid binding protein 4, insulin sensitivity ∞↓cholesterol ester accumulation and inflammatory responses	***	[90–92, 206–212]
IL-1β	expression of various cytokines, chemokines, adhesion molecules ↑leukocytes↑ platelet adhesion to collagen and thrombin↑ VCAM-1↑MCP-1 recruitment↑∞IL-10 produce↓ SMC proliferation↑ and macrophage proliferation in plaques ↑ vascular smooth muscle cell calcium deposition ↑ smooth muscle markers ↑ intimal proliferation↑ advance atherosclerosis: outward remodeling, SMC- and collagen-fibrous cap↑	*****	[95, 97–106, 213, 214]
IL-18	cholesterol efflux (lipoprotein cholesterol↑ serum cholesterol↑) oxidative stress ↑ endothelial dysfunction	*	[110, 111]
	IL18r no differences in atherogenesis induct MMP-9 to promote plaque rupture involve IFN-γ-dependent mechanism to develop atherosclerosis combine with IL-17 promote the diagnostic value of CT	***	[112–118]
IL-6	↑IL-6 ∞ macrophage infiltration in plaque ↑ anti-inflammatory cytokines level in plaques ↑ recruitment of inflammatory cells to the atherosclerotic plaque↑ ↑IL-6 ∞ SMC↑ ↑IL-6 ∞ lipid content ↑ TG ↑ LDL ↑ lipid accumulation↓	****	[121, 122, 126, 215]
	IL-6$^{-/-}$∞lesion formation↑MMP-9↓pro-inflammatory cytokines↑ IL-6$^{-/-}$∞serum cholesterol↑	**	[119, 120]
IFN-γ	↓ plaque destabilization,↑ foam cell,↑macrophage activity, ↑oxidative stress,↓IFN-γ∞↓ macrophage, ↓IFN-γ∞↓T lymphocyte ↑mini-TrpRS, ↑VSMC, ↑monocyte adhesion, ↓ECs glucose metabolism, ↑IFN-γ∞↑ECs dysfunction	***	[127, 128, 130, 131, 133, 135–138]
TNF-α	↑pro-atherosclerotic factors, such as ICAM-1, VCAM-1, MCP-1 the paracrine ring between adipose cells and macrophages ↑the migration and proliferation of medial smooth muscle cells ↑the transcytosis of lipoproteins (e.g., LDL) across endothelial cells and macrophages ↑the intracellular cAMP level and the expression level of SRA co-activation of NF-κB and PPAR-γ ↑ DNA binding of Osf2, AP1, CREB and ↑vascular calcification	****	[141–149]
PAI-1	↑neointima formation ↑fibrin(ogen) accumulation; ↑thrombosis ↑cell proliferation and SMCs senescence ↑macrophage invasion	****	[151–155, 158]
RBP4	↑macrophage cholesterol uptake and foam cell formation ↑RBP4 serum levels in patients with established carotid atherosclerosis∞ the severity of atherosclerosis	**	[161, 162]

Table 2 (continued)

Adipokines	Major function	Rank of evidence	References
LCN2	↓the stimulatory effect of lipopolysaccharide on cytokine gene expression ↑the development of aortic atherosclerotic lesions ↑intraplaque monocyte/macrophage infiltration and pentraxin-3 and collagen-1 expressions ↑ the production of IL6 ↑IL-8 ↑ monocyte chemotactic protein-1 in human macrophages ↑human coronary artery smooth muscle cells ↑ THP1 monocyte adhesion to HUVECs accompanied with upregulation of intercellular adhesion molecule-1 ↑vascular cell adhesion molecule-1 ↑E-selectin associated with nuclear factor-κB (NF-κB) upregulation	***	[163, 166, 167]
	∞↓Plaque size		[216]

Rank of evidence: Weak (*), moderate (**), strong (***), stronger (****), Strongest (*****)

Table 3 Adipokines with undefined roles in atherosclerosis

Adipokines	Major function	References
Adipsin	↑adipsin ∞ ↑ all-cause death and rehospitalization in CAD patients	[169]
	adipsin do not impact atherosclerosis in Ldlr-/- mice	[170]
IL-17	monocytes/chemokines/inflammatory cytokines produce ↑ monocyte chemotaxis ↑ macrophage differentiate↑ foam cell formation↓ immunization recruitment↑	[172–174]
	protective and regulatory role Inhibit pathogenic Th1 differentiate to Anti-inflammatory different gene backgrounds induce difference different atherosclerosis stage	[175–178]
Omentin	circulating and EAT-derived omentin level ↓ in patients with CAD ↓macrophage accumulation, foam cell formation and mRNA expression of pro-inflammatory mediators (TNF-α, IL-6 and MCP-1); ↑anti-inflammatory M2 phenotype during macrophage phenotypic differentiation ↓lipid droplets and plasma total cholesterol levels ↓angiotensin II-induced VSMC migration and platelet-derived growth factor-BB-induced proliferation	[179, 180]
	an increased cardiovascular risk with high plasma omentin levels	[182]
BMPs	↑monocyte recruitment and chemoattraction through direct activation of BMPRII ↑endothelial inflammation and endothelial dysfunction ↑Hepatic Cholesterol Biosynthesis ↑vascular calcification	[183, 184]
	BMPRII knockdown ↑ endothelial inflammation, atherosclerosis	[185]
NAMPT	↑neutrophil infiltration; ↓collagen levels; ↑ MMP-9 content, CXCL1 levels, inflammation, macrophage number and apoptosis; ↓plasma HDL-C levels and cholesterol efflux ↑plaque area;	[186, 187]
	$Ldlr^{-/-}$ $iNAMPT^{hi}$ ↓plaque burden; ↑ lesion stabilization; ↓macrophages to apoptosis	[188]
Vaspin	↓inflammatory phenotypes and foam cell formation; ↓migration and proliferation, ↑ collagen production Vaspin↑in macrophages/vascular smooth muscle cells (VSMCs) within human coronary atheromatous plaques	[190]
	circulating vaspin and severity of AS: no association ↓vaspin serum concentrations ∞the recent presence of ischemic events in patients with carotid stenosis	[189]
	vaspin is linked to CV risk factors serum vaspin concentration is genetically modulated	[191]

insulin sensitivity [21]. Kobashi et al. revealed that adiponectin could inhibit IL-8 through the cAMP–PKA–TNFα signaling pathway in human aortic endothelial cells (HAEC) [22]. Similarly, another study found that adiponectin could inhibit vascular endothelial growth factor (VEGF)-mediated endothelial cell (EC) migration through the cAMP–PKA

signaling pathway in human coronary artery endothelial cells (HCAECs) [23]. To investigate the direct involvement of adiponectin with atherosclerosis outcome, the Scherer group employed adiponectin knockout mice and adiponectin overexpressing mice crossed with either low-density lipoprotein-deficient ($Ldlr^{-/-}$) or $apoE^{-/-}$ mice. Surprisingly, the study conveyed no difference in lipoprotein profile, lesion area, and plaque morphology in either model [24]. Despite this, using mouse studies with T-cadherin and apoE double knockout mice, Fujishima et al. found an increase in atherosclerosis severity at 12 weeks on a high-cholesterol diet compared to control $apoE^{-/-}$ mice. The data further confirms adiponectin as an anti-atherogenic adipokine due to its required interactions with T-cadherin for proper functioning [25]. Overall, numerous studies indicate a protective role of adiponectin in atherosclerosis, although the undergoing molecular mechanism remains complex (Table 1, adiponectin).

FGF-21

FGF-21 is mainly secreted by the liver and skeletal muscle. FGF-21 has also been identified in adipose tissue as an adipokine and can enhance insulin sensitivity through regulating lipid metabolism [26–28]. In atherosclerosis, FGF-21 can alter the lipid profile by modulating transcription factors and key transporters involved in lipid metabolism. FGF-21 induces liver X receptors (LXR) to upregulate the expression of ABCA1 and ABCG1 in macrophages and promote cholesterol efflux [29]. Concurrently, FGF-21 lessens hypercholesterolemia by inhibiting the transcription factor sterol regulatory element-binding protein-2 (SREBP-2) in hepatocytes, which is involved in cholesterol biosynthesis [30]. In diabetic monkeys, FGF-21 treatment has been shown to reduce circulating TG and low-density lipoprotein (LDL), accompanied by an increase in HDL [31]. In oxidized low-density lipoprotein (oxLDL)-loaded THP-1 macrophages, FGF-21 can regulate foam cell formation, cell migration and death, inflammatory response, and lipid metabolism [32]. FGF-21 can further promote the secretion of the previously mentioned protective adipokine, adiponectin, which in turn can reduce endothelial dysfunction, suppress the proliferation of smooth muscle cells, and prevent the transformation of macrophages to foam cells [30]. In human umbilical vein endothelial cells (HUVECs), treatment with FGF-21 diminished the cytotoxic and apoptotic effects of hydrogen peroxide. Exogenous FGF-21 impeded the apoptosis of microvascular endothelial cells in rat hearts under atherosclerotic conditions, further suggesting a protective role in early atherosclerosis [33]. Another study presented FGF-21 to be protective against dyslipidemia in $apoE^{-/-}$ mice by inhibiting the inflammasome through NLRP3, preventing ROS buildup and production, and reducing ER stress [34]. As another well-established protective adipokine in atherosclerosis, FGF-21 is a promising therapeutic target (Table 1, FGF-21).

CTRP9

CTRP9, a newly discovered adipokine [35], can activate a variety of signaling pathways that exert anti-atherogenic effects, particularly in stabilizing carotid plaque. It is documented that CTRP9 attenuates vascular smooth muscle cell (VSMC) proliferation and VSMC phenotype switching by activating AMP-dependent kinase [36, 37]. CTRP9 decreases neointimal lesion formation [37], limits endothelial cell senescence through the AMPKα/KLF4 signaling pathway [38], and retards oxLDL-induced endothelial dysfunction through PGC-1α/AMPK-mediated antioxidant enzyme induction [39]. In the inflammatory response, CTRP9 downregulates pro-inflammatory cytokine secretion in macrophages [40] and upregulates the autophagy in atherosclerotic lesions through the AMPK/mTOR pathway [41]. In addition, the AMPK–NLRP3 inflammasome signaling pathway is involved in the atheroprotective function of CTRP9 [42]. Furthermore, CTRP9 lowers cholesterol uptake in VSMCs with an increase in the expression of cholesterol efflux-related molecules [36]. Besides these direct protections, CTRP9 may benefit atherosclerosis through improving glucose metabolism, particularly in the setting of T2DM [35, 43, 44] (Table 1, CTRP9).

Progranulin

Progranulin (PGRN) is a unique anti-inflammatory growth factor that regulates cell cycle and cell motility [45]. Progranulin is abundantly expressed in various cell types besides adipocytes, including immune cells, epithelial cells, neurons, and chondrocytes [46]. The anti-atherogenic effects of progranulin are mediated through influencing local and/or systemic inflammation and chemotaxis of VSMCs and macrophages, with the opposite occurring in studies with PGRN knockout mice [45, 47]. Kawase et al. proved that the protective effects of PGRN depended on anti-TNF-α [48]. There was a similar study showed that PGRN protected vascular endothelium countered with atherosclerotic inflammation and reduced TNF-α expression [49]. It is also demonstrated that PGRN directly binds to TNF receptors to affect the TNFα/TNFR interaction [46, 50]. Additionally, another mouse study by Nguyen et al. showed that hematopoietic deficiency of PGRN in $Ldlr^{-/-}$ mice promotes cholesterol uptake and foam cell formation [51] (Table 1, PGRN).

Deteriorative adipokines for atherosclerosis

Leptin

Leptin is the adipokine that declares adipose tissue as an endocrine organ [52]. Pathogenic leptin (in obesity) can accelerate atherogenesis [53]. A cross-sectional study involving 174 men and 26 women with T2DM found that plasma leptin levels were tightly correlated to coronary atherosclerosis [54]. In systemic lupus erythematosus (SLE) patients, leptin levels were also strongly associated with an increased risk of atherosclerosis, as well as lipid markers of inflammation, such as piHDL, Lp(a), and apoB100 [55]. In *apoE*$^{-/-}$ mice, 4 week administration of leptin (125 μg/day) significantly increased atherosclerosis and thrombosis after vascular injury [56]. Leptin-deficient mice (*ob/ob*) suppress atherogenesis when crossed with *apoE*$^{-/-}$ mice, independent of serum cholesterol, TNF-α, or adiponectin [57]. Consistent with the findings in *apoE*$^{-/-}$ mouse mode, *ob/ob:Ldlr*$^{-/-}$ mice are protected from atherosclerosis by reducing the T-cell helper type 1 (Th1) response and promoting regulatory T-cell (Treg) function [58]. Singh et al. showed that leptin could upregulate caveolin-1 and activate ERK1/2 and eNOS signaling in vascular endothelial cells [59]. Schroeter et al. found that apoE and caveolin-1 are critical in leptin-induced lesion development, ROS formation, and smooth muscle cell proliferation [60]. Raman et al. also demonstrated that leptin could induce atherosclerosis progression in *apoE-/-* mice, subsequently showing that this process can be reversed by knocking out thrombospondin-1 (TSP-1) [61]. TSP-1 deficiency inhibits leptin-induced atherosclerosis progression and reduces CREB activation and vimentin protein expression in aortic lysates without changing the plasma lipid profile [61].

However, the Multi-Ethnic Study of Atherosclerosis (MESA) revealed that leptin does not have a correlation with cardiovascular events. The study was conducted in men and women in different ethnic backgrounds, adjusted for multiple risk factors [62]. Additional animal studies with conflicting outcomes show varying roles of leptin in atherosclerosis. Severe hypercholesterolemia was observed in *ob/ob:Ldlr*$^{-/-}$ mice compared to *Ldlr*$^{-/-}$ mice despite chow diet feeding (0.075% cholesterol) [63]. Jun et al. found that a type 1 diabetes model, Ins2 + /Alkita:apoE$^{-/-}$ mouse, had 92% less leptin but an increased risk for atherosclerosis compared to nondiabetic Ins2 + /+ :apoE$^{-/-}$ mice. Daily supplements of leptin reversed this risk in Ins2 + /Alkita:apoE$^{-/-}$ mice by significantly decreasing aortic arch lesion area, accompanied by upregulated hepatic sortilin-1, which is a receptor for LDL clearance [64]. Wei et al. showed that leptin receptor-mediated STAT3-independent signaling pathways offer protection against atherosclerosis in a model of obesity and hyperlipidemia using a selective leptin receptor-STAT3 signaling deficiency mouse model: *Lepr*$^{s/s}$*:ApoE*$^{-/-}$ [65]. Collectively, these data suggest that, although leptin can offer metabolism benefits, increased leptin levels are more likely to contribute to atherosclerosis progression through acting on multiple signaling pathways, including ROS, JNK, and STAT3, with obesity exacerbating the leptin-induced pathogenesis of CVDs (Table 2, leptin).

Chemerin

Similar to leptin, chemerin is a white-adipocyte-enriched adipokine [66]. A clinical study in patients with chest pain revealed a positive association between chemerin secretion and plasma levels of high-sensitivity C-reactive protein (CRP), IL-6, TNF-α, resistin, leptin, triglycerides, as well as body mass index (BMI) and hypertension. An inverse correlation was seen with circulating HDL-C. Despite this, after adjusting for established risk factors, chemerin is not a significant biomarker of atherosclerosis [67]. Another clinical study involving 367 hypertensive patients suggested plasma levels of chemerin to be an independent biomarker of arterial integrity and early stage atherosclerosis [68]. Chemerin mRNA levels in human epicardial adipose tissue are positively associated with TNF-α, BMI, waist circumference, fasting blood glucose, and Gensini score, which is an indication for the severity of atherosclerosis [69]. Adenovirus-mediated knockdown of chemerin in high-fat-diet-fed *apoE*$^{-/-}$ mice ameliorated atherosclerosis outcome, followed by decreasing pro-inflammatory cytokines, such as TNF-α and IL-1β [70] (Table 2, chemerin).

Resistin

Another representative white adipocyte-derived adipokine is resistin, which has multiple roles in the development of atherosclerosis, such as vascular inflammation, lipid accumulation, and plaque destabilization [71]. Clinical data imply that after an atherothrombotic ischemic stroke event, patients with high plasma resistin levels have an increased risk of 5-year mortality or disability [72]. Reilly et al. demonstrated that plasma resistin levels correlated with markers of inflammation and can predict coronary atherosclerosis in asymptomatic humans [73]. Animal studies also confirm the link between resistin and inflammation in CVDs. In obese and atherogenic albino rats, higher resistin levels are associated with worse pro-atherogenic lipid profile and inflammation [74]. In rabbits, resistin exacerbates atherosclerosis by inducing vascular inflammation [75]. Consistently, resistin overexpression in *Ldlr*$^{-/-}$ mice aggravates atherosclerosis

burden, reduces brown fat tissue activity, and induces insulin resistance. These outcomes are attributed to resistin-mediated hypothalamic leptin resistance [76]. Resistin expression is notably increased in *apoE*$^{-/-}$ mice too. Additionally, Burnett et al. found that recombinant resistin treatment of murine aortic endothelial cells increased soluble vascular cell adhesion molecule (sVCAM) and monocyte chemoattractant protein (MCP)-1, two pro-atherogenic factors [77]. Resistin also significantly promotes the proliferation of rat VSMCs [78]. A study using patients' samples showed that resistin inhibited neutrophil infiltration, likely contributing to the alleviated atherosclerotic plaque inflammation [79]. These studies conducted in various animal models and human samples are overall consistent in supporting a pro-atherogenic role of resistin (Table 2, resistin).

FABP4

Adipocyte fatty acid-binding protein (A-FABP; also known as FABP4 or aP2) is expressed in adipocytes and macrophages, influencing metabolic activity in a variety of ways. FABP4 was initially discovered in adipocytes as an intracellular protein activated by PPARγ to regulate lipid transport and fatty acid metabolism [80–83]. Early animal studies have shown that FABP4 deficiency in both adipocytes and macrophages improves hyperinsulinemia, hyperglycemia, insulin resistance, dyslipidemia, and fatty liver disease in the context of genetic and dietary obesity [84–86]. FABP4 was soon found to be secreted by adipocytes and abundantly present in the circulation and correlate with metabolic risks [87], macrovascular complications [88], and atherosclerosis [89, 90] in humans. From a large-cohort prospective study, serum FABP4 is a biomarker of higher risk of CVD mortality [91]. In another clinical study in a Chinese cohort, FABP4 was found to be positively associated with carotid atherosclerosis in Chinese women but not in men. This sex difference may be due to lower baseline serum FABP4 levels in men [90]. FABP4 also functions in macrophages to regulate the accumulation of cholesterol esters and inflammatory response [92]. Finally, atherosclerosis *in apoE*$^{-/-}$ mice was significantly reduced by FABP4 deficiency in macrophages [93]. (Table 2, FABP4).

IL-1β

Adipocytes also produce many nonexclusive cytokines that are expressed in the other tissues and types of cells. Among them, Interleukin-1β (IL-1β) is an innate inflammatory response factor that plays an important role in promoting the development of atherosclerosis [94, 95]. IL-1β is secreted upon the activation of the NLRP3 inflammasome. When stimulated, IL-1β triggers macrophages to release pro-inflammatory cytokines and activates T-helper cells. In atherosclerosis, IL-1β promotes immune cell recruitment and increases vascular permeability [96–98]. The size of aortic lesions in IL-1β knockout [99, 100] and neutralizing mice [101] are significantly reduced because of the dampened recruitment of monocytes and activation of macrophages to the intima. Serum IL-1β levels can serve as a biomarker of advanced stages of atherosclerosis [102], plaque calcification, and potentially fibrous caps formation [103].

Interestingly, IL-1β has an endogenous inhibitor, IL-1Ra. Deficiency in IL-1Ra promotes neointimal formation in mice after injury [104, 105]. Consistently, IL-1β inhibition with canakinumab significantly improved the reendothelialization of denuded carotid arteries and limited neointimal formation, an inflammatory response in the incidence of cardiovascular events [106]. It is thus plausible that targeting IL-1β offers therapeutic promise in atherosclerosis (Table 2, IL-1β).

IL-18

Interleukin-18 (IL-18) is a pro-inflammatory and pro-atherogenic cytokine modulating cholesterol efflux [107], plaque stabilization [108], and plaque rupture susceptibility [109, 110]. Genetic analysis of IL-18 variations in CAD patients suggests a causal role of IL-18 in atherosclerosis associated with higher mortality [111]. IL-18 inhibitors have been shown to prevent plaque progression and promote plaque stability [112]. It remains unclear whether IL-18 is an independent predictor of atherosclerosis or an indirect influencing factor. A more plausible consensus is that the pro-atherogenic effects of IL-18 are more likely to be dependent on IFN-γ [112–114] or other relevant factors [115–118] (Table 2, IL-18).

IL-6

Studies in IL-6 knockout atherogenic mouse models have shown that IL-6 can promote plaque formation, influence serum cholesterol, and upregulate matrix metalloprotein-9 (Mmp-9), which is associated with vulnerable plaques [119, 120]. Other work has shown that IL-6 is independently associated with the early onset of atherosclerosis [121]. IL-6 stimulation of VSMCs in vivo and in vitro activates the renin-angiotensin system, expands vascular oxidative stress and endothelial dysfunction, and impacts the migration and proliferation of VSMCs [122, 123]. In aged animals, elevated IL-6 levels induced vascular mitochondrial dysfunction and accelerated atherogenesis [124, 125]. Therapeutically, treatment of mice with an IL-6 inhibitor significantly suppressed endothelial activation, intimal smooth muscle cell infiltration, and monocyte recruitment, and subsequently impacted plaque progression [126]. The pathogenesis of

IL-6 in atherosclerosis has been extensively studied in mice, potentially making it a desirable target for treatment (Table 2, IL-6).

IFN-γ Interferon γ (IFN-γ) is a major inflammatory cytokine in atherosclerosis [127]. A prospective study of 2380 CAD patients followed for 56 months has revealed IFN-γ activity as a predictor for a long-term prognosis of major coronary events [128]. Both the pro- and anti-atherogenic effects of IFN-γ have been documented due to the complexities of its role in atherosclerosis [129, 130]. Previous studies have highlighted IFN-γ expression in lipid-laden macrophages of atherosclerosis lesions [131, 132] and at all stages of development [133]. In vitro, treatment of oxLDL-loaded THP-1 human macrophages with IFN-γ promoted foam cell formation and inhibited cholesterol 27-hydroxylase [134]. Endothelial cell function is imperative in maintaining normal vessel integrity. Lee et al. performed transcriptomic and metabolic analyses of HCAECs treated with IFN-γ and unraveled a metabolic shift in endothelial function with worsened glucose metabolism and increased fatty acid oxidation [135]. Sáez et al. validated these findings by linking IFN-γ and high glucose levels to endothelial dysfunction [136]. The plaque area was decreased by 75% in IFN-γ-deficient *Ldlr*$^{-/-}$ mice after 8 weeks on cholesterol-enriched diet feeding [137]. IFN-γ deficiency also decreased lesion size in *apoE*$^{-/-}$ mice fed with a cholesterol-enriched diet (0.15% cholesterol) for 12 weeks [138]. However, Niwa et al. found that IFN-γ produced by bone marrow-derived cells inhibited the advancement of atherosclerosis. After 6 weeks on a high-fat diet (HFD), *Ldlr*$^{-/-}$ mice received IFN-γ-deficient bone marrow developed larger lesions than those received control bone marrow without affecting lipid profiles [139]. The majority of studies on IFN-γ suggest a role of this cytokine in atherosclerosis progression and prove a benefit to consider IFN-γ therapies (Table 2, IFN-γ).

TNF-α

TNF-α is a cytokine of high biological value, and its production in adipose tissue is increased in obesity and T2DM [140]. Indeed, TNF-α is expressed by many cells, including adipocytes, monocytes, macrophages, endothelial cells, and VSMCs. It is appreciated that TNF-α promotes the progression of atherosclerosis through a variety of factors [141–149]. TNF-α upregulates the expression of intercellular cell adhesion molecule-1 (ICAM-1), scavenger receptor class A (SRA), and MCP-1 both in vitro and in vivo [143, 146, 149], and induces the migration and proliferation of medial smooth muscle cells in the vascular wall to the intima [145]. TNF-α also advances vascular calcification, mediated by the cAMP signaling pathway [141]. In mature bone marrow dendritic cell-derived exosomes, stimulating TNF-α can trigger the NF-κB pathway and elicit endothelial inflammation [148]. In regards to lipid and fatty acid metabolism, TNF-α can increase the transcytosis of lipoproteins (e.g., LDL) across endothelial cells and macrophages, eventually leading to LDL retention in the vascular wall [143, 147]. One study found no correlation between plaque progression and instability and the TNF-α receptor p55, suggesting that other receptors may mediate the TNF-α activity [150]. Altogether, TNF-α is a critical factor that warrants clinical significance for populations susceptible to CVDs. Meanwhile, the impact of its receptors and mediators need further characterization (Table 2, TNF-α).

PAI-1

Fibrinolytic imbalances in the progression of atherosclerosis have been observed in various experimental and clinical studies. Fibrous deposits in plaques can be removed by plasminogen activators. In advanced atherosclerosis, fibrin depositions are rampant, and plasminogen activators are downregulated [151–155]. Type 1 plasminogen activator inhibitor (PAI-1) is the primary inhibitor of plasminogen activators. Elevated expression levels of PAI-1 in the plasma and coronary plaques were found in metabolic syndrome patients [156]. It was also shown that male patients with metabolic syndrome were prone to thrombosis due to the increased PAI-1 [157]. The upregulation of PAI-1 induces neointima formation, fibrin(ogen) accumulation, and thrombosis [151–155]. Protection against atherosclerosis in PAI-1-deficient mice has ascertained its pro-atherogenic role, primarily improving fibrin clearance in plaques [151, 153]. Consistently, the expression of PAI-1 mRNA is found to increase in the arteries of patients with advanced atherosclerosis [158]. However, Sjoland et al. found that aortic PAI-1 expression has little to do with atherosclerosis progression [159]. Indeed, adipose tissue, particularly metabolically detrimental visceral fat, is a major source of PAI-1 in obesity and insulin resistance [160]. The effects of PAI-1 on neointimal lesion formation represent a previously unwitnessed role for the plasminogen activation system in the pathogenesis of atherosclerosis [151, 153] (Table 2, PAI-1).

RBP4

Retinol-binding protein 4 (RBP4), an adipokine mainly secreted from the liver and adipose tissue, negatively impacts glucose metabolism and insulin sensitivity [161]. Serum RBP4 levels positively correlated with the severity of carotid atherosclerosis in patients [162]. RBP4 invokes atherogenesis by promoting cholesterol uptake and inducing macrophage-derived foam cell formation. Elevated levels of circulating RBP4 can potentially be a predictor of atherosclerosis [161] (Table 2, RBP4).

LCN2

Lipocalin-2 (LCN2) is a complex bioactive hormone expressed in adipocytes, neutrophils, osteoblasts, and macrophages, primarily exhibiting antimicrobial effects, activating inflammatory cytokines, and regulating glucose homeostasis [163–165]. Serum LCN2 levels are positively correlated with the severity of CAD [166]. In *apoE*$^{-/-}$ mice, chronic administration of LCN2 accelerated the development of aortic lesions with increased monocyte and macrophage within plaques and increased plaque instability. LCN2 can also enhance the production of inflammatory cytokines such as IL-6, IL-8, and MCP-1 in macrophages and human coronary smooth muscle cells. In HUVECs co-cultured with THP1 monocytes, LCN2 treatment stimulates cell adhesion and increases gene expression of ICAM-1, VCAM-1, and NF-κB [167]. Additionally, LCN2 can impact endothelial cell and VSMC proliferation. Overall, LCN2 systemically contributes to atherosclerosis by activating inflammation, cell adhesion, foam cell formation, and plaque vulnerability [167] (Table 2, LCN2).

Adipokines with undefined roles in atherosclerosis

In addition to the adipokines mentioned above, other adipokines such as adipsin, Interleukin-17 (IL-17), omentin, bone morphogenetic proteins (BMPs), nicotinamide phosphoribosyl transferase (NAMPT), and Vaspin have been shown to somewhat be involved in atherosclerosis. Due to limited evidence or conflicting data, more work is needed to illustrate their explicit roles in atherosclerosis. In this review, we refer to these factors as undefined adipokines in atherosclerosis.

Adipsin

Adipsin (complement factor D) is the first cytokine identified to be produced in white adipose tissue, hence the discovery of adipocyte-derived cytokines: adipokines [168]. Ohtsuki et al. studied 370 patients with CAD and found plasma adipsin to be positively associated with mortality and rehospitalization, illuminating a potential role as a biomarker [169]. However, in animal studies, *Adipisin*$^{-/-}$*:Ldlr*$^{-/-}$ double knockout mice displayed no significant differences in the aortic root and arch lesion area after 14 weeks on a western diet feeding [170]. Further studies are needed to establish a working model for adipsin in atherosclerosis (Table 3, adipsin).

IL-17

To date, there lacks consensus on whether IL-17 is protective or deteriorative in atherosclerosis [171]. Several mouse models and in vitro studies support a pro-atherogenic effect of IL-17 [172–174]. Here, IL-17 sustains an inflamed plaque microenvironment. Additional studies showed that IL-17 could be both pro- and anti-atherogenic [175, 176], whereas some studies stated that IL-17 has only protective effects. In the presence of well-known anti-inflammatory cytokines, IL-17 can be induced and may play a protective and regulatory role in atherogenesis. This may be due to anti-inflammatory Th17 cells that inhibit the differentiation of pathogenic Th1 cells. Taken together, IL-17 in the pathogenesis of atherosclerosis is unresolved and behaves differently based on the experimental models and context [175–178]. Moderate or severe atherosclerosis, a single gene or multiple gene knockouts, and patterns of dietary intervention all manifest varying outcomes. Establishing more consistent models to study IL-17 in atherosclerosis is thus needed (Table 3, IL-17).

Omentin

Omentin is a relatively new adipokine mainly expressed in visceral adipose tissue. It is documented that omentin can inhibit macrophage accumulation, foam cell formation, and the expression of pro-inflammatory genes (TNF-α, IL-6, and MCP-1) and promote an anti-inflammatory (M2-like) phenotype during macrophage differentiation in vitro and in vivo [179, 180]. Du et al. observed the down-regulation of omentin in the serum and epicardial adipose tissue (EAT) in patients with CAD [181]. On the contrary, Saely et al. found increased plasma omentin as a predictor of cardiovascular events in CAD patients [182]. Therefore, the role of omentin in CVDs remains uncertain [180] (Table 3, omentin).

BMPs

The expression of BMPs is known to increase in atherosclerosis. BMPs induce monocyte recruitment, endothelial inflammation, and endothelial dysfunction, particularly BMP4 and BMP2 [183, 184]. The balance between BMPs (2 and 4) and BMP antagonists influences these outcomes. Inhibition of BMPs in *Ldlr*$^{-/-}$ mice by a potent pharmacological BMP inhibitor (LDN-193189) influenced atherosclerosis regression [183, 184]. Simoes Sato et al. found that BMPs secreted by VSMCs in atherosclerotic lesions can induce monocyte chemotaxis via direct activation of BMP receptor II (BMPRII), while Kim et al. found that BMPRII down-regulation resulted in endothelial inflammation and atherosclerosis progression [184, 185]. The exact role of each individual BMP in atherosclerosis should be distinguished, so do their functioning mechanism (Table 3, BMPs).

NAMPT

NAMPT, also known for another name visfatin, is the key enzyme for NAD + biosynthesis from the precursor nicotinamide. It is produced by adipocytes and other inflammatory cells in adipose tissue, and has been connected to atherosclerosis and insulin resistance. Nencioni et al. used a pharmacological inhibitor of NAMPT to mitigate inflammation and downregulate neutrophil activation and recruitment in an atherosclerotic mouse model [186]. In cholesterol metabolism, NAMPT knockdown manifested protection by enhancing cholesterol efflux through the PPARα-LXRα- ABCA1/G1 pathway [187]. Notably, what is mentioned above involves the actions of extracellular NAMPT (eNAMPT). It has an intracellular isoform (iNAMPT). Bermudez et al. studied the leukocyte-specific overexpression of iNAMPT in mice and observed less plaque burden and increased lesion stabilization. The effects of iNAMPT are influenced by PPARγ and is independent of changes in eNAMPT [188]. Given the opposite functions of eNAMPT and iNAMPT in atherosclerosis, though the former is the true cytokine, we temporarily put NAMPT in this class of undefined adipokines (Table 3, NAMPT).

Vaspin

Visceral adipose tissue-derived serpin (vaspin) was initially identified as a novel adipokine related to obesity with insulin-sensitizing effects [189, 190]. Sato et al. indicated that vaspin is anti-atherosclerotic and improves plaque stability in *apoE*$^{-/-}$ mice [190]. In a large cohort of patients with axial spondylarthritis, serum vaspin is associated with CVD risk factors [191]. Another study found the down-regulation of serum vaspin levels to be a trace marker of recent ischemic events in patients with carotid stenosis [189]. The relation between circulating vaspin levels and the severity of atherosclerosis, therefore, needs further data both clinically and pre-clinically to be determined [189, 191] (Table 3, vaspin).

Discussion

Obesity can significantly increase the risk of T2DM and CAD. It is well known that besides the primary function in lipid storage, adipose tissue impacts the whole body via producing numerous adipokines. The secretion patterns of adipokines change in dysfunctional adipose tissue (such as in obesity) compared to normal functioning adipose tissue vary in depots, such as subcutaneous, visceral, and perivascular, and are also affected by nutrient status. Despite the keep-growing list of adipokines and new functions and mechanisms to be discovered, there is concrete evidence to conclude that adipose tissue can regulate atherosclerosis outcomes by means of adipokine.

Although different adipokines regulate the process of atherosclerosis in different ways, there is some commonality in the pathways shared by adipokines (Fig. 1). Representative protective adipokines such as adiponectin, CTRP9, and FGF-21 vary in their regulatory mechanisms. Adiponectin reduces MCP-1 expression in macrophages and VEGF in ECs; FGF-21 mainly impacts circulating levels of TG and LDL; and CTRP9 inhibits the adhesion of macrophages to VSMCs. Both adiponectin and FGF21 can reduce LDL-C and increase HDL-C to offer additional protection from atherosclerosis. Adipokines like leptin, chemerin, resistin, and LCN2 can activate pro-inflammatory cytokines, such as TNF-α and IL-1β, and thus accelerate the progression. The pro-inflammatory adipokines secreted from adipose tissue, including IL-1β, IL-18, IL-6, IFN-γ, and TNF-α, worsen the atherosclerosis burden and are exacerbated in obesity.

In summary, adipokines underlie the increased risk of atherosclerosis in obesity and T2DM and may serve as biomarkers of atherogenesis. However, investigating the exact roles of adipokines in atherosclerosis is warranted for future clinical applications. It should also be reminded that adipokines function in orchestration and changes in one adipokine may affect others. Categorizing adipokines into protective or deteriorative classes may incite synergetic strategies to treat atherosclerosis and CVDs.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

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