A novel therapeutic strategy of obesity from the perspective of SPMs

Ze-Wei Zhao[*] [ORCID]

Shenzhen Key Laboratory of Systems Medicine for Inflammatory Diseases & Department of Biochemistry, School of Medicine, Sun Yat-sen University, Shenzhen 518107, Guangdong, China

*Correspondence: Ze-Wei Zhao, Shenzhen Key Laboratory of Systems Medicine for Inflammatory Diseases & Department of Biochemistry, School of Medicine, Sun Yat-sen University, Shenzhen 518107, Guangdong, China. zhaozw5@mail2.sysu.edu.cn

Abstract

The global prevalence of obesity and type 2 diabetes mellitus (T2DM)—the most common metabolic disorders—has reached epidemic proportions over the past half-century, with obesity being a key driver of insulin resistance and T2DM development. These disorders are characterized by metaflammation (chronic low-grade inflammation across multiple metabolic organs like adipose tissue, liver, muscle, and the gut), which disrupts metabolic homeostasis, exacerbates insulin resistance, impairs insulin secretion, and links to other comorbidities such as cardiovascular diseases. A major advance in understanding inflammation resolution is the identification of specialized pro-resolving mediators (SPMs), a family of lipid mediators including resolvins, lipoxins, protectins, and maresins. Derived from polyunsaturated fatty acids (e.g., EPA, DHA), SPMs actively regulate inflammation resolution by constraining pro-inflammatory cell infiltration (e.g., neutrophils), promoting anti-inflammatory macrophage polarization (M2), enhancing efferocytosis (clearance of apoptotic cells), and preserving tissue barrier integrity—without inducing immunosuppression. This review summarizes evidence from human and animal studies on obesity-related metaflammation in metabolic tissues and the role of SPMs in resolving this inflammation. It details SPM mechanisms (e.g., maintaining adipose tissue homeostasis, improving insulin sensitivity, alleviating hepatic steatosis) and highlights their dysregulation in obesity (e.g., impaired biosynthesis, reduced receptor expression) as a critical driver of metabolic dysfunction. Finally, the review discusses the therapeutic potential of SPM-targeted strategies (e.g., ω-3 PUFA supplementation, SPM receptor activation) for alleviating obesity, T2DM, metabolic dysfunction-associated steatotic liver disease (MAFLD), and other metabolic disorders, along with future research directions in this field.

Keywords

obesity, inflammation, specialized pro-resolving mediators (SPMs)

Introduction

In the last half-century, the prevalence of obesity and type 2 diabetes mellitus (T2DM) has been rapidly increasing on a global scale and has now reached epidemic proportions [1–4]. Obesity is the crucial cause of insulin resistance and a driver of the global epidemic of type 2 diabetes [5]. As a well-recognized underlying abnormality, insulin resistance stems from an imbalance between energy intake and expenditure—one that favors the pathways of nutrient storage. These pathways evolved to promote energy conservation (rather than utilization) during periods of scarcity, but in the modern context of excess energy, they exacerbate the development of obesity [6]. At the outset of the energy imbalance, lesions of white adipose tissue and circulating metabolites modulate tissue communication and insulin signaling [7, 8]. When it sinks into persistent state, obesity-related chronic inflammation accelerates these abnormalities [9]. Obesity-induced chronic tissue inflammation underlines the predominant role of dysmetabolism under these circumstances [9, 10]. Chronic tissue inflammation exerts a series of effects on adipose tissue, muscle, liver, pancreatic islets, the gut, and hypothalamus [5]. These inflammatory shifts conduce to insulin resistance (fat, muscle, liver) [11, 12], reduced insulin secretion (islets) [13], gut microbial dysbiosis and increased intestinal permeability (gut) [14], and increased food intake (hypothalamus) [15].

Obesity-induced excessive inflammation is diffusely appreciated to be a unifying element in many chronic diseases, including cardiovascular diseases (CVDs) [16], cancer [17], and metabolic syndrome [18], and thus is a public health issue. Comprehending endogenous monitoring points within the inflammatory response will inspire us with novel perspectives on pathogenesis and therapeutic approaches to dysmetabolism. The acute inflammatory response is divided into initiation and resolution by pathologists. After the identification of lipid mediators with pro-resolving competence that could be biosynthesized from Ω-3 essential fatty acids, some reports demonstrated that resolution of self-limited acute inflammation is an active, programmed reaction but not merely a process of passive fluxing of chemoattractant cytokines [19, 20]. For these metabolites to play the role of resolution, they have to be synthesized in ample amounts in vivo to evoke bioactions. The Ω-3 fatty acids EPA and DHA, found in deep-sea fish oils, have been thought to have anti-inflammatory capabilities for a long while [21]. Resolving inflammatory exudates are comprised of structurally different families of signaling molecules—resolvins, protectins, and maresins, collectively termed specialized pro-resolving mediators (SPMs) [22]. SPMs are agonists with the potential to evoke key cellular resolution processes, namely restricting the infiltration of neutrophils and promoting macrophage to devour apoptotic cells [23].

Here, we focus on the mechanisms of SPMs in resolution that may work in metabolic disease, as it deals with the effects of chronic inflammation on metabolic disorders. We also aim to present a balanced view by addressing existing controversies in the field and briefly discussing prospective orientation in this gradually growing field.

The linkage between chronic inflammation and metabolic disease

Over the past few decades, there has been a great body of studies exploring the underlying cellular and physiologic mechanisms of how obesity-related inflammation initiates and aggravates insulin resistance and glucose intolerance (Figure 1). The effective mechanistic link that was established for the first time between inflammation and insulin resistance is focused on tumor necrosis factor-α (TNF-α) [24, 25]. Activation of other inflammatory signals, such as Jun amino-terminal kinases (JNKs), inhibitor of nuclear factor-kappaB kinase (IKKβ), and nuclear factor k-light-chain-enhancer of activated B cells (NF-κB), are the characteristics of chronic tissue inflammation induced by obesity, and genetic knockout or activity inhibition of these factors also results in protection from obesity-related inflammation and insulin resistance [12, 15, 26–28].

Metabolic inflammation, first mentioned in adipose tissue, has been evaluated at great length with numerous studies [25, 29–33]. Nevertheless, there is no doubt that adipose tissue is neither the only site of metabolic inflammation nor could it be considered as the sole participant in metabolic homeostasis or
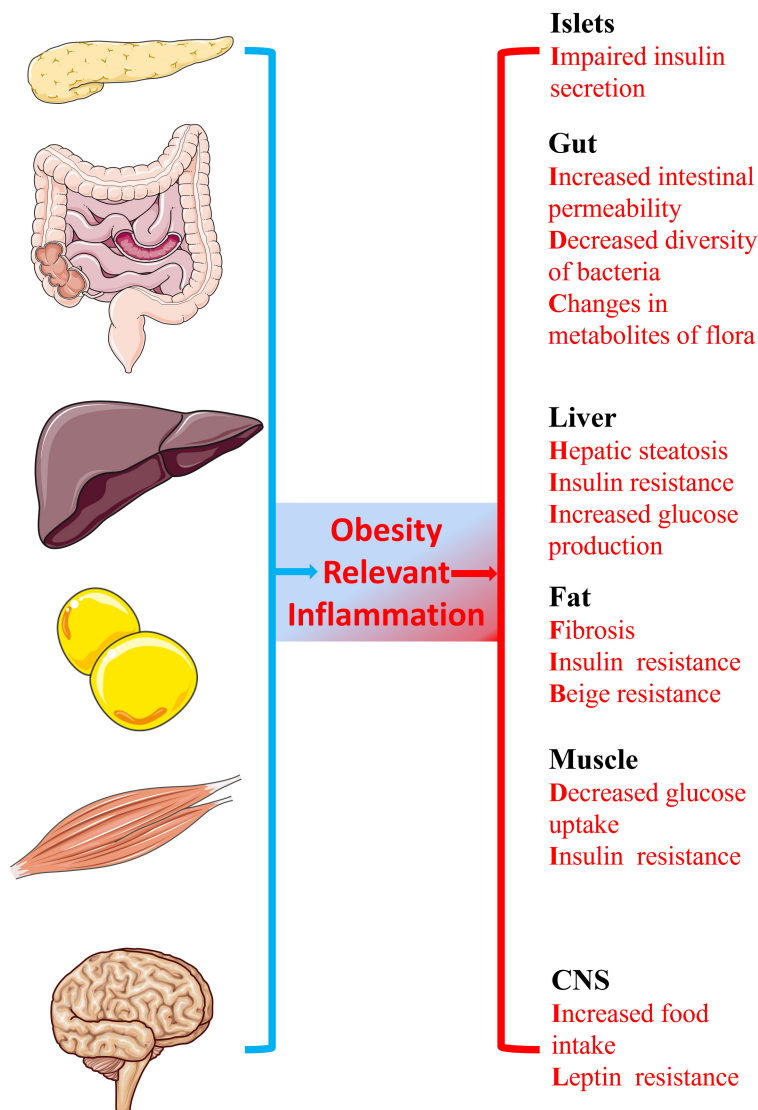
Figure 1. The metabolic consequences of obesity on distinct organs. Obesity relevant chronic tissue inflammation is one of the key mechanisms of dysmetabolism. The effects on the liver, adipose tissue, muscle, islets, the gut, and the central nervous system (CNS) induced by chronic tissue inflammation are listed.

relevant lesion. Subsequent studies have demonstrated that pro-inflammatory signals also increase in the other two classical insulin target tissues (liver [12, 28, 34], and muscle [11, 27, 35]), as well as in islets [13], the hypothalamus [15], and the gastrointestinal tract [14]. Metaflammation, regarded as chronic metabolic inflammation in multiple organs, is involved in metabolic disease (Figure 1). The interactions between inflammatory cells with themselves and their stromal components in the adipose tissue, liver, muscle, and other metabolic organs are a critical determinant of metabolic homeostasis and pathogenesis of metabolic disease [36]. Hence, the bidirectional interactions between inflammatory cells and their stromal components, as well as the systemic impact of metabolic inflammation, are crucial factors in determining physiological and pathological events of metabolism. Given the critical role of metaflammation in disrupting metabolic homeostasis across multiple organs and driving metabolic diseases, identifying effective regulators to modulate this chronic low-grade inflammation has become a key focus in related research. These regulators, which can target the bidirectional interactions between inflammatory cells and stromal components while mitigating the systemic impact of metaflammation, are essential for intervening in the pathogenesis of conditions like obesity, and SPMs emerge as prominent candidates in this context.

SPMs: key regulators in the pathogenesis of obesity via modulating metaflammation

SPMs, including resolvins, lipoxins, protectins, and maresins (Table 1), play a pivotal regulatory role in the pathogenesis of obesity by modulating metaflammation—the low-grade, chronic inflammation that characterizes obesity and links it to metabolic disorders [37–39].

Table 1. Summary of SPMs: classification, precursors, and functions.

Class	Subtypes/Structures	Precursors	Key functions
Resolvins	E-series (RvE1, RvE2): 18-carbon, 3 double bonds; D-series (RvD1–D6): 22-carbon, 4 double bonds	E-series: EPA; D-series: DHA	Inhibit neutrophil migration and pro-inflammatory cytokine release; Promote macrophage phagocytosis and resolution of inflammation; Enhance epithelial barrier function; Reduce atherosclerosis by suppressing endothelial adhesion molecules
Lipoxins	LXA4, LXB4: 20-carbon, 4 double bonds; 15-epi-LXA4: Isomer with distinct receptor affinity	Arachidonic acid (AA)	Block neutrophil recruitment and adhesion molecule expression; Induce apoptosis of pro-inflammatory macrophages; Protect against oxidative stress in tissues; Reduce airway hyperresponsiveness in asthma
Protectins	PD1 (Neuroprotectin D1): 22-carbon, 5 double bonds; PDX: Modified structure with enhanced stability	DHA	Protect neurons from excitotoxicity and oxidative damage; Modulate microglial polarization toward anti-inflammatory M2 phenotype; Improve cognitive function in Alzheimer's models; Reduce hepatic steatosis by enhancing fatty acid oxidation
Maresins	MaR1, MaR2: 22-carbon, 4 double bonds MCTRs (maresin-coupled tissue repair molecules): Peptide-lipid conjugates	DHA	Promote macrophage clearance of apoptotic cells; Inhibit Th1/Th17 cell differentiation while enhancing Treg cell function; Accelerate skin and corneal wound healing

SPMs: specialized pro-resolving mediators; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

Under physiological conditions, SPMs maintain adipose tissue homeostasis by constraining inflammatory amplification [40, 41]. They inhibit the migration of monocytes to visceral adipose tissue and their differentiation into pro-inflammatory M1 macrophages, while promoting the polarization of anti-inflammatory M2 macrophages [40, 42, 43]. This reduces the release of pro-inflammatory cytokines, preventing adipocyte dysfunction and preserving insulin sensitivity—for instance, maresin 1 enhances adipocyte glucose and fatty acid uptake by activating insulin signaling pathways [44, 45]. Additionally, SPMs protect intestinal barrier integrity, limiting lipopolysaccharide (LPS) translocation and subsequent toll-like receptor 4 (TLR4)-mediated systemic inflammation, which indirectly suppresses aberrant adipose tissue expansion [46–48].

In obesity, however, SPM function is severely impaired, fueling disease progression [49–53]. Nutrient excess and adiposity disrupt SPM biosynthesis: insufficient ω-3 polyunsaturated fatty acid (PUFA) intake (the precursor of resolvins/protectins) and elevated oxidative stress reduce the activity of lipoxygenases (key enzymes for SPM production) [54–56]. Concurrently, adipocytes and immune cells downregulate SPM receptors (e.g., ALX/FPR2, GPR32), diminishing SPM-mediated anti-inflammatory signaling [57, 58]. This "synthesis deficit plus functional resistance" breaks inflammatory resolution: persistent pro-inflammatory cues induce adipocyte insulin resistance, impair glucose uptake, and promote leptin resistance—creating a vicious cycle of inflammation, metabolic dysfunction, and further fat accumulation [50, 52, 59, 60].

Notably, reduced SPM levels correlate with obesity-related comorbidities [e.g., metabolic dysfunction-associated steatotic liver disease (MAFLD), atherosclerosis], as impaired inflammation resolution exacerbates hepatic lipid deposition and vascular endothelial damage [61–63]. Clinical data confirm lower serum SPM concentrations (e.g., resolvin E1) in obese individuals, with SPM levels inversely associated with body weight and inflammatory markers [51, 52, 64].

It is noteworthy that a large body of current research is primarily correlational. Although reduced SPM levels are associated with obesity-related comorbidities, such as MAFLD and atherosclerosis, this is because

impaired resolution of inflammation exacerbates hepatic lipid deposition and vascular endothelial damage. Clinical data also confirm that obese individuals have lower serum SPM concentrations (e.g., resolvin E1), and SPM levels are negatively correlated with body weight and inflammatory markers. However, these studies only demonstrate a correlation between SPM and obesity; they cannot confirm that SPM is a causative factor of obesity, and the causal relationship between the two remains unclear.

Controversies surrounding SPMs: existence, concentration, and receptor responsiveness

Multiple laboratories have reported difficulties in detecting SPMs in physiological samples (e.g., serum, tissue homogenates) at concentrations sufficient to evoke the proposed bioactions [65, 66]. Potential explanations for this discrepancy include technical limitations (e.g., loss of SPMs during sample extraction, lack of highly specific antibodies for immunoassays) and tissue-specific localization (e.g., SPMs may act locally in tissues at high concentrations but dilute rapidly in circulation). A number of studies have challenged the responsiveness of proposed SPM receptors to their ligands [65, 67, 68]. These findings suggest that either SPMs require co-receptors or accessory molecules to exert their effects, or that some reported receptor-ligand interactions may be context-dependent (e.g., cell-type specific).

A few studies have even questioned the existence of endogenously produced SPMs with functional relevance [69]. However, these results may be attributed to compensatory mechanisms (e.g., upregulation of other anti-inflammatory pathways) or the use of experimental conditions that do not fully mimic physiological inflammation [54, 70, 71].

SPMs are leads for resolution physiology and thus may play as novel therapeutic strategies for metabolic disease

SPMs are lipid micromolecules that include lipoxins, resolvins, protectins, and maresins that are biosynthesized from distinct PUFAs at the onset of inflammation (Table 1) [65, 72, 73]. As part of the inflammatory initiation phase, Ω-6 fatty acid arachidonic acid transforms into lipoxins to begin the resolution of the acute inflammatory response [74], whereas resolvins, protectins, and maresins are derived from the Ω-3 essential fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [19, 75, 76]. Limited to the length, lipoxins aren't described next, but we have to emphasize that this doesn't mean that lipoxins are trivial in metabolic diseases. SPMs evoke the active resolution processes of inflammation by restraining the infiltration of polymorphonuclear neutrophil (PMN) into tissues, inhibiting the production of pro-inflammatory mediators, regulating the apoptosis of PMN and the efferocytosis of macrophages, and promoting the dilution of chemokine [22, 23]. In general, these SPMs commence resolution and regeneration programs through regulation of innate immunocytes in an inflammatory environment. Here, we cover the resolving functions of SPMs and focus on SPMs' actions in metabolic disease on the basis of their inflammatory pathogenesis (Figure 2).

SPMs play crucial roles in the vascular response and neutrophil trafficking, from acute inflammation initiation to resolution or continuation. The SPMs, lipoxins, resolvins, protectins, and maresins are produced during this self-limited process. When acute inflammation occurs in local tissues, a large number of chemokines (PGE2, PGI2 (vasodilation), and LTB4 (chemotaxis and adhesion) are released to make the neutrophils chemotactic to the tissue. As one of the initiating parts of resolution, eicosanoids are converted to lipoxins, signaling and beginning the end of the acute inflammatory response [74, 77, 78]. Lipoxins and resolvins limit the infiltration of polynuclear neutrophils and promote their apoptosis. Resolving macrophages induced by resolvins and protectins then clear the apoptotic neutrophils in a process known as efferocytosis, which restores the immunity homeostasis of the inflammatory tissue. Resolution failure leads to the continued accumulation of various inflammatory factors, the development of chronic inflammation (which can be suppressed by resolvins), and fibrosis (which can be inhibited by resolvins and lipoxins). Figure 2 shows that resolvins play a key role in different resolution processes for acute and chronic inflammation, suggesting that they may be the most potent of the SPMs.
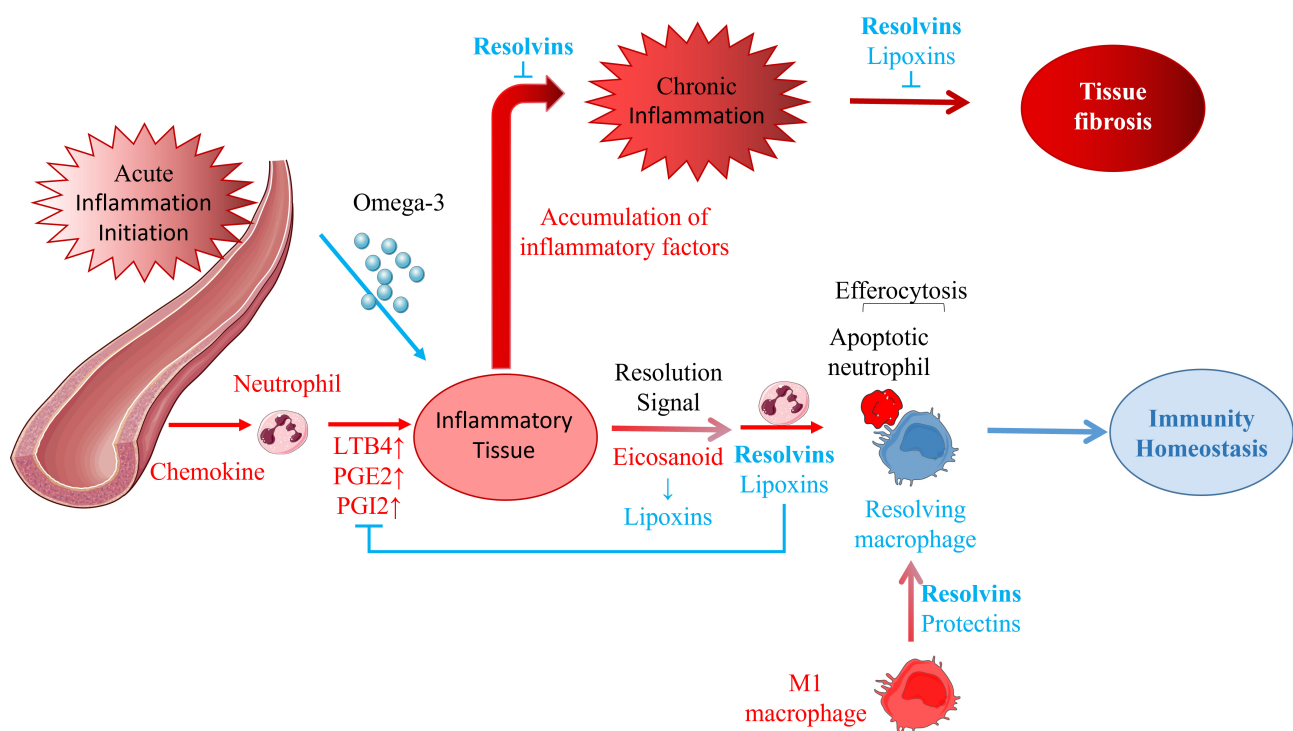
Figure 2. The role of SPMs in the initiation, resolution, and chronic progression of acute inflammation.

Resolvins

Resolvins, including the D, E, and T series, are endogenous lipid metabolites biosynthesized during the resolution phase of acute inflammation from the ω-3 PUFAs (Table 1), primarily EPA, DHA, and docosapentaenoic acid (DPA) [79–81]. Their anti-inflammatory and pro-resolving properties have been confirmed with great evidence from multiple animal inflammatory models [82–86]. Resolvins have been evaluated to evoke the resolving process not only in acute inflammation but also in chronic inflammation. Sima et al. [87] summarized the role of RvE1 in inflammation resolving and focused on its function in type 2 diabetes in light of its inflammatory pathogenesis (Figure 1). In population-based research on the association between resolvin E1 (RvE1) and adiposity, univariate analysis has linked obesity to reduced RvE1, and multiple regression analysis has further shown plasma RvE1 to be negatively correlated with various adiposity metrics (BMI, waist circumference, waist-to-height ratio, abdominal subcutaneous fat volume, skinfold thicknesses) in both genders [51]. Recent studies have demonstrated that resolvins have the function of treating metabolic diseases and their complications, mainly diabetes, which illustrates the therapeutic potential of resolvins in the field of metabolic disorders [52, 88–94].

Protectins

Protectin D1 (PD1), currently the most active protectin, also referred to as neuroprotectin D1 (NPD1), which in vivo possesses a potent anti-apoptotic, anti-inflammatory, and neuroprotective activity in its localized tissues (Table 1) [83, 95]. The main PD1 precursor, DHA, exists mainly in tissues such as the retinal synapses, photoreceptors, the lungs, and the brain, implying that PD1 are supposed to protect these tissues most possibly and less likely to participate in metabolism [96–98]. However, PD1 exerts a protective effect against metabolic dysfunction-associated steatohepatitis (MASH) in mice by suppressing the activation of TLR4-mediated downstream signaling pathways [99]. Moreover, protectin DX (PDX), an isomer of PD1, has been demonstrated to alleviate insulin resistance in *db/db* mice and simultaneously optimize core parameters linked to the diabetic condition in T1DM mouse model [100, 101]. In addition, White et al. [102] reported that both PD1 and PDX were capable of modulating PPARγ transcriptional activity, which showed their potential of anti-obesity and anti-diabetes.

Maresins

At present, there are mainly three kinds of maresins found, namely maresin 1, maresin2, and maresin-Ls (can be divided into maresin-L1 and maresin-L2), which all derive from DHA, and possess robustly anti-inflammatory, pro-resolving, protective, and pro-healing properties similar to other SPMs (Table 1) [72, 103, 104]. Martínez-Fernández et al. [105] suggested that treatment with maresin 1 can improve insulin sensitivity and attenuate adipose tissue inflammation in ob/ob and diet-induced obese mice. In addition to the anti-inflammatory effects of maresin 1, some studies believe that the ability to regulate FGF21 contributes to its beneficial metabolic effects [106]. Jung et al. [107] confirmed that maresin 1 can ameliorate liver steatosis by decreasing lipogenic enzymes in ob/ob and diet-induced obese mice, which showed that maresin 1 may be a practical therapeutic strategy to treat MAFLD [107, 108]. In addition, maresin 1 modulates the basal expression levels of adipokines in human adipocytes and mitigates the TNF-α-induced aberrations in adipokine expression under in vitro conditions, and such regulatory effects may underlie the metabolic advantages exerted by this lipid mediator [109].

Future prospects

Current insights into SPMs provide a clear roadmap for developing clinical treatment strategies that address the root of metabolic disorders—metaflammation—while avoiding the limitations of traditional anti-inflammatory therapies. These strategies prioritize restoring SPM function, leveraging their ability to resolve inflammation without immunosuppression, and can be tailored to target obesity, T2DM, and MAFLD specifically. SPMs have emerged as latent regulators in physiological pathways of resolution and chronic inflammation that can improve obesity, T2DM, MAFLD, and other metabolic diseases [87, 107, 110] beyond the roles of their precursors in metabolism and membrane dynamics. In view of the ability of SPMs to initiate inflammation resolution without immunosuppression, it is promising that therapeutic delivery of lipid agonists in the form of SPMs may be a prospective strategy for alleviating the resolving failure and remodeling homeostasis in chronic metabolic diseases, including obesity, T2DM, MAFLD, as well as CVD, and so on [87, 90, 107]. Here, we can imagine a future where SPMs are well understood, play a role in distinct metabolic diseases, and serve as supplements to existing therapeutic strategies.

Conclusions

The global epidemics of obesity and type 2 diabetes are fundamentally fueled by a state of chronic, low-grade inflammation known as metaflammation, which disrupts metabolic health across multiple organs. SPMs, such as resolvins and maresins, represent the body's own sophisticated system for actively shutting down this inflammation, which goes beyond mere suppression to orchestrate complete resolution and tissue repair. In obesity, this natural defense is compromised; a combination of impaired SPM production and tissue resistance creates a resolution deficit, allowing inflammation to persist and drive metabolic deterioration. While human data primarily show correlation, animal studies robustly demonstrate that restoring specific SPM levels can directly improve insulin sensitivity, reduce liver fat, and calm adipose tissue inflammation. This reveals a profound therapeutic potential: instead of broadly suppressing immune responses, we can aim to treat metabolic disease by replenishing these native resolution signals. The future lies in leveraging these findings to develop strategies that reignite the body's innate ability to resolve inflammation, thereby restoring metabolic equilibrium from within.

Abbreviations

CVDs: cardiovascular diseases

DHA: docosahexaenoic acid

EPA: eicosapentaenoic acid

MAFLD: metabolic dysfunction-associated steatotic liver disease

PD1: protectin D1

PDX: protectin DX

PMN: polymorphonuclear neutrophil

PUFA: polyunsaturated fatty acid

SPMs: specialized pro-resolving mediators

T2DM: type 2 diabetes mellitus

TLR4: toll-like receptor 4

TNF-α: tumor necrosis factor-α

Declarations

Acknowledgments

Images in Figure 1 and Figure 2 are provided by Servier Medical Art (https://smart.servier.com/) and are licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Author contributions

ZWZ: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. The author read and approved the submitted version.

Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Copyright

© The Author(s) 2026.

Publisher's note

Open Exploration maintains a neutral stance on jurisdictional claims in published institutional affiliations and maps. All opinions expressed in this article are the personal views of the author(s) and do not represent the stance of the editorial team or the publisher.

References

1. Zhang X, Zhang M, Zhao Z, Huang Z, Deng Q, Li Y, et al. Geographic Variation in Prevalence of Adult Obesity in China: Results From the 2013-2014 National Chronic Disease and Risk Factor Surveillance. Ann Intern Med. 2020;172:291–3. [DOI] [PubMed]

2. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81. [DOI] [PubMed]

3. Collaborators G2AB. Global, regional, and national prevalence of adult overweight and obesity, 1990-2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. Lancet. 2025;405:813–38. [DOI] [PubMed] [PMC]

4. World Obesity Atlas 2025 [Internet]. Wales: World Obesity Federation; c2022 [cited 2025 Aug 20]. Available from: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-20 25

5. Lee YS, Wollam J, Olefsky JM. An Integrated View of Immunometabolism. Cell. 2018;172:22–40. [DOI] [PubMed] [PMC]

6. Roden M, Shulman GI. The integrative biology of type 2 diabetes. Nature. 2019;576:51–60. [DOI] [PubMed]

7. Fasshauer M, Blüher M. Adipokines in health and disease. Trends Pharmacol Sci. 2015;36:461–70. [DOI] [PubMed]

8. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med. 2017;23:804–14. [DOI] [PubMed] [PMC]

9. Lee YS, Li P, Huh JY, Hwang IJ, Lu M, Kim JI, et al. Inflammation is necessary for long-term but not short-term high-fat diet-induced insulin resistance. Diabetes. 2011;60:2474–83. [DOI] [PubMed] [PMC]

10. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol. 2010;72:219–46. [DOI] [PubMed]

11. Fink LN, Costford SR, Lee YS, Jensen TE, Bilan PJ, Oberbach A, et al. Pro-inflammatory macrophages increase in skeletal muscle of high fat-fed mice and correlate with metabolic risk markers in humans. Obesity (Silver Spring). 2014;22:747–57. [DOI] [PubMed]

12. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat Med. 2005;11:183–90. [DOI] [PubMed] [PMC]

13. Eguchi K, Nagai R. Islet inflammation in type 2 diabetes and physiology. J Clin Invest. 2017;127:14–23. [DOI] [PubMed] [PMC]

14. Winer DA, Winer S, Dranse HJ, Lam TKT. Immunologic impact of the intestine in metabolic disease. J Clin Invest. 2017;127:33–42. [DOI] [PubMed] [PMC]

15. De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollner RL, Boschero AC, et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology. 2005;146:4192–9. [DOI] [PubMed]

16. Kim SH, Després JP, Koh KK. Obesity and cardiovascular disease: friend or foe? Eur Heart J. 2016;37:3560–8. [DOI] [PubMed]

17. Moley KH, Colditz GA. Effects of obesity on hormonally driven cancer in women. Sci Transl Med. 2016;8:323ps3. [DOI] [PubMed] [PMC]

18. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56:1761–72. [DOI] [PubMed]

19. Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med. 2000;192:1197–204. [DOI] [PubMed] [PMC]

20. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol. 2005;6:1191–7. [DOI] [PubMed]

21. Swanson D, Block R, Mousa SA. Omega-3 fatty acids EPA and DHA: health benefits throughout life. Adv Nutr. 2012;3:1–7. [DOI] [PubMed] [PMC]

22. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510: 92–101. [DOI] [PubMed] [PMC]

23. Tabas I, Glass CK. Anti-inflammatory therapy in chronic disease: challenges and opportunities. Science. 2013;339:166–72. [DOI] [PubMed] [PMC]

24. Feingold KR, Soued M, Staprans I, Gavin LA, Donahue ME, Huang BJ, et al. Effect of tumor necrosis factor (TNF) on lipid metabolism in the diabetic rat. Evidence that inhibition of adipose tissue lipoprotein lipase activity is not required for TNF-induced hyperlipidemia. J Clin Invest. 1989;83: 1116–21. [DOI] [PubMed] [PMC]

25. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259:87–91. [DOI] [PubMed]

26. Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K, et al. A central role for JNK in obesity and insulin resistance. Nature. 2002;420:333–6. [DOI] [PubMed]

27. Austin RL, Rune A, Bouzakri K, Zierath JR, Krook A. siRNA-mediated reduction of inhibitor of nuclear factor-kappaB kinase prevents tumor necrosis factor-alpha-induced insulin resistance in human skeletal muscle. Diabetes. 2008;57:2066–73. [DOI] [PubMed] [PMC]

28. Son G, Iimuro Y, Seki E, Hirano T, Kaneda Y, Fujimoto J. Selective inactivation of NF-kappaB in the liver using NF-kappaB decoy suppresses CCl4-induced liver injury and fibrosis. Am J Physiol Gastrointest Liver Physiol. 2007;293:G631–9. [DOI] [PubMed]

29. Hausberger FX. Pathological changes in adipose tissue of obese mice. Anat Rec. 1966;154:651–60. [DOI] [PubMed]

30. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112:1796–808. [DOI] [PubMed] [PMC]

31. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112:1821–30. [DOI] [PubMed] [PMC]

32. Unamuno X, Gómez-Ambrosi J, Ramírez B, Rodríguez A, Becerril S, Valentí V, et al. NLRP3 inflammasome blockade reduces adipose tissue inflammation and extracellular matrix remodeling. Cell Mol Immunol. 2021;18:1045–57. [DOI] [PubMed] [PMC]

33. Zhao Z, Yang Z. Reduction of serum lipids by liver-specific knockout of chemerin in DIO mice. Biochem Biophys Res Commun. 2025;778:152321. [DOI] [PubMed]

34. Koyama Y, Brenner DA. Liver inflammation and fibrosis. J Clin Invest. 2017;127:55–64. [DOI] [PubMed] [PMC]

35. Fink LN, Oberbach A, Costford SR, Chan KL, Sams A, Blüher M, et al. Expression of anti-inflammatory macrophage genes within skeletal muscle correlates with insulin sensitivity in human obesity and type 2 diabetes. Diabetologia. 2013;56:1623–8. [DOI] [PubMed]

36. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542: 177–85. [DOI] [PubMed]

37. Schleh MW, Caslin HL, Garcia JN, Mashayekhi M, Srivastava G, Bradley AB, et al. Metaflammation in obesity and its therapeutic targeting. Sci Transl Med. 2023;15:eadf9382. [DOI] [PubMed] [PMC]

38. Barden A, Shinde S, Tsai IJ, Croft KD, Beilin LJ, Puddey IB, et al. Effect of weight loss on neutrophil resolvins in the metabolic syndrome. Prostaglandins Leukot Essent Fatty Acids. 2019;148:25–9. [DOI] [PubMed]

39. Alnouri MW, Roquid KA, Bonnavion R, Cho H, Heering J, Kwon J, et al. SPMs exert anti-inflammatory and pro-resolving effects through positive allosteric modulation of the prostaglandin EP4 receptor. Proc Natl Acad Sci U S A. 2024;121:e2407130121. [DOI] [PubMed] [PMC]

40. Clària J, López-Vicario C, Rius B, Titos E. Pro-resolving actions of SPM in adipose tissue biology. Mol Aspects Med. 2017;58:83–92. [DOI] [PubMed]

41. Han YH, Lee K, Saha A, Han J, Choi H, Noh M, et al. Specialized Proresolving Mediators for Therapeutic Interventions Targeting Metabolic and Inflammatory Disorders. Biomol Ther (Seoul). 2021;29:455–64. [DOI] [PubMed] [PMC]

42. Titos E, Rius B, López-Vicario C, Alcaraz-Quiles J, García-Alonso V, Lopategi A, et al. Signaling and Immunoresolving Actions of Resolvin D1 in Inflamed Human Visceral Adipose Tissue. J Immunol. 2016;197:3360–70. [DOI] [PubMed] [PMC]

43. Kwon Y. Immuno-Resolving Ability of Resolvins, Protectins, and Maresins Derived from Omega-3 Fatty Acids in Metabolic Syndrome. Mol Nutr Food Res. 2020;64:e1900824. [DOI] [PubMed]

44. Martínez-Fernández L, González-Muniesa P, Sáinz N, Escoté X, Martínez JA, Arbones-Mainar JM, et al. Maresin 1 regulates insulin signaling in human adipocytes as well as in adipose tissue and muscle of lean and obese mice. J Physiol Biochem. 2021;77:167–73. [DOI] [PubMed]

45. Laiglesia LM, Escoté X, Sáinz N, Felix-Soriano E, Santamaría E, Collantes M, et al. Maresin 1 activates brown adipose tissue and promotes browning of white adipose tissue in mice. Mol Metab. 2023;74: 101749. [DOI] [PubMed] [PMC]

46. Croasdell A, Sime PJ, Phipps RP. Resolvin D2 decreases TLR4 expression to mediate resolution in human monocytes. FASEB J. 2016;30:3181–93. [DOI] [PubMed] [PMC]

47. Wang RX, Colgan SP. Special pro-resolving mediator (SPM) actions in regulating gastro-intestinal inflammation and gut mucosal immune responses. Mol Aspects Med. 2017;58:93–101. [DOI] [PubMed] [PMC]

48. Gobbetti T, Dalli J, Colas RA, Canova DF, Aursnes M, Bonnet D, et al. Protectin $D1_{n\text{-}3\,DPA}$ and resolvin $D5_{n\text{-}3\,DPA}$ are effectors of intestinal protection. Proc Natl Acad Sci U S A. 2017;114:3963–8. [DOI] [PubMed] [PMC]

49. López-Vicario C, Titos E, Walker ME, Alcaraz-Quiles J, Casulleras M, Durán-Güell M, et al. Leukocytes from obese individuals exhibit an impaired SPM signature. FASEB J. 2019;33:7072–83. [DOI] [PubMed]

50. Kim N, Shin HY. Deciphering the Potential Role of Specialized Pro-Resolving Mediators in Obesity-Associated Metabolic Disorders. Int J Mol Sci. 2024;25:9598. [DOI] [PubMed] [PMC]

51. Barden A, Shinde S, Beilin LJ, Phillips M, Adams L, Bollmann S, et al. Adiposity associates with lower plasma resolvin E1 (Rve1): a population study. Int J Obes (Lond). 2024;48:725–32. [DOI] [PubMed] [PMC]

52. Zhao Z, Liu S, Qian B, Zhou L, Shi J, Liu J, et al. CMKLR1 senses chemerin/resolvin E1 to control adipose thermogenesis and modulate metabolic homeostasis. Fundam Res. 2022;4:575–88. [DOI] [PubMed] [PMC]

53. Zhao Z, Hu L, Song B, Wu Q, Lin J, Liu Q, et al. DNA-mediated UCP1 overexpression in adipose tissue: A promising anti-obesity gene therapy. Clin Transl Med. 2025;15:e70491. [DOI] [PubMed] [PMC]

54. Singh NK, Rao GN. Emerging role of 12/15-Lipoxygenase (ALOX15) in human pathologies. Prog Lipid Res. 2019;73:28–45. [DOI] [PubMed] [PMC]

55. Leiria LO, Wang CH, Lynes MD, Yang K, Shamsi F, Sato M, et al. 12-Lipoxygenase Regulates Cold Adaptation and Glucose Metabolism by Producing the Omega-3 Lipid 12-HEPE from Brown Fat. Cell Metab. 2019;30:768–83.e7. [DOI] [PubMed] [PMC]

56. Jiménez-Franco A, Castañé H, Martínez-Navidad C, Placed-Gallego C, Hernández-Aguilera A, Fernández-Arroyo S, et al. Metabolic adaptations in severe obesity: Insights from circulating oxylipins before and after weight loss. Clin Nutr. 2024;43:246–58. [DOI] [PubMed]

57. Park J, Langmead CJ, Riddy DM. New Advances in Targeting the Resolution of Inflammation: Implications for Specialized Pro-Resolving Mediator GPCR Drug Discovery. ACS Pharmacol Transl Sci. 2020;3:88–106. [DOI] [PubMed] [PMC]

58. Chiurchiù V, Leuti A, Dalli J, Jacobsson A, Battistini L, Maccarrone M, et al. Proresolving lipid mediators resolvin D1, resolvin D2, and maresin 1 are critical in modulating T cell responses. Sci Transl Med. 2016;8:353ra111. [DOI] [PubMed] [PMC]

59. Liu X, Tang Y, Luo Y, Gao Y, He L. Role and mechanism of specialized pro-resolving mediators in obesity-associated insulin resistance. Lipids Health Dis. 2024;23:234. [DOI] [PubMed] [PMC]

60. Zhao Z, Hu L, Song B, Jiang T, Wu Q, Lin J, et al. Constitutively active receptor ADGRA3 signaling induces adipose thermogenesis. Elife. 2024;13:RP100205. [DOI] [PubMed] [PMC]

61. Dubé L, Spahis S, Lachaîne K, Lemieux A, Monhem H, Poulin S, et al. Specialized Pro-Resolving Mediators Derived from N-3 Polyunsaturated Fatty Acids: Role in Metabolic Syndrome and Related Complications. Antioxid Redox Signal. 2022;37:54–83. [DOI] [PubMed]

62. Mariqueo TA, Zúñiga-Hernández J. Omega-3 derivatives, specialized pro-resolving mediators: Promising therapeutic tools for the treatment of pain in chronic liver disease. Prostaglandins Leukot Essent Fatty Acids. 2020;158:102095. [DOI] [PubMed]

63. Kim AS, Conte MS. Specialized pro-resolving lipid mediators in cardiovascular disease, diagnosis, and therapy. Adv Drug Deliv Rev. 2020;159:170–9. [DOI] [PubMed] [PMC]

64. Szczuko M, Szwec-Nadworna N, Palma J, Tomasik M, Ziętek M. Increased Demand of Obese Women for Protectins, Maresin, and Resolvin D1 in the Last Trimester of Pregnancy. Nutrients. 2023;15: 4340. [DOI] [PubMed] [PMC]

65. Zhang Q, Wang Y, Zhu J, Zou M, Zhang Y, Wu H, et al. Specialized pro-resolving lipid mediators: a key player in resolving inflammation in autoimmune diseases. Sci Bull (Beijing). 2025;70:778–94. [DOI] [PubMed]

66. Schebb NH, Kühn H, Kahnt AS, Rund KM, O'Donnell VB, Flamand N, et al. Formation, Signaling and Occurrence of Specialized Pro-Resolving Lipid Mediators-What is the Evidence so far? Front Pharmacol. 2022;13:838782. [DOI] [PubMed] [PMC]

67. Säfholm J, Abma W, Bankova LG, Boyce JA, Al-Ameri M, Orre A, et al. Cysteinyl-maresin 3 inhibits IL-13 induced airway hyperresponsiveness through alternative activation of the $CysLT_1$ receptor. Eur J Pharmacol. 2022;934:175257. [DOI] [PubMed]

68. Pamplona FA, Ferreira J, Menezes de Lima O Jr, Duarte FS, Bento AF, Forner S, et al. Anti-inflammatory lipoxin A4 is an endogenous allosteric enhancer of CB1 cannabinoid receptor. Proc Natl Acad Sci U S A. 2012;109:21134–9. [DOI] [PubMed] [PMC]

69. Chiang N, Serhan CN. Specialized pro-resolving mediator network: an update on production and actions. Essays Biochem. 2020;64:443–62. [DOI] [PubMed] [PMC]

70. Liu Y, Zheng Y, Karatas H, Wang X, Foerch C, Lo EH, et al. 12/15-Lipoxygenase Inhibition or Knockout Reduces Warfarin-Associated Hemorrhagic Transformation After Experimental Stroke. Stroke. 2017; 48:445–51. [DOI] [PubMed] [PMC]

71. Serhan CN, Chiang N. Endogenous pro-resolving and anti-inflammatory lipid mediators: a new pharmacologic genus. Br J Pharmacol. 2008;153 Suppl 1:S200–15. [DOI] [PubMed] [PMC]

72. Serhan CN, Chiang N, Dalli J, Levy BD. Lipid mediators in the resolution of inflammation. Cold Spring Harb Perspect Biol. 2014;7:a016311. [DOI] [PubMed] [PMC]

73. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest. 2018;128:2657–69. [DOI] [PubMed] [PMC]

74. Serhan CN, Hamberg M, Samuelsson B. Lipoxins: novel series of biologically active compounds formed from arachidonic acid in human leukocytes. Proc Natl Acad Sci U S A. 1984;81:5335–9. [DOI] [PubMed] [PMC]

75. Serhan CN, Hong S, Gronert K, Colgan SP, Devchand PR, Mirick G, et al. Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J Exp Med. 2002;196:1025–37. [DOI] [PubMed] [PMC]

76. Dalli J, Serhan CN. Specific lipid mediator signatures of human phagocytes: microparticles stimulate macrophage efferocytosis and pro-resolving mediators. Blood. 2012;120:e60–72. [DOI] [PubMed] [PMC]

77. Schwab JM, Serhan CN. Lipoxins and new lipid mediators in the resolution of inflammation. Curr Opin Pharmacol. 2006;6:414–20. [DOI] [PubMed]

78. Brennan EP, Mohan M, McClelland A, Gaetano Md, Tikellis C, Marai M, et al. Lipoxins Protect Against Inflammation in Diabetes-Associated Atherosclerosis. Diabetes. 2018;67:2657–67. [DOI] [PubMed]

79. Serhan CN, Gotlinger K, Hong S, Arita M. Resolvins, docosatrienes, and neuroprotectins, novel omega-3-derived mediators, and their aspirin-triggered endogenous epimers: an overview of their protective roles in catabasis. Prostaglandins Other Lipid Mediat. 2004;73:155–72. [DOI] [PubMed]

80. Dalli J, Chiang N, Serhan CN. Elucidation of novel 13-series resolvins that increase with atorvastatin and clear infections. Nat Med. 2015;21:1071–5. [DOI] [PubMed] [PMC]

81. Chiang N, Sakuma M, Rodriguez AR, Spur BW, Irimia D, Serhan CN. Resolvin T-series reduce neutrophil extracellular traps. Blood. 2022;139:1222–33. [DOI] [PubMed] [PMC]

82. Arita M, Yoshida M, Hong S, Tjonahen E, Glickman JN, Petasis NA, et al. Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis. Proc Natl Acad Sci U S A. 2005;102:7671–6. [DOI] [PubMed] [PMC]

83. Schwab JM, Chiang N, Arita M, Serhan CN. Resolvin E1 and protectin D1 activate inflammation-resolution programmes. Nature. 2007;447:869–74. [DOI] [PubMed] [PMC]

84. Haworth O, Cernadas M, Yang R, Serhan CN, Levy BD. Resolvin E1 regulates interleukin 23, interferon-gamma and lipoxin A4 to promote the resolution of allergic airway inflammation. Nat Immunol. 2008;9:873–9. [DOI] [PubMed] [PMC]

85. Jin Y, Arita M, Zhang Q, Saban DR, Chauhan SK, Chiang N, et al. Anti-angiogenesis effect of the novel anti-inflammatory and pro-resolving lipid mediators. Invest Ophthalmol Vis Sci. 2009;50:4743–52. [DOI] [PubMed] [PMC]

86. Qu Q, Xuan W, Fan GH. Roles of resolvins in the resolution of acute inflammation. Cell Biol Int. 2015; 39:3–22. [DOI] [PubMed]

87. Sima C, Paster B, Van Dyke TE. Function of Pro-Resolving Lipid Mediator Resolvin E1 in Type 2 Diabetes. Crit Rev Immunol. 2018;38:343–65. [DOI] [PubMed] [PMC]

88. Herrera BS, Hasturk H, Kantarci A, Freire MO, Nguyen O, Kansal S, et al. Impact of resolvin E1 on murine neutrophil phagocytosis in type 2 diabetes. Infect Immun. 2015;83:792–801. [DOI] [PubMed] [PMC]

89. Ma Y, Li C, Zhu Y, Xu X, Li J, Cao H. The mechanism of RvD1 alleviates type 2 diabetic neuropathic pain by influencing microglia polarization in rats. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2017;33: 277–81. Chinese. [DOI] [PubMed]

90. Pascoal LB, Bombassaro B, Ramalho AF, Coope A, Moura RF, Correa-da-Silva F, et al. Resolvin RvD2 reduces hypothalamic inflammation and rescues mice from diet-induced obesity. J Neuroinflammation. 2017;14:5. [DOI] [PubMed] [PMC]

91. Sima C, Montero E, Nguyen D, Freire M, Norris P, Serhan CN, et al. ERV1 Overexpression in Myeloid Cells Protects against High Fat Diet Induced Obesity and Glucose Intolerance. Sci Rep. 2017;7:12848. [DOI] [PubMed] [PMC]

92. Yin Y, Chen F, Wang W, Wang H, Zhang X. Resolvin D1 inhibits inflammatory response in STZ-induced diabetic retinopathy rats: Possible involvement of NLRP3 inflammasome and NF-κB signaling pathway. Mol Vis. 2017;23:242–50. [PubMed] [PMC]

93. Zhang Z, Hu X, Qi X, Di G, Zhang Y, Wang Q, et al. Resolvin D1 promotes corneal epithelial wound healing and restoration of mechanical sensation in diabetic mice. Mol Vis. 2018;24:274–85. [PubMed] [PMC]

94. Morshedzadeh N, Saedisomeolia A, Djalali M, Eshraghian MR, Hantoushzadeh S, Mahmoudi M. Resolvin D1 impacts on insulin resistance in women with polycystic ovary syndrome and healthy women. Diabetes Metab Syndr. 2019;13:660–4. [DOI] [PubMed]

95. Serhan CN, Gotlinger K, Hong S, Lu Y, Siegelman J, Baer T, et al. Anti-inflammatory actions of neuroprotectin D1/protectin D1 and its natural stereoisomers: assignments of dihydroxy-containing docosatrienes. J Immunol. 2006;176:1848–59. [DOI] [PubMed]

96. Mukherjee PK, Marcheselli VL, Serhan CN, Bazan NG. Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. Proc Natl Acad Sci U S A. 2004;101:8491–6. [DOI] [PubMed] [PMC]

97. Ariel A, Li PL, Wang W, Tang WX, Fredman G, Hong S, et al. The docosatriene protectin D1 is produced by TH2 skewing and promotes human T cell apoptosis via lipid raft clustering. J Biol Chem. 2005;280:43079–86. [DOI] [PubMed]

98. Calandria JM, Marcheselli VL, Mukherjee PK, Uddin J, Winkler JW, Petasis NA, et al. Selective survival rescue in 15-lipoxygenase-1-deficient retinal pigment epithelial cells by the novel docosahexaenoic acid-derived mediator, neuroprotectin D1. J Biol Chem. 2009;284:17877–82. [DOI] [PubMed] [PMC]

99. Liu H, Li N, Kuang G, Gong X, Wang T, Hu J, et al. Protectin D1 inhibits TLR4 signaling pathway to alleviate non-alcoholic steatohepatitis via upregulating IRAK-M. Free Radic Biol Med. 2024;210: 42–53. [DOI] [PubMed]

100. White PJ, St-Pierre P, Charbonneau A, Mitchell PL, St-Amand E, Marcotte B, et al. Protectin DX alleviates insulin resistance by activating a myokine-liver glucoregulatory axis. Nat Med. 2014;20: 664–9. [DOI] [PubMed] [PMC]

101. Waltrick APF, Radulski DR, de Oliveira KM, Acco A, Verri WA, da Cunha JM, et al. Early evidence of beneficial and protective effects of Protectin DX treatment on behavior responses and type-1 diabetes mellitus related-parameters: A non-clinical approach. Prog Neuropsychopharmacol Biol Psychiatry. 2024;133:111028. [DOI] [PubMed]

102. White PJ, Mitchell PL, Schwab M, Trottier J, Kang JX, Barbier O, et al. Transgenic ω-3 PUFA enrichment alters morphology and gene expression profile in adipose tissue of obese mice: Potential role for protectins. Metabolism. 2015;64:666–76. [DOI] [PubMed]

103. Shinohara M, Mirakaj V, Serhan CN. Functional Metabolomics Reveals Novel Active Products in the DHA Metabolome. Front Immunol. 2012;3:81. [DOI] [PubMed] [PMC]

104. Wang CW, Colas RA, Dalli J, Arnardottir HH, Nguyen D, Hasturk H, et al. Maresin 1 Biosynthesis and Proresolving Anti-infective Functions with Human-Localized Aggressive Periodontitis Leukocytes. Infect Immun. 2015;84:658–65. [DOI] [PubMed] [PMC]

105. Martínez-Fernández L, González-Muniesa P, Laiglesia LM, Sáinz N, Prieto-Hontoria PL, Escoté X, et al. Maresin 1 improves insulin sensitivity and attenuates adipose tissue inflammation in *ob/ob* and diet-induced obese mice. FASEB J. 2017;31:2135–45. [DOI] [PubMed]

106. Martínez-Fernández L, González-Muniesa P, Sáinz N, Laiglesia LM, Escoté X, Martínez JA, et al. Maresin 1 Regulates Hepatic FGF21 in Diet-Induced Obese Mice and in Cultured Hepatocytes. Mol Nutr Food Res. 2019;63:e1900358. [DOI] [PubMed]

107. Jung TW, Kim HC, Abd El-Aty AM, Jeong JH. Maresin 1 attenuates NAFLD by suppression of endoplasmic reticulum stress via AMPK-SERCA2b pathway. J Biol Chem. 2018;293:3981–8. [DOI] [PubMed] [PMC]

108. Laiglesia LM, Lorente-Cebrián S, Martínez-Fernández L, Sáinz N, Prieto-Hontoria PL, Burrell MA, et al. Maresin 1 mitigates liver steatosis in ob/ob and diet-induced obese mice. Int J Obes (Lond). 2018; 42:572–9. [DOI] [PubMed]

109. Martínez-Fernández L, Burgos M, Sáinz N, Laiglesia LM, Arbones-Mainar JM, González-Muniesa P, et al. Maresin 1 Exerts a Tissue-Specific Regulation of Adipo-Hepato-Myokines in Diet-Induced Obese Mice and Modulates Adipokine Expression in Cultured Human Adipocytes in Basal and Inflammatory Conditions. Biomolecules. 2023;13:919. [DOI] [PubMed] [PMC]

110. Hansen TV, Vik A, Serhan CN. The Protectin Family of Specialized Pro-resolving Mediators: Potent Immunoresolvents Enabling Innovative Approaches to Target Obesity and Diabetes. Front Pharmacol. 2019;9:1582. [DOI] [PubMed] [PMC]