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Function of Pro-Resolving Lipid Mediator Resolvin E1 in Type 2 Diabetes

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Abstract

Programming of inflammation resolution is governed by a class of specialized pro-resolving lipid mediators (SPMs) that act in concert to modulate epithelial, endothelial, and immune cell function for restoration of homeostasis. The resolution circuits are altered in obesity and associated morbidities, including type 2 diabetes mellitus (T2D), through reduced production and/or action of SPMs, which can be rescued by therapeutic SPM delivery or up-regulation of SPM receptors. Resolvin E1 (RvE1), an eicosapentaenoic acid derivative, has potent pro-resolving and insulin-sensitizing actions mediated by BLT1 and ERV1 receptors in the vasculature and metabolic organs. Nonetheless, the RvE1-mediated increase in protective adipokines such as adiponectin in white adipose tissues, the enhancement of monocyte patrolling function in the vasculature, as well as the macrophage-clearing functions improve metabolic control in obese-prone conditions. RvE1-enhanced resolving function in obesity prevents dysbiosis of the gut microflora and increased gut permeability. These functions suggest that RE1 has therapeutic potential for immunometabolic alterations associated with T2D in patients with reduced inflammation resolving capacity. SPM profiling in individuals at risk for T2D and associated complications will help to advance personalized disease management and precision medicine.

Keywords

inflammation resolution; Ω -3 polyunsaturated fatty acids; immunometabolism; dysbiosis

I. INTRODUCTION

Specialized pro-resolving lipid mediators (SPMs) are small lipid molecules that include lipoxins (LX), resolvins (RVs), protectins (PDs), and maresins (MaRs) and are derived from the metabolism of polyunsaturated fatty acids (PUFAs). SPMs participate in the active process of inflammation resolution through inhibition of polymorphonuclear neutrophil (PMN) infiltration into tissues, inhibition of pro-inflammatory mediator production,

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regulation of PMN apoptosis and uptake by macrophages, and stimulation of chemokine scavenging and bacterial clearance.¹ The precursor for lipoxins is the Ω -6 fatty acid arachidonic acid, whereas RVs, PDs, and MaRs are derived from the Ω -3 essential fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although SPM discovery and structural and functional characterization is an ongoing process, paralleling the unravelling of inflammation resolution pathways, Drs. Charles Serhan and colleagues pioneered much of this work.²⁻⁷ RVs were originally identified and characterized in inflammatory exudates of mice during the resolution phase of inflammation.^{4,6} Similar to LXs, RVs act through specific G-protein-coupled receptors (GPCRs), GPR32/DRV1 (RVD1 receptor), GPR18/DRV2 (RVD2 receptor), GPR120 (ω -3 PUFA receptor), and ChemR23/ERV1 (a Resolvin E1 [RvE1] receptor).^{1,8-10} Collectively, these SPMs and newly characterized DHA-derived MaRs initiate resolution and regeneration programs by acting on innate immune cells at sites with inflammation.

At the same time, it became apparent that resolution of inflammatory is not a passive process, but rather an active one involving phenotypic shifts in innate immune cells that culminate in clearance of pro-inflammatory stimuli and restoration of tissue homeostasis.^{2,3,11} The essential role of recognizing and eliminating possible causes of imbalance makes immunity a key coordinator of body homeostasis by resolving responses to non-self and altered self. Most of the original findings on resolution pathways in mice have recently been confirmed in humans, indicating well-conserved resolution processes in vertebrates.^{12,13} Vertebrate research on the course of pathogen-induced inflammation revealed that local restoration of homeostasis is not the common endpoint but rather “resolution leading to adapted homeostasis,” as described by Motwani et al.¹² This process is characterized by immunological events coordinated by innate myeloid and lymphoid cells that dictate subsequent response to infection, which may be essential for the maintenance of immune tolerance to endogenous antigens.^{12,14} Similarly, the course of non-pathogen-induced or sterile inflammation, that is, inflammation triggered by altered self, depends on the balance between induced inflammatory and resolution pathways.¹⁵ The level of tolerance to stress and tissue damage can be regulated by environmental cues through pathways with molecular details that are still being unveiled and open a way to new treatment strategies for many human conditions, including infectious, inflammatory, and autoimmune diseases.¹⁶ Therapeutic delivery of lipid resolution agonists in the form of SPMs is one such strategy to mitigate resolution failure and restore homeostasis in chronic conditions including type 2 diabetes mellitus (T2D), cardiovascular disease (CVD), inflammatory bowel disease, and autoimmune and infectious diseases.

T2D is a metabolic disorder marked by decreased insulin-stimulated glucose uptake (insulin resistance, IR) and associated hyperglycemia and progressive failure of pancreatic β -cells to produce sufficient levels of insulin. Interestingly, only about one-third of obese insulin-resistant individuals develop T2D due to failure of the pancreas to compensate for peripheral IR, which is partially explained by genetic and epigenetic contributing factors. Overnutrition causes cellular stresses including endoplasmic reticulum stress, oxidative stress, amyloid deposition in pancreas, ectopic lipid deposition, lipotoxicity, and glucotoxicity that lead to IR and β -cell dysfunction.¹⁷ Importantly, all of these cellular stresses induce and are exacerbated by metabolic inflammation, thus sustaining a vicious cycle that prevents

resolution and restoration of homeostasis.^{18–20} Obesity is a chronic inflammatory state associated with increased plasma concentrations of C-reactive protein, interleukin-6 (IL-6), and plasminogen activator inhibitor 1 (PAI-1) that can predict IR and T2D.^{21,22} The ubiquitous pathological involvement of the immune system in onset and progression of IR and chronic hyperglycemia suggests that pathogenesis of T2D can be viewed as an “autoinflammatory disease.”^{17,23} Recent evidence shows that resolution programs can be altered in obesity and T2D imposes re-thinking of its management in the era of precision medicine. Here, we provide an overview of the resolving functions of SPMs and focus on RvE1 actions in T2D in light of its inflammatory pathogenesis.

II. SPMs

A. Synthesis and Metabolism of SPMs

Lipid mediators of immune function include fatty acids (e.g., eicosanoids), phospholipids (e.g., platelet activating factor [PAF]), lysophospholipids (e.g., lysophosphatidic acid), and others (e.g., ceramide).²⁴ They are synthesized from cell membrane phospholipids with contribution of phospholipase A2 (PLA2), acyltransferases and acetyltransferases, cyclooxygenases (COXs), and lipoxygenases (LOs) to generate PUFA-derived mediators including prostaglandins (PGs), leukotrienes (LTs), LXs, RVs, PDs, and MaRs. Phospholipases and acyltransferases are responsible for membrane phospholipid recycling in the so-called Lands’ cycle.^{24,25} The characterization of intricate COX and LO functions in lipid mediator synthesis are central to our current understanding of aspirin’s contribution to resolution of inflammation. Although it was originally thought that aspirin abolishes COX’s enzymatic activity through acetylation near the catalytic pocket, it became apparent that this modification transforms the COX into an LO-like enzyme that generates precursors for different classes of mediators acting in the resolution phase of inflammation.^{4,26}

Mammals are inefficient at synthesizing Ω -3 PUFAs and can only endogenously produce EPA and DHA from another Ω -3 PUFA, alpha linolenic acid (ALA) (Fig. 1). They cannot convert Ω -6 to Ω -3 PUFAs because mammalian cells lack Δ -12 and Δ -15 (Ω -3) desaturases, which are present in some lower eukaryotes such as *Caenorhabditis elegans*.^{27,28} The conversion rate for ALA to EPA and DHA is approximately 20% and significantly lower in males compared with females, which may be due to regulatory actions of estrogen.²⁹ Therefore, humans rely on dietary or extracted Ω -3 supplements to maintain a balanced Ω -6 to Ω -3 ratio and maintain optimal tissue function (Fig. 2A).^{30,31} However, the average low purity of Ω -3 PUFAs in commercial preparations combined with a limited rate of gut absorption requires high doses necessary to achieve significant positive biological effects. Kang et al. have generated a mouse that carries Fat-1, an enzyme expressed by *C. elegans*, which adds a double bond into an unsaturated fatty-acid hydrocarbon chain converting Ω -6 to Ω -3 PUFAs.³² Not surprisingly, Fat-1 transgenic mice were protected from becoming diabetic in response to streptozocin through regulation of inflammation by reducing levels of IL-1 β , tumor necrosis factor-alpha (TNF- α), nuclear factor kappa beta (NF- κ B), and 12-hydroxyeicosatetraenoic acid.³³ In humans, genetic variance in the fatty acid desaturase (FADS) gene cluster (FADS1 and FADS2) regulates the fatty acid composition in phospholipids, suggesting a potential genetic basis for differential processing of PUFAs to

pro-inflammatory and anti-inflammatory lipid mediators.^{34,35} Therefore, current evidence points to two major rate-limiting steps in the metabolism of Ω -3 PUFAs in humans: absorption in the intestine and enzymatic processing to active metabolites (Fig. 2B).

Studies that determined the physiological levels of SPMs in human healthy tissues and secretions, in particular serum/plasma, lymph organs, placenta, milk, and tears, identified LXs, RVs, and MaRs in the nanogram to picogram per milliliter range in individuals with or without Ω -3 PUFA supplementation.^{36–40} Sex differences in SPM production were identified in emotional tears and in exudates of cantharidin-induced skin blisters.^{40,41} Interestingly, females produced almost no SPMs in emotional tears while producing significantly higher levels than males in skin blister exudates. Sex differences in SPM production and inflammation resolution were attributed to testosterone affecting 5-LO production and subcellular localization.⁴² These findings suggest that SPM production is necessary for maintenance of homeostasis, that males and females coordinate resolution programs differently, and that deregulated resolution circuits lead to conditions associated with non-resolving inflammation. In support of this hypothesis, SPM production was recently found altered in sepsis, CVD, and Alzheimer's disease.^{43–45} Because there are multiple and complex resolution pathways governed by SPMs, the potential for SPM profiling relative to pro-inflammatory mediators (e.g., LTB₄) has recently been validated and proposed to be used for precision/personalized medicine.^{45–48} Computational and cluster analyses of these pathway mediators in serum and other exudates allows for interrogation of their relationships as well as the use of diagnostic fingerprints to assess the potential for resolution of inflammation.

B. SPM Actions during Resolution of Inflammation

Resolution of inflammation is an active and coordinated process aimed at restoration of tissue integrity and function that is associated with the elimination of PMN and the return to basal levels of tissue mononuclear cells (M and lymphocytes). It is widely accepted that resolution of inflammation is controlled by a range of tightly regulated biochemical and cellular mechanisms. PMN apoptosis is central to inflammation resolution. Cessation of pro-inflammatory signaling through depletion of chemokines by scavenging (decoy) receptors and enzymatic degradation is a prerequisite for PMN apoptosis and removal from inflamed tissues.⁴⁹ The duffy antigen receptor for chemokines (DARC), D6 and CCR5 sequester, and matrix metalloproteases (MMPs), in particular MMP12, cleave CC and CXC pro-inflammatory chemokines, reducing PMN and classical (inflammatory) monocyte (iMo) influx.⁵⁰ Spontaneous resolution is driven by PMN apoptosis and expression of “find-me” and “eat-me” signals to resolving M (rM) for removal through efferocytosis. Four major find-me signals, including lysophosphatidylcholine (LPC), sphingosine 1-phosphate (S1P), fractalkine (CX3CL1), and the nucleotides ATP and UTP, guide efferocytosis through the involvement of G2A, S1P1–5, CX3CR1, and P2Y2 receptors, respectively.^{51–54} Cell surface eat-me signals that facilitate identification of dying PMN include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), oxidized phospholipids, and carbohydrates including fucose and N-acetyl-glucosamine, which are recognized (XCL1, CCL5 and CXCL13) for B and regulatory T lymphocytes that exert and protective role in the

post-resolution phase.^{56–59} In particular, regulatory T-cells (TREGs, a subset of CD4+by rM directly or through bridging molecules to initiate efferocytosis.⁵⁵

Upon apoptotic cell efferocytosis, macrophages undergo a functional switch to cease pro-inflammatory signaling and execute resolving actions that govern the return of tissue homeostasis. rMs up-regulate molecules critical for antigen processing and presentation (MHC class II, CD74, CD86), clearance of inflammatory cells (TIM4, transforming growth factor-beta [TGF- β]), reduce responsiveness to TLR4 and CD11b expression, and secrete chemoattractants CD25+ enhance PMN apoptosis and efferocytosis by macrophages and secrete anti-inflammatory cytokines (IL-10, TGF- β).^{50,60} Further, active suppression of pro-inflammatory mediators (TNF- α , IL-1 β , and granulocyte-macrophage colony-stimulating factor) and secretion of anti-inflammatory cytokines (IL-10, TGF- β) by rMs that have phagocytosed apoptotic PMN is required for resolution.⁶¹ Dexamethasone and SPMs (resolvins E1 and D1) reduce CD11b expression and pro-inflammatory cytokine secretion (TNF- α and IL-1 β) and enhance secretion of anti-inflammatory cytokines (IL-10) and phagocytosis of apoptotic PMNs.⁵⁸ This process ensures PMN clearance without release of histotoxic cellular contents.³ Persistent inflammatory stimuli corroborated with dysregulated mechanisms of resolution result in chronic inflammation that critically contributes to progression of a wide range of conditions, including atherosclerosis, arthritis, periodontitis, diabetes, and chronic neurodegenerative diseases such as Alzheimer's disease.

SPMs act at different stages of inflammation to primarily coordinate resolution programs that restore homeostasis. In histopathological terms, the resolution phase is defined as the interval between leukocyte infiltration and complete removal from the tissue. The cellular and molecular mechanisms governing resolution are triggered by a switch from synthesis of pro-inflammatory lipid mediators PGs, LTs, and PAFs to SPMs including LXs, RVs, PDs, and MaRs acting via G-protein-coupled receptors on leukocytes, epithelial cells, and endothelial cells within hours of inflammatory stimulation.⁴⁶ This occurs through mobilization of fatty acid precursors that appear in exudates (arachidonic acid, EPA, and DHA). Importantly, PG biosynthesis is critical to resolution by up-regulating 15-LO necessary for the production of SPMs, and therefore, NSAIDs disrupt resolution through inhibition of PGs.⁵ SPMs mediate PMN apoptosis and uptake by macrophages, enhanced microbial clearance, chemoattractant scavenging that reduces further PMN recruitment, nonphlogistic monocyte recruitment, reduction pain signaling, and synthesis of anabolic factors involved in healing and regeneration of injured tissues.^{8,62} Over the past two decades, numerous animal studies have demonstrated the benefits of therapeutic SPMs in the picogram to nanogram range for management of arthritis, periodontitis, peritonitis, colitis, allergic airway inflammation, skin infections, neurodegenerative vascular disease, CVD, and T2D.^{6,63–67} Each of the SPMs binding to specific GPCR receptors counterregulates PGs, LTs, PAFs, and pro-inflammatory cytokines through NF- κ B down-regulation and increases IL-10.⁴⁹ Altogether, these findings suggest that comprehensive diagnosis of resolution failure through SPM metabolomics and recovery of resolution potential through SPM-mediated activation of immune cells holds promise for management of chronic inflammatory diseases in the era of precision medicine.

To aid in further understanding, the inflammatory mechanisms underlying T2D and associated morbidities, functional assessments, proteomics, and metabolomics can be integrated to assess immune cells such as PMNs and monocytes/macrophages that play central roles in disease onset and progression. Using such an approach, activation states can be investigated to identify biomarkers associated with specific cellular phenotypes, stratify subjects for improved clinical trial design, and get insights into molecular mechanisms explaining the diabetic phenotype per individual. Assessing the inflammation-resolving capacity of innate immune cells through measurements of efferocytosis efficiency (functional assessment), SPM production (lipidomics), and expression of receptors for SPMs (immunophenotyping) may help to achieve these goals. Further, tissue epigenomic and metabolomic approaches can profile healthy and diseased human tissues for precision personalized medicine.⁶⁸ Integration of these analyses may aid in identifying prevailing inflammation resolution failure pathways, choosing appropriate treatment strategies, and anticipating the response to therapy in an individual. One such example is the Pioneer P100 wellness project conducted at the Institute for Systems Biology, Seattle, Washington, USA. This study prospectively profiled 108 individuals using whole-genome sequencing, proteomics, metabolomics, 16S ribosomal RNA-based gut microbial community analyses, and hundreds of clinical tests every 3 months.⁶⁹ Initial results over 9 months demonstrated the feasibility of the approach and its potential to revolutionize medical practice through personalized diagnosis and co-management of diseases in an individual.

C. RvE1

1. Synthetic Pathways—RvE1 was first identified *in vivo* in murine dorsal air pouch exudates after treatment with aspirin and EPA. The endothelial cell-PMN transcellular biosynthesis was confirmed by treating human microvascular endothelial cells with aspirin and EPA and incubating the resulting products with human PMNs.⁴ RvE1 results from EPA modification by aspirin acetylated or statin S-nitrosylated COX-2, cytochrome P450, or 15-LO-1 in endothelial cells and uptake of 18R-HEPE and further processing in leukocytes through 5-LO pathway.^{70,71} RvEs were characterized and tested *in vivo* and *in vitro* demonstrating potent anti-inflammatory and pro-resolution properties.⁶ RvE1 (5S, 12R, 18R-trihydroxy-eicosapentaenoic acid) is structurally defined as an Ω -3 eicosanoid with five double bonds grouped as one conjugated diene and one conjugated triene that confer molecular stability.^{70,72} The complete RvE1 stereochemical assignment was established by Arita et al. as 5*S*,12*R*,18*R*-trihydroxy-6*Z*,8*E*,10*E*,14*Z*,16*E*-eicosapentaenoic acid, which had potent stereoselective actions *in vivo* and with isolated cells.⁷⁰ Importantly, existing evidence suggests that aspirin via acetylated COX-2, statins via S-nitrosylated COX-2, and thiazolidinediones via phosphorylation of 5-LO may promote RvE1 synthesis.^{71,73,74}

2. Actions—Two GPCR receptors ChemR23 (now named ERV1) and LTB4 receptor 1 (BLT1) have been shown to signal in response to high-affinity binding by RvE1.⁷⁵ ERV1 binding reduced IL-12 production by dendritic cells, whereas BLT1 binding competitively blocked LTB4, suggesting a potential mechanism for its anti-inflammatory action. In a murine model of zymosan-induced peritonitis, RvE1 regulated leukocyte infiltration, up-regulated CCR5 expression on late apoptotic PMNs, and stimulated M phagocytosis of apoptotic PMNs and migration of phagocytes carrying zymosan to lymph nodes and spleen.

^{76–78} In PMNs, RvE1-BLT1 activation leads to enhanced apoptosis via caspases 3 and 8 and induction of mitochondrial dysfunction by attenuating ERK and Akt-mediated apoptosis-suppressing signals.⁷⁹ RvE1 binds to BLT1 on PMN (K_d of ~48 nM) with lower affinity than LTB₄, and to ERV1 on M (K_d of ~11 nM) with higher affinity than chemerin, the other known endogenous ligand for ERV1, having a B_{max} of ~4200 binding sites per cell.^{70,75,80} In macrophages, RvE1 inhibited TNF- α and IL-12p40 production and TNF- α -induced nuclear translocation of NF- κ B in an ERV1-dependent manner.⁸¹ Further, RvE1-ERV1 axis activation stimulated efferocytosis and IL-10 production while reducing CD11b, interferon-gamma (IFN- γ), and IL-6, consistent with an rM phenotype.^{58,78,82} These actions were attributed to RvE1-stimulated S6 phosphorylation downstream of the PI3K/Akt and Raf/ERK pathways.⁸³ Therefore, RvE1 acting on BLT1 is likely central to control of PMN recruitment and survival at sites of inflammation in response to LTB₄, whereas actions via ERV1 in monocytes and macrophages control pro-inflammatory signaling and activate rMs.

3. Degradation and Elimination—Enzymatic conversion of RvE1 generates inactive or less potent compounds with one exception, 20-hydroxy-RvE1, in blood, lung, liver, kidney, and spleen: 20-carboxy-RvE1, 20-hydroxy-RvE1 (major metabolite in PMNs, as potent as RvE1), 19-hydroxy-RvE1, 18-oxo-RvE1, 12-oxo-RvE1, 11,12-dihydro-RvE1 and 11,12-dihydro-12-oxo-RvE1. Metabolomic profiles of RvE1 are species, tis-sue, and cell-type specific. 18-oxo-RvE1 is the major RvE1 metabolite in murine liver, lung, and kidney and 11,12-dihydro-RvE1 is the major metabolite in spleen. Murine kidney and liver generate more 18-oxo-RvE1 than other RvE1-derived metabolic products compared with lung and spleen.^{84,85} Three compounds, 20-hydroxy-RvE1, 18-oxo-RvE1, and 11,12-dihydro-RvE1, are the major metabolites in human blood.⁸⁵ The major RvE1 metabolite in human PMNd is 20-hydroxy-RvE1, followed by 19-hydroxy-RvE1 and 18-oxo-RvE1. Although 20-hydroxy-RvE1 retains biological activities of RvE1, 18-oxo-RvE1 is its inactive metabolite. RvE1 is converted to 18-oxo-RvE1 *in vitro* by human recombinant 15-prostaglandin dehydrogenase. An RvE1 analog, 19-(*p*-fluorophenoxy)-RvE1 methyl ester, which was designed with bulky substitutions placed adjacent to the 18 position to prevent con-version to 18-oxo-RvE1, resists rapid metabolic inactivation while retaining biological activity by reducing PMN infiltration and pro-inflammatory cytokine/chemokine production *in vivo*.⁸⁴ Because some mammalian cells possess 5- and 12-dehydro-genases, oxidation at either the C5 or C12 hydroxyl group is also possible, but such metabolites were not identified for RvE1.

III. RESOLVIN E1 ACTIONS IN T2D

A. Management of Inflammation in T2D

1. Metabolic and Endotoxemic Stress—In recent years, immunometabolism has emerged as a field addressing the interactions between metabolic changes and the immune system. This is in contrast to the traditional view that metabolism and immunity have distinct functions: disposal and transformation of nutrients by the former and host defense by the latter. It is now clear that chronic hyperactivation of the immune system by metabolic stress can lead to T2D, likely precipitated by genetic predispositions.^{86,87} Central to metabolic stress-induced inflammation are macrophages in metabolic organs, liver, and visceral adipose tissues. In obesity, macrophage-derived cytokines, reactive oxygen species,

and other factors produced by immune cells and adipocytes activate important stress pathways and disrupt critical metabolic processes, such as the insulin signaling cascade.⁸⁸ Nutrient-induced M activation through tricarboxylic acid cycle disruption, altered glycolysis and protein metabolism, and fatty acid oxidation favors a pro-inflammatory and pro-thrombotic phenotype that contributes to onset of obesity-associated metabolic syndrome.

The increased fat tissue turnover in obesity can be dominated by adipocyte necrosis acting as a pro-inflammatory stimulus for adipose tissue macrophages, which induces a switch from pro-resolution (rM) to pro-inflammatory (iM) phenotype in these cells. The caloric overload associated with a Western-type high-fat diet (HFD) leads to ectopic accumulation of lipids in liver (steatosis) and skeletal muscle and to adipocyte dysfunction that induces iMo infiltration and iM activation and favors lipolysis in white adipose tissue.⁸⁹ The increased fatty acid flux to liver promotes esterification and triglyceride synthesis further exacerbating the metabolic stress and hepatic steatosis. Ultimately, the obese adipose tissues throughout the body will sustain local and systemic inflammation and IR.^{90,91} Adipose tissue iMs are activated in response to saturated fatty acid-modified low-density lipoproteins, heat shock proteins, endotoxins (lipopolysaccharide [LPS]), high-mobility group box 1 (HMGB1), and extracellular matrix degradation products via TLRs, in particular TLR2 and TLR4, to engage pro-inflammatory pathways that lead to secretion of cytokines such as TNF- α , IL-1 β , and IL-6, which then block insulin signaling to produce the overall IR state *in vivo*.^{91,92} Therefore, activation of iMs is central to imbalance between lipogenesis and lipolysis in favor of the latter and to hepatic steatosis, both being driven by inflammation-mediated IR^{93–95} (Fig. 3).

At the same time, HFD feeding induces gut dysbiosis and increased intestinal permeability (leaky gut) that lead to systemic LPS dissemination (metabolic endotoxemia) and iMo/iM activation that sets the tone of insulin sensitivity, obesity, and T2D.^{96,97} The excess dietary saturated fats combined with gut dysbiosis activate TLRs and NOD-like receptors (NLRs) on intestinal epithelial cells, resulting in secretion of alarmins and inflammatory cytokines, which can directly compromise intestinal epithelial barrier integrity. This allows for translocation of food antigen and bacterial products from the gut to the tissues. Low-grade bowel inflammatory changes occur early on a HFD and precede detectable systemic metabolic disease, suggesting a critical role of gut dysbiosis and associated gut inflammation in onset of obesity and IR.⁹⁸ Obesity-associated gut dysbiosis characterized by increase ratio of *Firmicutes* to *Bacteroidetes* phyla results in altered microbial metabolite production, such as reduced short-chain fatty acids (e.g., butyrate) that promote mucus secretion by intestinal epithelial cells, TREG differentiation, IgA expression by B-cells, and inhibition of NF- κ B.^{99,100} Conversely, a lack of dietary fruits and vegetables reduces generation of dietary aryl hydrocarbon receptor ligands that are directly involved in production of IL-17 and IL-22 critical in maintaining barrier function.^{101,102} These microbial and dietary changes are associated with increased proportions of IFN- γ -secreting Th1 and CD8⁺ T-cells and reduced proportions of TREGs, IL-22-producing intraepithelial lymphocyte subsets, Th17 cells, and eosinophils, which favor non-resolving intestinal inflammation.

2. Resolution Failure and Systemic Inflammation—In the absence of excess calorie use or storage, a metabolic insult is sustained by adipocytes and hepatocytes, a

response that begins the inflammatory program mediating the interface between metabolic input and inflammatory output and leading to a chronic unresolved inflammatory state.¹⁰³ Although the mechanisms of failed resolution associated with obesity and IR are incompletely understood, mounting evidence suggests that excess saturated free fatty acids, increased gut permeability and dysbiosis, persistence of hyperglycemia, hypoxia, and tissue damage contribute to resolution failure by sustaining iM activation.^{17,104} Endoplasmic reticulum stress in response to fatty acids, excess of nutrients, improperly folded proteins, microhypoxia, and LPS activate iMs that sustain local inflammation and IR through activation of NF- κ B and inhibition of insulin receptor substrates (IRS1 and IRS2) by phosphorylation, respectively.¹⁰⁵ Metabolic inflammation is similar to classical inflammation in the sense that it involves similar molecules and pathways but with a dual role as inflammatory mediators and as regulators of energy storage and metabolism. The combination of increased pro-inflammatory adipokines (TNF- α , IL-6, IL-1 β , MCP-1, leptin, and resistin) and decreased anti-inflammatory and insulin-sensitizing adipokine adiponectin is believed to signal the onset of metabolic dysfunction by sustaining continuous recruitment and activation of iMo/iM in adipose tissues.¹⁰⁶ This vicious inflammatory cycle centered on iM seems to be perpetuated by both persistent metabolic stress and failure of natural resolution programs locally and systemically.

Unresolved inflammation in obese adipose tissue also appears to be associated with impaired biosynthesis of anti-inflammatory mediators. Indeed, the obese state leads to consistent reduction in the circulating levels of adiponectin, one of the few adipokines with anti-inflammatory and insulin-sensitizing actions.¹⁰⁷ Low SPM levels were found in adipose tissues of patients with metabolic syndrome and in animal models of IR.^{108–110} Because SPMs are synthesized locally and act in an autocrine and paracrine manner, their loss in adipose tissues may be a consequence of Ω -3 PUFAs (substrates for SPM synthesis) deficiency in the tissue. In support of this hypothesis, the transgenic restoration of ω -3 PUFAs using *fat-1* transgenic mice reversed the inefficient resolution capacity in adipose tissue from mice with HFD-induced obesity.¹¹¹ Impaired SPM production other tissues was found associated with T2D, including the liver, cutaneous wounds, and skeletal muscle, suggesting a generalized deficit in all metabolic tissues.^{111,112} Altogether, these findings support the notion that obesity-associated unresolved inflammation results in altered resolution capacity that favors chronicity and T2D progression.

3. Anti-Inflammatory and Pro-Resolution Therapies—Mounting evidence that T2D has an inflammatory pathogenesis indicates that comprehensive and personalized management should include therapeutics that address the unregulated inflammatory responses to altered-self, in addition to blood glucose-normalizing agents. Because iMo/iM recruitment into adipose tissue and pancreatic islets contributes to IR and impaired insulin secretion, chemokines and receptors involved in monocyte migration are potential therapeutic targets for diabetes mellitus (DM). Monocyte chemotactic protein 1 (MCP1, CCL2) is a chemokine involved in recruitment and tissue infiltration of macrophages in patients with T2D favoring onset of IR.^{113–115} CCX140-B, an orally available antagonist of MCP-1 receptor CCR2, was able to reduce HbA1C levels by 0.14% in patients with T2D during a 4-week clinical trial.¹¹⁶ The same antagonist reduced the number of adipose tissue

iMs and improved glycemic control and insulin sensitivity in diabetic mice.¹¹⁷ These actions support a significant role of CCR2 in sustained adipose tissue inflammation mediated by iM as previously observed in animal studies.¹¹⁸

The prevention of primary myocardial infarction (MI) in patients with DM with daily aspirin was first addressed in a randomized, double-blind, placebo-controlled trial by the Physicians' Health Study Research Group including 22,071 participants with an average of 5 years follow-up completed in 1989.¹¹⁹ The study had found a 44% reduction in MI risk but a slightly increased risk of hemorrhagic stroke. Reduction in MI risk was apparent only in patients over 50 years of age. Based on these observations and a few supporting studies that followed, the American Diabetes Association strongly recommended long-term daily aspirin for primary prevention of MI in DM. The efficiency of daily aspirin (75–325 mg/dose/day) and other anticoagulants alone or in combination with statins (HMG-CoA10 reductase inhibitors) on prevention of CV events and stroke in patients with DM has since been tested in large trials.¹²⁰ Consistent with these observations, the American Diabetes Association and the American Heart Association recommend daily low-dose aspirin (75–162 mg/day) for the prevention of primary CV events in patients with DM and no previous history of vascular disease who are at increased risk for CVD (10-year risk of CVD events over 10%) and who are not at increased risk for bleeding.^{121,122} Adults with increased CVD risk are most men over age 50 years and women over age 60 years diagnosed with DM who have one or more additional major risk factors including smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria.

NF- κ B treatment strategy for DM emerged from compelling evidence that this pro-inflammatory pathway is central to iM activation of adipose tissue macrophages. TNF- α and IL-1 β are major cytokines involved in activation of NF- κ B. Additionally, TNF- α produced by pro-inflammatory adipose tissue macrophages demonstrated a significant role in induction of IR in rodents, which led to attempts to translate these findings in humans. Despite original conclusions from a limited number of underpowered clinical studies that TNF- α does not have an important role in T2D in humans, recent reports are consistent with findings from animal studies.⁸⁶ One such study found that 6-month TNF- α inhibition via entanercept in obese individuals without DM resulted in significant decrease in fasting plasma glucose and increase in adiponectin, probably reflecting improved insulin sensitivity.¹²³ Additionally, TNF- α inhibition in patients with rheumatoid arthritis results in improved insulin sensitivity and blood glucose levels, suggesting that TNF- α may play an important role in the pathogenesis of T2D.¹²⁴ Similar results were found by antagonizing IL-1 β with specific antibodies (gevokizumab or canakinumab) or anakinra, a recombinant human IL-1 receptor antagonist, in pre-diabetic individuals and those with impaired glucose tolerance.^{125,126} These therapies led to improved β -cell secretory function that may prevent onset of T2D, improve insulin sensitivity and glycemic control, and reduce systemic inflammatory markers. In support of a role of both IL-1 β and TNF- α in pathogenesis of T2D and glycemic control, it was found that diacerein, which reduces the levels of both cytokines via unknown mechanisms, improved insulin secretion and reduced HbA1C levels in drug-naïve patients with T2D.¹²⁷ Altogether, these findings support the two major pro-inflammatory cytokines TNF- α and IL-1 β as therapeutic targets for management of T2D-associated inflammation in humans.

The use of Ω -3 PUFAs in patients with vascular disease gained increasing interest since it was found that Greenland Inuits have a lower prevalence of coronary heart disease compared with Scandinavian control subjects.^{128,129} It was later shown that Inuits also had reduced platelet reactivity and prolonged bleeding time compared with Scandinavian controls.¹³⁰ This was attributed to the Inuit diet, which has an extremely high content of fish abundant in Ω -3 PUFAs, mainly EPA and DHA.¹³¹ Subsequent observations have indicated a significant role of dietary Ω -6 to Ω -3 PUFA ratio in the incidence of DM in different populations.¹³² Numerous studies have shown significant beneficial effects of Ω -3 PUFAs in patients with DM regarding leukocyte function, glucose metabolism, IR, and diabetic complications.¹³³ It is believed that Ω -3 PUFAs modulate inflammation by partially replacing cell-membrane-bound Ω -6 PUFAs when the former are at a high enough concentration in the diet, subsequently generating SPMs. Although the exact mechanisms of this pro-resolving loop in DM are unclear, Ω -3 PUFAs seem to prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome in macrophages.¹³⁴ Increased intake of Ω -3 PUFAs alleviated obesity-induced IR in and hepatic steatosis through up-regulation of genes involved in insulin sensitivity and glucose transport.¹⁰⁸ However, contradictory findings of human studies on the benefits of Ω -3 PUFAs on incident T2D and its management after onset has prompted the American Diabetes Association to not recommend Ω -3 PUFAs for T2D patients.^{135–137} Aside from heterogeneity in study designs, it is also likely that the complexity of absorption, processing to SPMs, and cell activation *in vivo* underlie different responses to the Ω -6 PUFAs in patients at risk for T2D.

B. Inflammation-Resolving Actions of RvE1 in T2D

RvE1, an EPA-derived SPM, has shown potent inflammation-resolving actions through direct actions on immune cells via BLT1 on PMNs and ERV1 (also called ChemR23) on monocytes/macrophages. Earlier reports have shown that RvE1 in nanogram quantities promotes PMN removal from inflamed sites by reducing infiltration and increasing uptake by rMs.^{75,77,78} The administration of RvE1 or RvD1 led to reduced CD11b expression on macrophages upon uptake of apoptotic PMNs and the production of pro-inflammatory cytokines in response to LPS during acute peritonitis.⁵⁸ When incubated with human whole blood, RvE1 down-regulated the expression of the adhesion molecules CD18 and L-selectin on PMNs and monocytes, as well as platelet aggregation in response to adenosine diphosphate.¹³⁸ RvE1 reduces adenosine diphosphate-stimulated P-selectin mobilization in platelets through ERV1, suggesting that RvE1 may regulate platelet–PMN aggregates in patients with T2D and CVD.^{139,140} RvD1 and RvE1 decrease MI size, infiltration of PMNs, and fibrosis in models of ischemia and reperfusion, leading to improved cardiac function.^{141,142} Because platelet–PMN aggregates formed during self-limited, acute inflammation lead to SPM biosynthesis but also contribute to atherosclerotic plaque inflammation, it is likely that these aggregates in CVD are deficient in producing SPMs.⁴⁷ The levels of SPMs, particularly RvD1, and the ratio of SPMs to LTB₄ were found to be significantly decreased in the vulnerable regions of human carotid atherosclerotic plaques.⁴⁴ Further, CVD patients had low levels or absence of specific SPMs that were restored with Lovaza (3360 mg EPA and DHA daily for 1 year), suggesting an important role of deficient SPM production in the progression of chronic vascular inflammation predisposing to coronary atherosclerosis and to thrombosis.¹⁴³ Administration of RvD1 promoted plaque stability by decreased oxidative

stress and necrosis, improved efferocytosis, and thicker fibrous cap. RvE1 attenuated atherosclerosis comparable to atorvastatin and reduced activation of IFN- γ and TNF- α pathways and the expression of specific pro-atherogenic inflammatory factors in a model of diet-induced atherosclerosis without altering serum cholesterol levels, indicating a therapeutic potential for CVD.¹⁴⁴

Using a murine model of chronic hyperglycemia, the Akita mouse, we had found that chronic hyperglycemia results in a PMN hyperadhesive phenotype resulting in increased margination in periodontal microvasculature in the absence of exogenous pro-inflammatory stimuli.^{145,146} However, despite being able to reduce leukocyte margination and recruitment in wild-type mice, RvE1 was less efficient in Akita mice, which suggested that chronic hyperglycemia may have a negative impact on RvE1 receptors. Indeed, it was subsequently found that BLT1 and ERV1 expression by PMNs is altered in patients with T2D and that human ERV1 overexpression in transgenic (ERV1tg) mice reduces PMN infiltration and rescues PMN uptake by rM in *db/db* diabetic mice.^{147,148} ERV1tg mice overexpress the human ERV1 receptor in mature myeloid cells (CD11b promoter-linked expression), particularly in response to pro-inflammatory stimulation. RvE1 and RvD1 activate rMs and anti-inflammatory mediator production and reduce iM-derived pro-inflammatory mediators in obese mice.^{149,150} ERV1 expression was found to be increased in PMNs of diabetic patients, suggesting a potential compensatory up-regulation of RvE1 receptors in individuals with reduced resolving capacity who do not efficiently produce SPMs or lack sufficient dietary Ω -3 PUFAs for SPM synthesis. Other explanations for these findings may be unknown regulation of ERV1 by cytokines or heterodimerization of GPCRs. It is also likely that the ratio between SPMs, including RvE1 and others, and LTB₄ that has potent chemotactic properties for PMNs, is critical to resolution capacity in obesity and T2D.¹⁰⁹ Consistent with this hypothesis, we recently found that the ratio between SPMs and the pro-inflammatory lipid mediators LTB₄ and PGE₂ increased in mice overexpressing ERV1 in myeloid cells when fed a HFD.¹⁵⁰ Morbidly obese individuals carrying a C allele in the rs1878022 polymorphism of ERV1, which increases its expression, had reduced levels of pro-inflammatory cytokines in adipose tissues and plasma and enhanced leukocyte responsiveness to RvE1.¹⁵¹ These findings indicate that alterations in the RvE1–ERV1 axis contribute to the loss of resolving immune function associated with T2D.

Although RvE1 functions on platelets and PMNs predominantly reduce adhesiveness and infiltration into tissues, RvE1–ERV1 induction in monocytic cells results in patrolling monocytes (pMo) recruitment and rM activation in obesity-associated IR.¹⁵⁰ In humans and mice, two different monocyte populations, iMo and pMo, with distinct surface chemokine receptor profiles CCR2+CX3CR1^{int} (iMo) and CCR2–CX3CR1^{high} (pMo), share iM and rM phenotypes, respectively, which suggests that macrophages use different modes of tissue trafficking in inflammation and resolution.^{152–154} It has been suggested that enhanced recruitment of pMo and rM activation in visceral adipose tissues may contribute to inflammation resolution and prevention of glucose intolerance during dietary overload.^{155,156} We found that HFD feeding increases CCR2 and decreases CX3CR1 in monocytes of wild type but not ERV1tg mice, and that RvE1 treatment partially reversed these HFD-induced changes in monocytes, suggesting improved surveillance of metabolic overload upon RvE1–ERV1 activation.¹⁵⁰ Our work and that of others found that RvE1 induces rM

activation in metabolic organs in animal models of obesity and IR, which translated into reduced inflammation and improved insulin sensitivity. Although González-Pérez et al. and Hellmann et al. have found that RvE1 and RvD1 improves insulin sensitivity and glucose tolerance in *db/db* mice, we found that the dose of 2 ng/g body weight RvE1 twice weekly for 4 weeks was insufficient for reversing the diabetic phenotype in HFD-fed mice.^{108,149} Indeed, both have used more frequent delivery and a different animal model, suggesting that higher RvE1 doses and/or daily delivery may be needed to improve glucose tolerance in obesity-induced IR. The fact that regulatory functions of ERV1 on monocyte CCR2 and CX₃CR1 in favor of patrolling behavior in both steady state and during dietary fat overload corroborated with reduced inflammation and body weight gain suggests that ERV1 activation may be beneficial for prevention of T2D in obese-prone environments.

C. Metabolic Actions of the RvE1–ERV1 Axis

In addition to inflammation-resolving functions, RvE1, as well as RvD1, RvD2, and PD1, stimulate adiponectin production in animal models of T2D.^{108,110,157} Importantly, in addition to monocytes/macrophages, adipocytes from white adipose tissue depots express high levels of ERV1, suggesting an energy-storing function in these cells.^{158,159} Further, adiponectin up-regulates ERV1 hepatic expression, suggesting a positive feedback loop between RvE1, ERV1, and adiponectin.¹⁶⁰ Although the relationship between RvE1 and chemerin, an adipokine that also binds to ERV1, is incompletely understood, it is likely that RvE1 binding with higher affinity to ERV1 competes with chemerin to induce a resolving phenotype. Chemerin serum levels were found to be increased in patients with metabolic syndrome and both pro-inflammatory and anti-inflammatory actions were reported for chemerin and its derived peptides.^{161–165} It was therefore thought that chemerin can be a valuable marker for the degree of IR.^{166,167} However, a prospective study on a subset of participants from the Metabolic-Syndrome Berlin-Potsdam (MesyBepo) cohort found chemerin to be a weak predictor of T2D.¹⁶⁸ We found that ERV1 overexpression in myeloid cells increases the proportion of pMo (CX₃CR1^{high}) in blood and RvE1–ERV1 activation has a beneficial impact on HFD-induced changes in pancreatic islets and fasting serum insulin levels.¹⁵⁰ Therefore, it is likely that the links between resolution failure, metabolic distress, and IR leading to T2D are critical processes such as impaired β -cell function in the pancreas.

It is now clear that failure of β -cell expansion through enhanced cell mass and insulin secretory activity to compensate for the degree of IR results in insulin deficiency and onset of T2D. Although the insulinitis in T1D is driven by an autoimmune-mediated process, in T2D, it is now thought to be due to autoinflammation; the IL-1 β pathway is activated as a final effector in both types of diabetes, leading to the activation of the NF- κ B and JNK pathways and cytokine and chemokine release and to the recruitment of immune cells.¹⁶⁹ Our recent findings of increased fasting serum insulin levels and maintenance of a high insulin-to-glucagon ratio in pancreatic islets of HFD-fed ERV1^{tg} mice in the absence of hyperglycemia suggest a potent β -cell response to episodes of transient hyperglycemia combined with some degree of peripheral IR in these mice.¹⁵⁰ The increased proportion of pMo (CX₃CR1^{high}) through ERV1 activation may in part explain these findings. Indeed, previous reports have shown that the fractalkine/CX₃CR1 system plays an important role in

regulation of insulin secretion.¹⁷⁰ Although these studies have not addressed the contribution of monocyte CX₃CR1 in regulating β -cell function, they confirmed the impaired insulin secretion in CX₃CR1-knockout mice without altered intra-islet vascularization. Conversely, human pancreatic islets express BLT1 and respond directly to RvE1 by reducing the pro-inflammatory markers IL-8, MCP-1 (CCL2), tissue factor, and CCL5 in response to LPS.¹⁷¹ Therefore, the RvE1–ERV1 axis may prevent insulin deficiency in obesity through direct actions on pancreatic islets.

Ω -3 PUFAs and SPMs exert opposite roles in hepatic steatosis to those described for Ω -6-derived eicosanoids, especially LTB₄. The hepatoprotective actions of diets rich in Ω -3 PUFAs are associated with the increased generation of SPMs in liver tissue (i.e., PD1 and 17S-HDHA), which attenuate DNA damage and oxidative stress in hepatocytes and reduce macrophage-derived TNF- α .¹⁷² This anti-steatotic effect of RvE1 is associated with improved insulin tolerance and changes in the expression of adiponectin that orchestrate the interaction between adipose tissue and the liver.¹⁰⁸ RvE1 protective actions on liver are likely mediated through ERV1 in monocytes/macrophages, including Kupffer cells, because mice overexpressing this receptor in myeloid cells were protected from overt hepatic steatosis and morbid obesity when on HFD.¹⁵⁰ The up-regulation of *SREBP2* and *PPAR- α* in liver and the down-regulation of *FABP4* in VAT of ERV1tg mice indicate enhanced fatty acid oxidation and cholesterol removal from liver and storage of fatty acids in adipocytes. Further, the reduced hepatic glycogen depletion in fasted state and normal fasting glucose levels maintained on HFD by ERV1tg mice indicate that ERV1 in myeloid cells activates resolution programs that deal with dietary overload through promotion of excess nutrient storage or removal to maintain physiologic energy substrate levels (Fig. 4).

Existing evidence on RvE1 functions in the intestine points to a potential role in maintaining physiologic gut host–microbiome interactions. In murine colitis, RvE1 treatment improved survival and decreased leukocyte infiltration and pro-inflammatory gene expression, including IL-12 p40, TNF- α , and inducible nitric oxide synthase.¹⁷³ Campbell et al. found that RvE1 reduces transepithelial migration and promotes apical clearance of PMNs in an ERV1-dependent manner through up-regulation of CD55.¹⁷⁴ Using a murine model of colitis, the same group showed that RvE1 induces intestinal alkaline phosphatase (ALP) activity and promotes LPS detoxification by attenuation of NF- κ B activity.¹⁷⁵ Intestinal ALP is believed to directly influence gut microbial ecology through control of pH and LPS detoxification via lipid A dephosphorylation, which in turn alters bacterial growth, favors restoration of commensal gut microbiota, and prevents transmigration of bacteria through the epithelium.¹⁷⁶ HFD feeding results in epithelial TLR4 activation that correlates with gut dysbiosis, intestinal inflammation, reduced ALP activity, abnormal tight junction expression, and increased intestinal permeability.¹⁰⁴ We found that HFD-fed ERV1tg mice have a distinct gut microbial profile with increased a *Bacteroidetes* to *Firmicutes* ratio compared with wild-type mice, suggesting that RvE1–ERV1 may play a role in preventing HFD-induced gut dysbiosis and its metabolic impact (Fig. 5).

IV. CONCLUSIONS

New advances in our understanding of the impact of overnutrition on the immune system and pathogenesis of T2D point to a central role of resolution failure in IR and chronic hyperglycemia. SPM profiling has the potential to reveal specific alterations in inflammation resolution to aid in personalized diagnosis and therapy for patients with T2D. RvE1 has shown potent pro-resolving and metabolic stabilizing actions in animal models of diet-induced obesity and T2D. RvE1, together with SPMs, in particular the resolvin D series (e.g., RvD1, RvD2) and protectins (e.g., PD1), are promising therapeutic agents to be tested for the prevention and management of T2D. Despite inflammation resolution complexity and multiple implications of SPMs, mass spectrometric lipid profiling in serum and other accessible tissues holds promise for improved individualized diagnosis and therapy for metabolic diseases in humans. Future prospective clinical trials assessing the SPM profile changes in progression of obesity-associated T2D should provide a framework for the development of SPM-based therapeutics for primary and secondary prevention of diet-associated metabolic diseases.

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ABBREVIATIONS

ALA	alpha-linolenic acid
BLT1	LTB ₄ receptor 1
CCR	C-C chemokine receptor
CX₃CR	CX3C chemokine receptor
CD	cluster of differentiation
COX	cyclooxygenase
CVD	cardiovascular disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
GPCR	G-protein coupled receptors
IL	interleukin
iM	inflammatory macrophage
iMo	inflammatory monocyte
IR	insulin resistance

LO	lipoxygenase
LT	leukotriene
LX	lipoxin
LPS	lipopolysaccharide
MaR	maresin
PAF	platelet activating factor
PD	protectin
PG	prostaglandin
pMo	patrolling monocyte
PMN	polymorphonuclear neutrophil
PUFA	polyunsaturated fatty acid
rM	resolving macrophage
Rv	resolving
SPM	specialized pro-resolving lipid mediator
T2D	type 2 diabetes mellitus
TLR	toll-like receptor
TNF	tumor necrosis factor
TX	thromboxane

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FIG. 1:

SPM synthesis from Ω -3 PUFAs. Ω -3-derived SPMs are synthesized through enzymatic processing of EPA and DHA initially by epithelial and endothelial cells and subsequently by platelets and myeloid cells (PMNs, monocytes/macrophages). EPA and DHA from either diet/supplementation or from ALA are incorporated into cell membrane phospholipids and released intracellularly by phospholipase A2. The active metabolites of EPA and DHA, RVs, PDs, and MaRs, act in an autocrine and paracrine manner on leukocytes and platelets to resolve inflammation.

FIG. 2:

Synthesis of EPA, DHA, and derived lipid mediators of inflammation, SPMs. (A) Conversion of ALA to EPA and DHA is a multi-step enzymatic process taking place in the endoplasmic reticulum and peroxisomes of human cells. Sequential desaturation and elongation is carried by Δ -5 and Δ -6 desaturases and elongases. *Rate-limiting step. (B) A series of enzymatic steps involving epoxidation by lipoxygenases (5-LO, 12-LO, 15 LO) and hydrolysis generates RVs, PDs, and MaRs from EPA and DHA. The class representatives of these SPMs are RvE1, RvD1, PD1, and MaR1.

FIG. 3:

Systemic inflammation in deregulated metabolism. Inflammation is central to metabolic imbalance in obesity leading to T2D. Mounting evidence suggests that diet-induced gut inflammation and associated dysbiosis sustain systemic inflammation, metabolic imbalance, and in central metabolic organs, liver, and visceral adipose tissue. Gut dysbiosis is associated with predominant pro-inflammatory relative to the pro-resolving activation of intestinal macrophages. Dissemination of LPS from gut microbiota leads to metabolic endotoxemia that activates iMos in circulation. Predominance of iMs in central metabolic organs is associated with local inflammation.

FIG. 4:

RvE1 actions in deregulated metabolism and associated inflammation. RvE1 and activation of its receptor, ERV1, has been associated with reduced inflammatory cell infiltration and pro-inflammatory mediator production in visceral adipose tissue and liver. This was further linked to reduced hepatic steatosis and improved insulin sensitivity in adipose tissues. RvE1 actions on innate immune cells are mediated by GPCR receptor ligation, primarily BLT1 on PMN and ERV1 (also called ChemR23) on monocytes/macrophages. RvE1 is a partial agonist of BLT1 reducing infiltration and inflammatory activation and a high-affinity agonist of ERV1, insuring a pro-resolving phenotype in monocytes/macrophages.

FIG. 5:

Gut microbiome changes in HFD-induced obesity in ERV1tg mice. Stool samples from wild-type (WT) and ERV1tg male mice on HFD or normal control diet (NCD) for 24 weeks were analyzed for microbiome changes by 16S rDNA profiling (MiSeq, Illumina). (A) Principal component analysis found that microbiomes of ERV1tg HFD mice clearly differ from WT mice. Microbiomes from NCD-fed mice were different from their HFD-fed counterparts. (B) Microbial identities at the phylum level revealing a higher prevalence of *Proteobacteria* and *Bacteroidetes* in ERV1tg HFD-fed mice. In contrast, *Verrucomicrobia* were present in the NCD mice. (C) Alpha diversity analysis showing more species in the HFD-fed mice. (D) Microbial identities at the species level indicate that *Desulfovibrio* species (#) and *Bacteroides sartori*(&) are consistently the most prevalent species in HFD-fed ERV1tg mice compared with NCD-fed mice.