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Specialized Pro-resolving Lipid Mediators: Modulation of Diabetes-Associated Cardio-, Reno-, and Retino-Vascular Complications

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Diabetes and its associated chronic complications present a healthcare challenge on a global scale. Despite improvements in the management of chronic complications of the micro-/macro-vasculature, their growing prevalence and incidence highlights the scale of the problem. It is currently estimated that diabetes affects 425 million people globally and it is anticipated that this figure will rise by 2025 to 700 million people.

The vascular complications of diabetes including diabetes-associated atherosclerosis and kidney disease present a particular challenge. Diabetes is the leading cause of end stage renal disease, reflecting fibrosis leading to organ failure. Moreover, diabetes associated states of inflammation, neo-vascularization, apoptosis and hypercoagulability contribute to also exacerbate atherosclerosis, from the metabolic syndrome to advanced disease, plaque rupture and coronary thrombosis. Current therapeutic interventions focus on regulating blood glucose, glomerular and peripheral hypertension and can at best slow the progression of diabetes complications.

Recently advanced knowledge of the pathogenesis underlying diabetes and associated complications revealed common mechanisms, including the inflammatory response, insulin resistance and hyperglycemia. The major role that inflammation plays in many chronic diseases has led to the development of new strategies aiming to promote the restoration of homeostasis through the “resolution of inflammation.” These strategies aim to mimic the spontaneous activities of the ‘specialized pro-resolving mediators’ (SPMs), including endogenous molecules and their synthetic mimetics. This review aims to discuss the effect of SPMs [with particular attention to lipoxins (LXs) and resolvins (Rvs)] on inflammatory responses in a series of experimental models, as well as evidence from human studies, in the context of cardio- and reno-vascular diabetic complications, with a brief mention to diabetic retinopathy (DR).

These data collectively support the hypothesis that endogenously generated SPMs or synthetic mimetics of their activities may represent lead molecules in a new discipline, namely the ‘resolution pharmacology,’ offering hope for new therapeutic strategies to prevent and treat, specifically, diabetes-associated atherosclerosis, nephropathy and retinopathy.

Keywords: diabetic kidney disease, diabetes-associated atherosclerosis, diabetic retinopathy, lipoxins, resolvins

INTRODUCTION

Diabetes and its associated complications pose a challenge to human health on a global scale. It is estimated that 425 m people are currently living with diabetes and this is predicted to rise to 700 m by 2025 (The Lancet, 2018). The rapid rise in diabetes and its associated complications over the past three decades reflects numerous factors including aging, obesity, urbanization and greater longevity amongst patients (Zimmet et al., 2001). Among NCCDs, diabetes is one of the major global causes of premature mortality. It is frequently underestimated because very often persons with diabetes die from causes related to co-morbidities (Lee et al., 2012).

The prevalence of diabetes in adults worldwide is predicted to be higher in developed than in developing countries, while, the incidence of diabetes is predicted to be higher in developing

countries (Wild et al., 2004). Thus, by the year 2030, the countries with the largest number of people with diabetes are predicted to be India, China and the United States; the countries with increased prevalence of overweight and obese inhabitants, the main drivers of T2D (Yach et al., 2006). The burden on already challenged health care systems is unprecedented.

Diabetes is essentially a disorder of glucose homeostasis. Conventionally, diabetes has been classified as Type-1, Type-2 and gestational diabetes. In T1D, autoimmune destruction of the β -cells of the pancreas creates an insulin-deficient state where patients are dependent on exogenous insulin for survival. The precise mechanisms underlying the pathogenesis remain elusive, but it is likely that genetic and environmental factors converge to drive an autoimmune response. The observed increasing incidence of T1D in developed nations is thought to reflect responses to environmental triggers. Historically, T1D is considered to represent 10% of total number of persons with diabetes (You and Henneberg, 2016). In T2D, peripheral insulin resistance in target tissues (including skeletal muscle, adipose tissue and liver coupled with hypersecretion of insulin) typically precedes eventual β -cell loss. The diabetes epidemic is commonly attributed to T2D (Tuomi, 2005). Gestational diabetes describes insulin resistance observed during pregnancy, which generally resolves in the postnatal period. However, these mothers are at increased risk of T2D in later life (Buchanan and Xiang, 2005).

It is now clear that the above classifications are an oversimplification. It has recently been proposed to re-define diabetes based on six clinical parameters [BMI, age at diagnosis, hemoglobin A1c, glutamate decarboxylase autoantibodies (GADAs) (evidence of autoimmunity); β -cell function and insulin sensitivity]. This has led to the identification of five distinct pathologies associated with different disease progression and risks of complications. Further characterization of the genetic architecture of these subgroups may facilitate identification of patients most at risk of specific complications (Rossing, 2018). According to the proposed classification, the sub-groups can be defined as: (1) SAID: This is the least common subtype (6.4%) and traditionally classified as T1D. These patients had an early onset of disease and were positive for GADAs, had low BMI and were dependent on exogenous insulin (Abegunde et al., 2007). (2) SIDD: these defined as a group of patients who showed insulin deficiency and were GADAs negative. This group was at greatest risk of DR (Jingi et al., 2017). (3) SIRD: This group represented 15.3% of the whole cohort of participants. These patients had a high degree of insulin resistance and were likely to be overweight or obese and showed kidney damage more frequently than other groups. They also had a higher risk of non-alcoholic fatty liver

Abbreviations: 18R-/17S-HEPE, 18R-/17S-hydroecosapentaenoic acid; ABC-A/G, ATP-binding cassette-subfamily A/G; ACs, apoptotic cells; ACE, angiotensin-converting enzyme; AGE, advanced glycation end-product; AKI, acute kidney injury; ALX/FPR2, lipoxin/N-formyl peptide receptor-2; Apo, apolipoprotein; ATL, aspirin-triggered LX; ATLa, aspirin-triggered LX analog; BM, basement membrane; BMI, body mass index; BMP, bone morphogenetic protein; BRB, blood-retinal barrier; CAD, coronary artery disease; CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcome Study; CARDS, Collaborative Atorvastatin Diabetes Study; CCR, CC-chemokine receptor; CD, cluster of differentiation; ChemR23, chemerin-like-1; CTGF, connective tissue growth factor; CVD, cardiovascular disease; DAA, diabetes-associated atherosclerosis; DAMPs, damage-associated molecular patterns; DHA, docosahexaenoic acid; DKD, diabetic kidney disease; DPP-4, di-peptidyl peptidase-4; ECs, endothelial cells; ECM, extracellular matrix; eGRF, estimated glomerular filtration rate; EMT, epithelial-mesenchymal transition; EPA, eicosapentaenoic acid; ESRD, end stage renal disease; GADA, GAD autoantibody; GLP-1-RA, glucagon-like peptide-1 receptor agonist; GPCRs, G-protein coupled receptors; HDL, high density lipoprotein; HK-2, human proximal tubular epithelial; HO, heme-oxygenase; IHD, ischemic heart disease; IKK- β , inhibitor of nuclear factor kappa- β ; IRI, ischemia reperfusion injury; JAK/STAT, janus kinase/signal transducers and activators of transcription; LDL, low density lipoprotein; LDL-R, LDL-receptor; LO, lipoxygenase; LX, lipoxin; MaR, maresin; MARDs, mild age-related diabetes; M-CSF, macrophage colony-stimulating factor; MI, myocardial infarction; MMP, matrix metalloproteinase; MOD, mild obesity-related diabetes; NCCD, non-communicable chronic disease; NF- κ B, nuclear factor kappa beta; NLRP, NACHT, LRR and PYD domains-containing protein; Nrf2, nuclear factor (erythroid-derived 2)-like 2; ox-/ac-LDL, oxidized-/acetylated-LDL; PD, protectin; PDGF, platelet-derived growth factor; PMNs, polymorphonuclear neutrophils; PUFA, polyunsaturated fatty acid; RAAS, renin-angiotensin-aldosterone system; RAGE, receptor for advanced glycation end-product; RCT, reverse cholesterol transport; RF, renal fibrosis; ROS, reactive oxygen species; Rv, resolvins; SAID, severe autoimmune diabetes; SFA, saturated fatty acid; SGLT-2, sodium glucose cotransporter-2; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes; SMC, smooth muscle cell; SPM, specialized pro-resolving mediator; SR-A, class A-macrophage scavenger receptor; STZ, streptozotocin; T1D/T2D, type-1/type-2 diabetes; TF, tissue factor; TGF- β 1, transforming growth factor- β 1; Th, T helper; THBS-1, thrombospondin-1; TIE, tubulointerstitial fibrosis; TLR, toll-like receptor; VEGF, vascular endothelial growth factor.

disease (Dutta and Mukhopadhyay, 2018). (4) *MOD*: Around a fifth of all participants were classified in cluster 4. These patients typically had high BMIs but they did not show insulin resistance (Kahn et al., 2006). (5) *Mild age-related diabetes (MARD)*: Most of the patients (nearly 40%) in the cohort belonged to cluster 5. They were usually older adults with healthier metabolic profiles (including lower BMIs) than the other clusters (Ma et al., 2018).

Diabetes is associated with serious life-threatening and life limiting complications. Acute complications include hyperglycemia-induced ketoacidosis and hypoglycemia. The chronic vascular complications of diabetes have a massive impact on morbidity and mortality. These are classically defined as microvascular and macrovascular complications and reflect responses of susceptible individuals to hyperglycemia, dyslipidemia and hypertension associated with diabetes (Orban et al., 2018). The macrovascular complications include accelerated-CVD and accelerated-atherosclerosis, as discussed below (Duncan et al., 2003).

Complications of the microvasculature include retinopathy, neuropathy and nephropathy. DR is major cause of blindness in the working class (Duh et al., 2017). Diabetic neuropathy develops in almost half of all individuals with diabetes and the lifetime risk of lower limb amputation as much as 15% in certain populations. Diabetic neuropathy is a syndrome encompassing both somatic and autonomic branches of the peripheral nervous system, and, furthermore, contributes to the pathology of other diabetic complications, such as impaired wound healing and erectile dysfunction (Russell and Zilliox, 2014). As will be discussed in more detail below, DKD is the leading cause of ESRD (Piccoli et al., 2015). DKD typically develops over a long period (decades) and, importantly, it is a major risk factor for the development of macrovascular complications, including MI and stroke.

With best medical care the risk of major chronic complications for T1D are cited as 47% for retinopathy, 17% for nephropathy and 14% for CVD. These figures represent a lifetime risk. Figures for T2D are more complex. Although death rates are higher for people with diabetes, relative to age and sex matched cohorts, a recent study has shown that in the United States, whereas death rates for people with and without diabetes have fallen, the greatest decline in mortality was actually seen in those with diabetes, presumably reflecting improved management of glycemia, lipids and hypertension (Gregg et al., 2018). Moreover, in a United Kingdom study, patients with T2D initiated on metformin monotherapy had longer survival than did matched, non-diabetic controls (Bannister et al., 2014). However, the overall mortality in T2D is 60% higher than non-diabetic age and sex matched controls. One consideration on these data is that the lower rates reflect the relatively recent increase in incidence. Mortality is typically associated with chronic complications, such as DKD which develops over decades. The increased incidence may represent a timebomb of diabetes-associated mortality. Indeed, among adults with diabetes, in the United States the prevalence of ESRD has shown the smallest decrease as compared to other diabetic complications (Gregg et al., 2014). To an extent this may reflect the efficacy of preventing atherosclerosis,

resulting in increased survival and increased opportunity to develop complications as a consequence of chronic exposure to hyperglycemia. As discussed below, it also reflects the need for therapeutic interventions to specifically target DKD and associated-RF.

This review will focus on describing recent advances in the understanding and elucidation of the underlying mechanisms and in exploring the potential of novel therapeutic approaches for treating diabetes-accelerated atherosclerosis, kidney disease and retinopathy, by using animal and human studies. For more comprehensive reviews of diabetic complications, readers are referred to several excellent recent reviews (Forbes and Cooper, 2013; Papatheodorou et al., 2016; Lotfy et al., 2017).

DIABETES-ASSOCIATED ATHEROSCLEROSIS

Definition of DAA

Atherosclerosis is a leading cause of vascular disease worldwide and accounts for about 50% of all deaths in westernized societies and 30% in developing countries (Fuster and Kelly, 2011). Its major clinical manifestations include IHD and ischemic stroke (Lusis, 2000), being, respectively, the world's first and third causes of death (Barquera et al., 2015).

The strong association between diabetes, low-grade inflammation and atherosclerosis, accounts for one of the major diabetes complications worldwide: DAA (Duncan et al., 2003). Approximately 50% of patients with T2D die prematurely of a cardiovascular cause, and a further 10% die of renal failure (van Dieren S et al., 2010).

Since Ross and Libby redefined atherosclerosis as a progressive, chronic, dyslipidemic and also "inflammatory" disease, advances in basic knowledge of this multifactorial disease defined a key for inflammation in mediating all the phases of athero-progression (Ross, 1999; Libby et al., 2002). Among the numerous markers of high- and low-grade inflammation, C-reactive protein predicts the risk of atherosclerotic complications (see below) (Ross, 1999; Libby et al., 2002). In the recent trial of anti-IL-1 β antibody in a large population of high risk atherosclerosis patients (CANTOS), the intervention reduced inflammation and cardiovascular events. Greatest impact was seen in those with highest baseline markers of systemic inflammation. However, its efficacy was similar in those with and without diabetes and, despite decreasing inflammatory markers, did not reduce the incidence of diabetes (Weber and von Hundelshausen, 2017; Everett et al., 2018).

Risk Factors for DAA

The main modifiable risk factors for atherosclerosis have been identified, and they include, but are not limited to, smoking, adiposity, blood pressure, high levels of BMI, high level of LDL, low level of HDL and diabetes (Herrington et al., 2016). T2D is associated with an increased risk of CVD. A role for the lipid-lowering therapy with statins for the primary prevention of CVD in diabetes was demonstrated in CARDS, the first large primary prevention study determining the action of statins in

T2D patients, e.g., the efficacy of atorvastatin in preventing disease irrespective of LDL levels (Colhoun et al., 2004). Over the past two decades, developed countries have been able to reduce the contribution of the above mentioned risk factors to mortality, whereas developing countries show an increasing trend due to high BMI and glucose (Barquera et al., 2015).

More recently, the prevalence of coronary atherosclerosis was found to be higher in diabetic than in non-diabetic patients and to be similar for diabetic individuals without clinical CAD and non-diabetics with clinical CAD, implying that prevention measures for asymptomatic diabetic individuals should be similar to secondary preventive approaches among non-diabetic population, as an aggressive prevention measure for atherosclerosis in all diabetic patients, independently of their CAD symptoms (Goraya et al., 2002).

Cellular Pathogenetic Mechanism of DAA

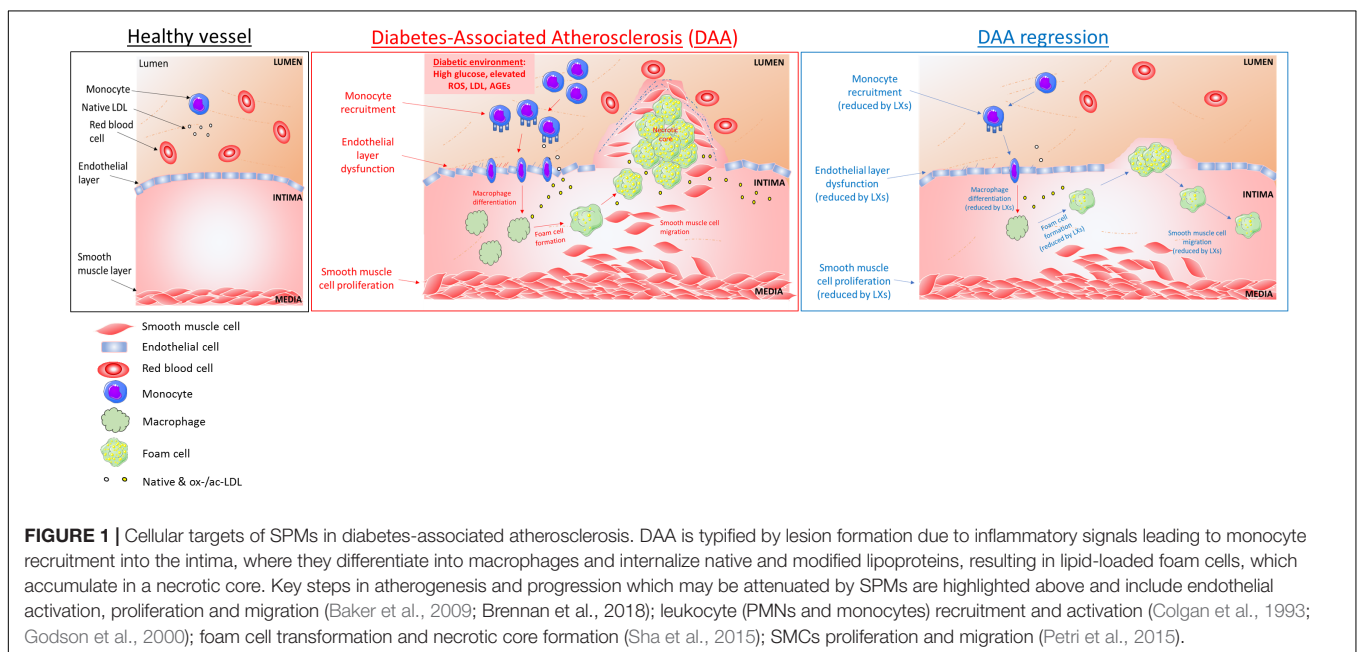
The pathogenesis of atherosclerosis shares several features with other inflammatory diseases, including the infiltration of monocytes and subsequent differentiation to macrophages in response to locally generated signals (Scrivo et al., 2011). At cellular and subcellular levels, inflammatory stimuli or a disturbed blood flow induce endothelial dysfunction (Cunningham and Gotlieb, 2005), altering the homeostatic equilibrium depicted in **Figure 1** (right). This vasoreactivity allows lipoproteins apo-B to enter the intima and bind to proteoglycans which trap the LDL particles and increase their susceptibility to oxidation, acetylation and hydrolysis by secretory phospholipases thus amplifying the inflammatory response, characterized by chemokine secretion and adhesion molecules expression on ECs surface. These modifications of lipoprotein induce their aggregation in complexes and

subsequent retention, and, additionally, induce monocytes recruitment, a crucial step in early phases of atherogenesis (Lusis, 2000).

Once chemoattracted to the inflammatory injury area, the monocyte undergoes a series of processes that allow cell locomotion (i.e., rolling, adhesion, polarization, crawling) to reach the endothelial transmigration sites, in proximity of low shear stressed athero-prone regions, where blood flow is disturbed, such as bifurcations of arteries (Cunningham and Gotlieb, 2005). Once transmigrated and eventually infiltrated into the intima layer, monocytes differentiate into macrophages in response to locally produced factors, such as M-CSF (Moore and Tabas, 2011). This program of differentiation includes upregulation of class A- macrophage scavenger receptor (SR-A), CD 36 (CD-36) and other cell surface receptors, to facilitate ox-LDL or ac-LDL uptake: in physiologic conditions, this process allows an efficient removal of excessive lipids from the blood circulation ("scavenging" action of macrophage). When homeostasis fails, dysregulation of this phenomenon leads to uncontrolled accumulation of lipids and cholesterol derivatives in macrophages, and their transformation into foam cells in the subintima endothelial layer (Kunjathoor et al., 2002).

Lipid-loaded foam cells, cellular debris, calcium deposits and connective tissue contribute to generate the so-called *fatty streak* (a hallmark and first sub-clinical sign of atherosclerosis), increasing inflammation and inducing necrosis and foam cell death. As the lesion grows invade both the luminal space and the intima. The necrotic area is confined within a fibrous cap made of connective tissue, composed of SMCs and collagen. Fibrous cap atheromas are the first clinically detectable atherosclerotic lesions (Li and Glass, 2002).

As the lipid core increases in size, the fibrotic cap is invaded by macrophages and lymphocytes, inducing the thinning of the cap. The mechanism by which a sustained macrophage



457 invasion weakens the fibrous cap involves phagocytosis of the
 458 ECM and the release of proteolytic enzymes (i.e., plasminogen
 459 activators and matrix metalloproteinases, MMPs). The thinned
 460 fibrous cap is prone to rupture, exposing the inflammatory and
 461 thrombogenic molecules (TF, collagen) of the lipid core, highly
 462 increasing the risk of thrombosis (Pepine, 1998).

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Molecular Pathogenetic Mechanisms of DAA

467 As above stated, diabetes accelerates atherosclerosis, contributing
 468 to higher rates of mortality and morbidity among diabetic
 469 patients. The molecular mechanisms behind this likely reflects
 470 increased inflammation and decreased blood flow (Abe and Berk,
 471 2013) but are not fully understood. Several possible triggers have
 472 been thus far hypothesized, including hyperglycemia, insulin
 473 resistance, increased activation of PDGF-dependent pathways,
 474 increased level of TF or decreased level of HDL, and AGEs
 475 and their receptors (RAGE) signaling activation (Beckman
 476 et al., 2002). Insulin and hyperglycemia play key roles in
 477 distinct phases of disease progression, *via* different mechanisms
 478 and differentially affecting the three major cell types: SMCs,
 479 macrophages and ECs (Bornfeldt and Tabas, 2011).

480 It has been hypothesized that, in advanced plaques, insulin
 481 resistance may promote apoptosis of PMNs, SMCs, and
 482 macrophages. In particular, death of SMCs can lead to the
 483 thinning of the fibrotic cap, whereas death of macrophages is
 484 associated with a defective phagocytic clearance of the cells
 485 (*efferocytosis*), promoting plaque necrosis (Greenlee-Wacker,
 486 2016). These processes converge to precipitate plaque rupture
 487 and acute thrombotic vascular occlusion (Brophy et al., 2017).
 488 A relation between diabetes obese-induced adiposity and
 489 atherosclerosis in young adults have been observed (McGill et al.,
 490 1995). Elevated SFAs has been associated with obesity and insulin
 491 resistance (Funaki, 2009) and causes defective *efferocytosis* of
 492 apoptotic macrophage (Li et al., 2009), subsequently causing
 493 a secondary cellular necrosis and inflammation amplifying the
 494 plaque necrosis (Thorpe and Tabas, 2009). The combined pro-
 495 apoptotic effect of macrophage insulin resistance and the anti-
 496 efferocytic effect of SFAs may create a “perfect storm” for plaque
 497 necrosis, as proposed by Bornfeldt and Tabas (2011).

498 Hyperglycemia accelerates formation of early/mid stage
 499 lesions of atherosclerosis by promoting an inflammatory
 500 phenotype of which adhesion molecule expression in ECs
 501 is a hallmark. Increased flux through the aldose reductase
 502 pathway accelerates glucose metabolism and generates ROS.
 503 Increased adhesion molecule expression leads to increased
 504 monocyte/macrophage accumulation and atherogenesis. In
 505 SMCs, a principal effect of increased glucose uptake appears to
 506 be increased secretion of the monocyte chemoattractant protein-
 507 1, a chemokine which acts in concert with ECs. This leads
 508 to an increased production of endothelium-derived contracting
 509 factors, which oppose the protective activity of nitric oxide
 510 (Meininger et al., 2000; vanDam et al., 2000). Ultimately, this
 511 leads to greater recruitment of monocytes into the growing
 512 lesion (Bornfeldt and Tabas, 2011), thereby further contributing
 513 to an enhanced inflammatory response. Those events have

514 been shown to promote adventitial inflammation and *vasa*
 515 *vasorum* neovascularization in experimental models of diabetic
 516 atherosclerosis. In particular, over the past two decades, the
 517 work from Cosentino and Luscher (1998) has established the
 518 strong relationship between hyperglycemia, oxidative stress and
 519 inflammation, together with an increased risk of CVD in T2D
 520 (Beckman et al., 2013; Paneni et al., 2013). Very recently, their
 521 studies demonstrated epigenetic regulation of immune-metabolic
 522 pathways to increased inflammation, neovascularization and
 523 intraplaque hemorrhage in human diabetic atherosclerosis
 524 (Guzik and Cosentino, 2018).

525 Insulin and hyperglycemia are not the only possible factors so
 526 far correlated to the underlying pathogenetic mechanism of DAA.
 527 Hyperglycemia enhances shear stress-induced platelet activation
 528 (Gresele et al., 2003). PDGF has been shown to play a major role
 529 in the pathology of vascular diseases. Inhibition of PDGF receptor
 530 activation attenuates DAA in experimental models (Lassila et al.,
 531 2004).

532 The inflammatory component of microangiopathic processes
 533 is independently associated with plaque rupture, leading to
 534 coronary thrombosis. TF, the most potent trigger of the
 535 coagulation cascade, is increased in diabetic patients with
 536 poor glycemic control. Circulating TF microparticles are also
 537 associated with apoptosis of plaque macrophages, closing the link
 538 among inflammation, plaque rupture and blood thrombogenicity
 539 (Fallon et al., 1997; Singh et al., 2012).

540 AGE/RAGE signaling has been a well-studied cascade in
 541 many different disease states, particularly diabetes. It heavily
 542 influences both cellular and systemic responses to increase bone
 543 matrix proteins through activation of PKC, p38 MAPK, TGF β ,
 544 NF κ B and ERK1/2 signaling pathways in both hyperglycemic
 545 and calcification conditions. AGE/RAGE signaling has been
 546 shown to increase oxidative stress and to promote diabetes-
 547 mediated vascular calcification through activation of NADPH
 548 oxidase-1 and decreased expression of superoxide dismutase-1.
 549 AGE/RAGE signaling in diabetes-mediated vascular calcification
 550 is also attributed to increased oxidative stress resulting in the
 551 phenotypic switch of SMCs to osteoblast-like cells in AGEs-
 552 induced calcification (Kay et al., 2016). HDL, responsible for
 553 free cholesterol removal, are reduced in patients with insulin
 554 resistance and diabetes, conditions for which the role of obesity
 555 is highly detrimental (Rashid and Genest, 2007; Barter, 2011). In
 556 addition to their role as lipid lowering agents, *via* inhibition of
 557 3-hydroxy-3-methylglutaryl coenzyme A reductase, pleiotropic
 558 responses to statins may include reduction of SMCs proliferation,
 559 as observed in *in vitro* and *ex vivo* models (Fleg et al., 2008).

Current Therapies in DAA

560 There are currently no available therapies for the regression
 561 of atherosclerosis (Fuster et al., 1998). Therefore, new
 562 therapeutic targets are needed in order to offer an alternative
 563 type of intervention to invasive surgery, such as stenting
 564 or endarterectomy. Current therapies in DAA adopted
 565 antiplatelet/anticoagulant therapy, stabilizing the plaque
 566 (Engelberg et al., 1956; Colwell, 1997), including the use of
 567 low-dose aspirin (75–162 mg/day) for secondary prevention
 568 of cerebrovascular and cardiovascular events in all diabetic
 569
 570

571 patients (Angiolillo, 2009). Evidence that LDL causes CVDs is
572 overwhelming. It has also been proven beyond all doubt that
573 lowering the level of LDL using statins reduces cardiovascular
574 risk. However, many people remain at high risk even when
575 their level of LDL has been reduced by aggressive treatment
576 with statins. One reason for this residual risk can be a low
577 level of HDL, an independent, inverse predictor for CAD. It
578 has therefore been suggested that raising the level of HDL
579 should be considered as a therapeutic strategy for reducing the
580 residual cardiovascular risk that persists in some people, despite
581 aggressive LDL-cholesterol lowering with statins. HDL particles
582 have several functions with the potential to protect against
583 arterial disease, the best known of which relates to their ability to
584 promote cholesterol efflux from macrophages in the artery wall.
585 However, HDLs have several additional protective properties that
586 are independent of their involvement in cholesterol metabolism.
587 For example, they have properties that reduce oxidation, vascular
588 inflammation and thrombosis, improve endothelial function,
589 promote endothelial repair, enhance insulin sensitivity and
590 promote insulin secretion by pancreatic β islet cells (Barter,
591 2011). These beneficial effects may be responsible for coronary
592 plaque stabilization in patients treated with those molecules
593 which can up regulate HDL expression including Apo-A1 or
594 peroxisomal proliferator-activated receptors agonists, holding
595 great promise in the treatment of diabetic atherosclerosis.

596 The Regression of DAA

597 The regression of existing lesions is the holy-grail in management
598 of atherosclerosis. Over the past two decades major advances have
599 been made to this end. Fisher's lab and his collaborators Young,
600 Hazen, Smith and Moore have firmly established the principle
601 that regression of atherosclerosis is a possible therapeutic goal
602 (Fisher, 2016).

603 Although monocytes are recruited into the plaque during
604 its growth, they also have the capacity to emigrate from
605 atherosclerotic lesion. Using murine models of regression,
606 including the "transplantation mouse," a transplant model in
607 which plaque-bearing aortic segments are transferred into
608 normolipidemic mice (Reis et al., 2001); the "reversa mouse,"
609 a genetic "switch" model in which LDL production can be
610 conditionally reduced in LDL-R^{-/-} mice (Feig et al., 2011); and
611 acute treatment models, in which Apo-E^{-/-} mice are injected
612 either with Apo-A1 (Hewing et al., 2014), with a microsomal
613 triglyceride transfer protein inhibitor or with an anti-microRNA
614 (miR) (anti-miR-33) (Rayner et al., 2011; Moore et al., 2013;
615 Distel et al., 2014) a decrease in plaque size and, consequently,
616 regression of pre-existing atherosclerosis was demonstrated
617 (Llodra et al., 2004; Randolph, 2008; Feig et al., 2009). A possible
618 explanation of the reduction in CD68⁺ macrophage cell content
619 is that monocytes can enter the lymphatic system, reaching
620 the lymph nodes, or they can migrate across the arterial
621 endothelium toward the artery lumen to directly enter the
622 circulating bloodstream (Llodra et al., 2004; Randolph, 2008).
623 The main processes involved in atherogenesis are also the main
624 target for regression, namely, the retention of apo-B-containing
625 lipoproteins in the arterial wall and the reaction of macrophages
626 to these particles (Williams and Tabas, 2005). The resulting foam
627

628 cells secrete pro-inflammatory cytokines and chemokines, as
629 well as retention factors that amplify the inflammatory response
630 and promote macrophage *chemostasis*. These accumulating
631 macrophages experience endoplasmic reticulum stress, which, if
632 prolonged, results in apoptosis. This cell death, coupled with
633 defective *efferocytosis*, due to an uncontrolled lipid accumulation,
634 in which essentially SFAs decrease the fluidity of the plasma
635 membrane, leads to the formation of the necrotic core that is
636 characteristic of advanced plaques (Funaki, 2009; Thorp and
637 Tabas, 2009; Bornfeldt and Tabas, 2011).

638 The key mechanisms that promote regression are: lipid unload
639 of the foam cell and promotion of RCT, *via* upregulation of the
640 efflux protein ABCA-1 expression on plaque macrophages and
641 the subsequent cholesterol efflux toward exogenous acceptors
642 (i.e., Apo-E-containing HDL) (Chinetti-Gbaguidi et al., 2011);
643 a decrease in the expression of retention factors (Brodsky
644 and Fisher, 2008); a reduced monocyte recruitment *via*
645 their transformation in monocyte-derived dendritic cells and
646 subsequent upregulation of CC-chemokine receptor (CC-R)-
647 7 on their surface, which allow emigration to the lymphatic
648 system, restoring permeabilization and reducing lymphatic vessel
649 fibrosis (Ivanov et al., 2016). Finally, the retention/migration
650 factors contributing to macrophage loss from the plaque, through
651 reverse transmigration to the lumen or through trafficking to the
652 adventitial lymphatic (Potteaux et al., 2011).

653 In the context of diabetes, as depicted in **Figure 1** (central
654 panel), regression of atherosclerosis is impaired. High glucose
655 levels modulate LXR-dependent gene expression, by inhibiting
656 the LXR-dependent expression of ABCA1, but not ABCG1
657 (Hussein et al., 2015) and by inducing miR-33, a key negative
658 regulator of the RCT factors, ABCA1 and HDL (Wijesekara
659 et al., 2012). In mouse models of insulin-deficient diabetes, it
660 has been shown that leukocytosis (monocytosis and neutrophilia)
661 is hyperglycemia-dependent. The myelopoiesis is driven by
662 increased expression of certain DAMPs, specifically, signaling
663 through the pattern recognition AGE/RAGE. The relevance
664 to human health and disease is suggested by the correlation
665 between serum S100A8/S100A9 (the associated DAMPs) and the
666 incidence of CAD in a subset of T1D patients from the Pittsburgh
667 EDC study, highlighting the potential importance of glucose
668 control and lipid-lowering therapy as strategies to promote
669 regression of atherosclerosis in diabetics and also suggesting
670 a number of therapeutic targets, including disruption of the
671 S100A8/S100A9-RAGE signaling axis (Nagareddy et al., 2013).

673 DIABETIC KIDNEY DISEASE

675 Definition of DKD

676 DKD typically develops over many decades. It is characterized
677 by progressive proteinuria (microalbuminuria 30–299 mg/24 h
678 to macroalbuminuria > 300 mg/24 h) with a subsequent decline
679 in glomerular filtration reflected by increased serum creatinine
680 (National Kidney Foundation, 2002). The pathophysiology
681 of DKD typically reflects the convergence of hemodynamic,
682 metabolic and inflammatory insults in susceptible individuals
683 (Harjutsalo and Groop, 2014). Current interventions focus on
684

685 tight glycemic control and RAAS blockade by ACE inhibition or
 686 angiotensin receptor antagonism to dilate the efferent arteriole
 687 and reduce glomerular hypertension. At best, these interventions
 688 slow the progress of disease (Forbes and Cooper, 2013). There
 689 is a growing appreciation that oxidative stress and inflammation
 690 are key drivers of DKD and may be appropriate targets
 691 for therapeutic intervention. Circulating inflammatory cytokine
 692 levels correlate with albuminuria and elevated levels of soluble
 693 TNF-receptor-1 is an independent predictor of decline in renal
 694 function (Krolewski et al., 2014).

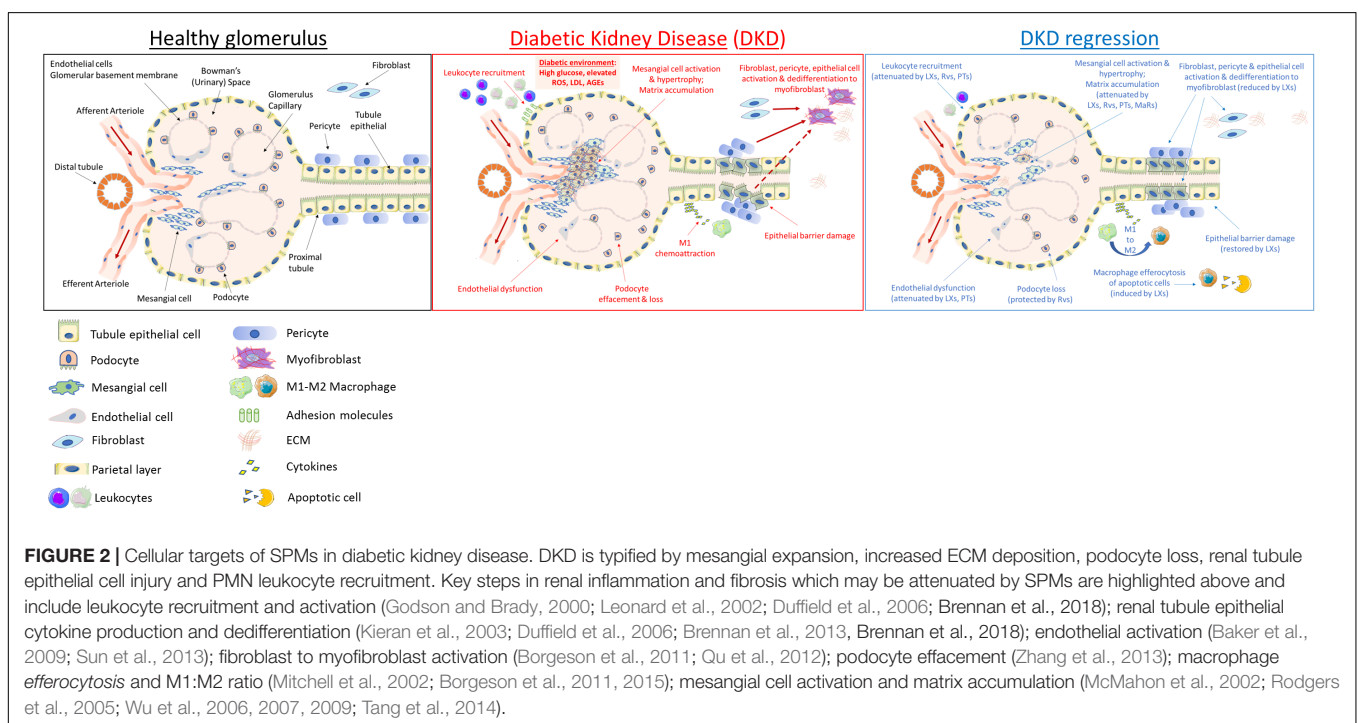
696 Cellular Pathogenetic Mechanisms of 697 DKD

699 The physiological functionality of a healthy glomerulus is
 700 outlined in **Figure 2** (left). Changes in renal hemodynamics,
 701 reflecting glomerular and systemic hypertension, arise early
 702 in DKD and lead to glomerular hyperfiltration. RAAS
 703 activation leads to increased angiotensin II and endothelin-
 704 1 causing efferent arteriolar vasoconstriction and hyperfiltration.
 705 Glomerular damage is characterized by podocyte effacement
 706 resulting in proteinuria. Renal hypertrophy is also observed in
 707 DKD reflecting accumulation of mesangial matrix, glomerular
 708 BM thickening and tubular hypertrophy. As matrix expands, it
 709 accumulates to form Kimmelstiel–Wilson nodules, a pathological
 710 feature of DKD. TIF is considered the major determinant
 711 of progression of DKD (Duffield, 2014). The mechanisms
 712 underlying TIF have been exhaustively investigated in the
 713 context of chronic kidney disease, including DKD (Leaf and
 714 Duffield, 2017). At a cellular level, several mechanisms have
 715 been proposed including activation of resident fibroblasts to
 716 matrix producing myofibroblasts, detachment of pericytes and

742 matrix production, recruitment of fibrocytes from bone marrow
 743 and EMT (Kalluri and Weinberg, 2009). Whereas the role of
 744 EMT in TIF has been questioned the loss of several epithelial
 745 cell markers (de-differentiation) has been observed together
 746 with expression of pro-fibrotic mediators such as CTGF and
 747 the TGF β 1 activator THBS-1 (Thiery et al., 2009). Experimental
 748 evidence suggests that partial EMT and chronic inflammation
 749 converge to create a profibrotic *milieu* facilitating collagen
 750 production by fibroblasts and recruited hematopoietic cells in
 751 the kidney (Zeisberg and Duffield, 2010; Buchtler et al., 2018).
 752 Glomerulosclerosis and TIF lead eventually to organ failure
 753 and a requirement for renal replacement therapy (hemodialysis
 754 or transplantation). Efforts to directly target inflammation in
 755 DKD have included manipulating chemokine and cytokine
 756 signals in T2D, such as antagonism of CCR2/CCR5 (Huh et al.,
 757 2018).

759 Molecular Pathogenetic Mechanisms of 760 DKD

762 As depicted in **Figure 2** (central panel), high glucose exerts
 763 specific toxic effects on the resident cells of the kidney, including
 764 specialized parietal epithelial cells (podocytes), mesangial
 765 cells, endothelia, fibroblasts and epithelia driving cellular de-
 766 differentiation (Eddy and Neilson, 2006; Liu, 2011). Many of
 767 these responses are driven by autocrine and paracrine mediators
 768 released by target cells and infiltrating monocytes/macrophages,
 769 as typified by responses to TGF- β 1 and its downstream targets,
 770 including CTGF (Murphy et al., 1999; Strutz et al., 2000; Boor
 771 and Floege, 2011). Hyperglycemia leads to ROS production and
 772 activation of inflammatory responses including NF- κ B and janus
 773 kinases and signal transducer and activator of transcription



799 proteins (JAK-STAT) activation and subsequent downstream
800 cytokine production (Sifuentes-Franco et al., 2018).

801 802 **Current Therapies in DKD**

803 Numerous large scale genome-wide association studies have
804 been carried out in DKD over recent years (Sandholm et al.,
805 2014; Ahlqvist et al., 2015; Teumer et al., 2015; Wuttke and
806 Köttgen, 2016; van Zuydam et al., 2018). These studies have
807 frequently implicated inflammatory pathways in the pathogenesis
808 of DKD. Such genetic validation of therapeutic targets includes
809 the JAK-STAT pathway. STAT-1,3 activation is observed in
810 renal biopsies from people with DKD (Berthier et al., 2008).
811 Baricitinib, a small molecule JAK-STAT inhibitor, has shown
812 efficacy in a small scale clinical trial. Treatment with baricitinib
813 was associated with decreased inflammatory biomarkers (e.g.,
814 urinary chemokine CCL-2, plasma soluble tumor necrosis factor
815 receptor-1, intracellular adhesion molecule-1 and serum amyloid
816 A). Baricitinib decreased albuminuria in participants with T2D
817 and DKD (Tuttle et al., 2018).

818 Glucose stimulates inflammasome assembly, caspase-1
819 activation and IL-1 β release (Schroder et al., 2010). IL-1 β
820 activation by the NACHT, LRR and PYD domains-containing
821 protein (NLRP) inflammasome is an important component of
822 CKD (Vilaysane et al., 2010). Blockade of IL-1 β activity in post
823 MI patients with CKD reduced the risk of adverse cardiovascular
824 events among those with CKD (Ridker et al., 2017). As described
825 above, the CANTOS trial targeted IL-1 β in atherosclerosis
826 patients and the intervention reduced inflammation and
827 cardiovascular events (Ridker et al., 2011). Comparable effects
828 were observed among those with baseline albuminuria or
829 diabetes. Canakinumab, however, was without effect on serial
830 measures of eGFR, creatinine, the urinary albumin:creatinine
831 ratio or reported adverse renal events during trial follow-up
832 (Ridker et al., 2018).

833 Despite the identification of numerous drivers of fibrosis,
834 such as the TGF superfamily, thus far efforts to target RF
835 *per se* have been unsuccessful. A recent double blind phase
836 II study assessed whether modulating TGF- β 1 activity with a
837 TGF- β 1-specific, humanized, neutralizing monoclonal antibody
838 was effective in slowing renal function loss in patients with
839 diabetic nephropathy on RAAS inhibition treatment over a 12-
840 month period. No significant impact on disease progression
841 was observed (Voelker et al., 2017). Other approaches have
842 focused on the balance between BMP family agonist-antagonist
843 activities and promoted BMP-7 and or small peptide mimetics,
844 such as THR-123 (Ali and Brazil, 2014; Tampe and Zeisberg,
845 2014; Brazil et al., 2015). However, some of these data have been
846 controversial (Sugimoto et al., 2012). Systemic administration
847 of BMP-7 protein is problematic due to the low availability in
848 the kidney, explaining the need for a huge amount of BMP-7
849 for its reno-protective action, which might exert adverse effects
850 elsewhere (Vukicevic et al., 1998; Yanagita, 2012). CTGF/CCN2
851 has also been proposed as a potential target (Falke et al.,
852 2014, 2017). Other therapeutic approaches which have been
853 proposed in the context of DKD include attenuation of NF-
854 κ B signaling (Lee et al., 2012), breakdown of AGEs (Rabani
855 and Thornalley, 2018) or RAGE antagonism (Bongarzone

et al., 2017). In this context, bardoxolone methyl is a novel
synthetic triterpenoid belonging to the antioxidant inflammation
modulator class. Antioxidant inflammation modulators potently
induce the antioxidant and cytoprotective transcription factor
Nrf2, reduce the pro-inflammatory activity of the IKK- β /NF-
 κ B pathway, increase the production of antioxidant and
reductive molecules, and decrease oxidative stress, thereby
restoring redox homeostasis in areas of inflammation. Activation
of anti-oxidant responses *via* Nrf2 and inhibition of NF-
 κ B by the triterpenoid bardoxolone methyl reduces oxidative
stress, inflammation and promotes mitochondrial function in
numerous experimental models of CKD, including DKD (Pergola
et al., 2011). Unfortunately, clinical trials of bardoxolone methyl
in patients with stage 4 CKD and T2D were prematurely
terminated for safety concerns (Tayek and Kalantar-Zadeh,
2013). Bardoxolone methyl treatment was associated with
approximately double the risk of heart failure as placebo.
Subsequent analysis suggests that these data did not represent
toxicity *per se* and that further development of this compound
may be warranted with more careful patient selection (Chin et al.,
2014, 2018).

877 878 **Novel Therapeutic Approaches in DKD**

879 It is important to note some recent advances that suggest
880 renoprotection in response to newer therapeutics which
881 regulate blood glucose and reduce cardiovascular risk in T2D.
882 Intriguingly these reno-protective responses may be independent
883 of glucose lowering. Such interventions include the incretin-
884 based therapeutics (GLP-1-RAs, e.g., liraglutide or DPP-4
885 inhibitors and SGLT-2 inhibitors) enhancing glycemic control
886 with a low risk of hypoglycemia. However, the use of these agents
887 is limited in those with significant renal impairment. A recent
888 trial treatment with liraglutide, a GLP-1 analog, was associated
889 with a 22% lower incidence of doubling serum creatinine,
890 persistent macroalbuminuria, development of ESRD or death
891 from renal disease relative to controls (Mann et al., 2017). Similar
892 data have been reported for other GLP-1 receptor agonists and
893 for DPP-4 inhibitors which inhibit breakdown of endogenous
894 GLP-1. SGLT-2 inhibitors suppress glucose reabsorption by
895 the proximal tubule and therefore increase glucose excretion.
896 The SGLT-2 inhibitors target reabsorption of both glucose and
897 sodium as a result there is increased sodium delivery to the
898 *macula densa* activating tubule-glomerular feedback afferent
899 arteriolar vaso-modulation, resulting in increased renal blood
900 flow and decreased glomerular hyperfiltration. SGLT-2 inhibition
901 is associated with lower rates of albuminuria and lowering rates
902 of eGFR decline (Tomkin, 2014). Intriguingly, bariatric surgery
903 in T2D appears to have specific reno-protective effects which
904 may relate to enhanced GLP-1 responsiveness (Docherty and
905 le Roux, 2014). Miras et al. (2015) reported that, 1-year post-
906 bariatric surgery, a decrease urinary albumin/creatinine ratio was
907 observed whereas no benefit was seen on other microvascular
908 complications, i.e., retinopathy or neuropathy. SGLT-2 inhibitors
909 and GLP-1 targeting drugs attenuate inflammatory responses
910 in DKD. As we will discuss below, we propose that exploiting
911 the bioactivity of endogenous lipid modulators that promote
912 the resolution of inflammation and suppress fibrosis is a novel

913 therapeutic paradigm worthy of consideration as adjuvant
914 therapy in DKD.

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THE ROLE OF MACROPHAGE IN DIABETES COMPLICATIONS

920 As described, macrophages are key players in atherosclerotic
921 lesions, regulating the local inflammatory milieu and plaque
922 stability by the secretion of many inflammatory molecules,
923 growth factors and cytokines (Wolfs et al., 2011). The
924 macrophage paradigm classically reflects the heterogeneity of
925 their monocyte progenitor: alternative crawling monocytes
926 continuously patrol the endothelium of blood vessels in
927 the steady state. The patrolling monocytes rarely extravasate
928 in the steady state. In contrast, during inflammation or
929 infection, classical monocytes are the first to extravasate when
930 inflammation signaling occurs, and, within few hours they
931 differentiate in M1 “pro-inflammatory macrophages,” induced
932 by $\text{INF}\gamma$ + LPS or by TNF α , characterized by a high
933 phagocytic profile. At later stages of inflammation, non-classical
934 monocytes (or *non-phlogistic* monocytes) *trans*-migrate and
935 initiate a differentiation program into ‘M2’-like macrophages,
936 which play a role in resolving of inflammation and tissue repair
937 (Geissmann et al., 2008). M2 macrophages can polarize toward
938 different phenotypes according to various stimuli present in
939 their surrounding micro-environment (Mosser and Edwards,
940 2008) and to their distinct gene expression profiles (Mantovani
941 et al., 2004). In particular, “M2a” or “*alternative*” macrophage
942 is the product of Th2 activation (by IL4 and IL13 cytokines
943 or fungal and helminth infections) and is responsible for a
944 type II inflammatory response (consisting in killing parasites
945 and inducing a Th2 response to allergy). “M2b” or “*type*
946 *II*” macrophage is elicited by IL-1 receptor ligands, immune
947 complexes and LPS, triggering the activation of Th2 system.
948 “M2c” or “*deactivated*” macrophage is induced by IL10, TGF- β
949 and glucocorticoids and is mainly immunoregulatory, through
950 matrix deposition and tissue re-modeling (Martinez and Gordon,
951 2014). A fourth type, “M2d,” or “*angiogenic*” macrophage is
952 elicited by IL-6 and adenosine and is mainly involved in wound
953 healing (Ferrante and Leibovich, 2012). However, recent findings
954 provide evidence for proliferation of local macrophages or *trans*-
955 differentiation from other vascular cells as alternative sources
956 (Nagenborg et al., 2017). In particular, it has been shown that
957 cholesterol-loading induces the *trans*-differentiation of SMCs to
958 macrophage-like cells (Rong et al., 2001) and more recently, it
959 has been shown that approximately 50% of foam cells might have
960 a SMC origin (Allahverdian et al., 2014). Linear tracing studies
961 from Randolph’s lab have shown that tissue-specific factors
962 drive highly specialized macrophage functions irrespective of
963 their ontological origin, suggesting tremendous plasticity and
964 redundancy in the mononuclear phagocyte system. Whether
965 embryonic and adult macrophages possess specialized roles has
966 yet to be formally tested. However, the conceptual understanding
967 and genetic tools are now sufficiently developed to precisely
968 follow both embryonic and adult macrophage subsets in health
969 and disease, which should allow important and unanswered

970 questions in the field to be addressed. In order to develop novel
971 therapies, a critical future goal is to harness this new found
972 understanding that different macrophage lineages exist within
973 tissues and clarify whether these distinct lineages differentially
974 contribute to tissue damage and repair (Epelman et al., 2014).

Role of Macrophage in DAA

975
976
977 In the context of atherosclerosis, macrophages uniquely possess a
978 dual functionality, regulating lipid accumulation and metabolism
979 and sustaining the chronic inflammatory response, two well-
980 documented pathways associated with the pathogenesis of the
981 disease (Moore and Tabas, 2011).

982 Established atherosclerotic plaques from patients with
983 existing CAD undergoing carotid endarterectomy classified
984 as *symptomatic* (where the patient has experienced previous
985 ischemic events but without any CVD diagnosis) or *asymptomatic*
986 (where a patient has no history of ischemic events or
987 CVD) have been recently comprehensively histologically and
988 immunohistochemically characterized for their cellular content
989 and macrophage subsets of atherosclerotic lesion. Symptomatic
990 plaques were defined as highly hemorrhagically active and
991 the internal carotid was the most diseased segment, based on
992 the predominant prevalence of fibrotic and necrotic tissue,
993 calcifications, and hemorrhagic events. Immunohistochemical
994 analysis showed that both M1 and M2 macrophages are present
995 in human plaques. However, M2 macrophages were localized
996 to more stable locations within the lesion. Importantly, M1
997 markers and Th 1-associated cytokines were highly expressed in
998 symptomatic plaques, whereas expression of the M2 markers,
999 mannose receptor and CD163 and Th2 cytokines were inversely
1000 related with disease progression (de Gaetano et al., 2016).
1001 A strong relation between macrophage, mitochondria and
1002 glucose dysregulation has recently emerged in a number of
1003 studies from Fredman and Tabas (2017). Clearance of ACs by
1004 phagocytes (*efferocytosis*) prevents post-apoptotic necrosis and
1005 dampens inflammation. Mitochondrial fission in response to
1006 AC uptake is a critical process that enables macrophages to
1007 clear multiple ACs and to avoid the pathologic consequences of
1008 defective *efferocytosis in vivo* (Yurdagul et al., 2017).

Role of Macrophage in DKD

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1010
1011 In a renal context, macrophages constitute a major subset of the
1012 infiltrating inflammatory cells and their contribution to renal
1013 fibrogenesis is well established (Duffield, 2010). Macrophage
1014 infiltration has been found to correlate with TIF on kidney
1015 biopsies (Young et al., 1995), and to correlate negatively with
1016 outcome in CKD of diverse etiologies (Tinckam et al., 2005;
1017 Duffield, 2010). However, the role of macrophages in this context
1018 is not entirely clear-cut. M1 macrophages are recruited to the
1019 kidney at early time points in a murine IRI model, whereas at
1020 later time points, M2 macrophages predominate. Additionally,
1021 in this model, depletion of macrophages prior to IRI has been
1022 found to attenuate inflammation and TIF, whereas macrophage
1023 depletion after 3–5 days is shown to slow tubular cell proliferation
1024 and repair (Lee et al., 2011). Macrophages exhibit some plasticity,
1025 and may not remain committed to a single phenotype. As a
1026 component of the programmed resolution of inflammation, a

phenotypic change is triggered by altered cytokine and lipid mediator profiles in the microenvironment, and M1 phenotype macrophages thus ‘switch’ to a pro-resolving M2 phenotype (Nathan and Ding, 2010; Lee et al., 2011). In the context of chronic inflammation, or repeated injuries, the factors that determine if macrophages are predominantly reparative *versus* predominantly pro-inflammatory remain unclear. Directing more of the macrophage population toward a pro-resolving phenotype may provide a novel therapeutic approach in CKD. Although much of our current understanding of the ontogeny and functional plasticity of macrophages has been derived from murine models, it is important to note that, together with the above mentioned contribution from Randolph on macrophage ontogeny, a recent study in human heart reveals two populations of macrophages with different origins and functions: CCR2 expressing macrophages are recruited from bone marrow and proliferate and are functionally proinflammatory and abundant in regions of scarring, whereas macrophages lacking CCR2 are maintained by local proliferation and express genes associated with tissue repair (Bajpai et al., 2018).

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DIABETIC RETINOPATHY: A BRIEF OVERVIEW

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Definition, Pathogenesis, and Current Therapies

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Diabetic retinopathy (DR) is a microvascular complication of diabetes, clinically characterized by progressive alterations in the microvasculature that lead to retinal ischemia, neovascularization, altered retinal permeability and macular edema. It is currently the leading cause of blindness in the adult working population (Congdon et al., 2004; Yau et al., 2012).

The disease can be divided into two main stages – non-proliferative retinopathy and proliferative retinopathy distinguished by the absence or presence of abnormal neovascularization, respectively. The final stage “proliferative retinopathy” is characterized by neovascularization of the disk or iris or vitreous hemorrhage or retinal detachment (Wilkinson et al., 2003). Macular edema or “diabetic maculopathy” can occur at both the non-proliferative and proliferative stages as a result of fluid accumulation under the macula.

The pathological and morphological alterations associated with DR were long considered to be primarily microvascular in nature, as a result of hyperglycemia and the metabolic pathways it activates. The onset of clinically detectable DR is characterized by changes in the micro-vessels of the eye which includes thickening of the BM, loss of vascular permeability, loss of pericytes, capillary occlusions and microaneurysms (Xu et al., 2014).

However, recent studies have demonstrated that retinal neurodegeneration is a critical feature associated with the progression of the disease and may in fact precede the development of clinically detectable microvascular damage (Lieth et al., 2000; Puro, 2002).

Under pathological DR conditions, break-down of the BRB occurs as a result of the presence of increased levels of vascular

permeability factors, such as VEGF in the vitreous of the eye. The resulting “leaky” vasculature leads to increased albumin flux into the retina and fluid accumulation resulting in macular edema and possible vessel hemorrhage (Klaassen et al., 2013).

Thickening of the vascular BM occurs early in the disease and represents one of the first histologically detectable structural alterations. Several biochemical alterations contribute to BM thickening *in vivo*. Increased expression of the matrix components of the BM, including fibronectin (Roy et al., 1996), collagen IV (Roy et al., 1994) and laminin (Ljubimov et al., 1996) can be detected long before the formation of diabetic lesions. BM turnover is tightly regulated by the delicate balance of synthesis and degradation of BM components by MMPs, urokinases and their inhibitors. This balance is disturbed during DR (Kowluru et al., 2012).

Several interconnected biochemical pathways associated with hyperglycemia have been implicated in the pathogenesis of DR, including increased polyol pathway flux, increased hexosamine pathway flux and activation of protein kinase C. A crucial role is played by hyperglycemia-induced ROS production and AGEs formation (Forbes and Cooper, 2013). The retina is the most metabolically active tissue in the body, rendering it particularly susceptible to oxidative stress (Wu et al., 2014). Although all retinal cells express RAGE ubiquitously, retinal pericytes, in particular, have been shown to accumulate AGEs, contributing to BRB breakdown, which is in part accredited to pericyte loss, but also to AGE-induced leukocyte adherence to retinal ECs (Moore et al., 2003).

Growing consensus is emerging in the predominant role of inflammation in the pathogenesis of DR (Rubsam et al., 2018). The formation of AGEs and the activation of PKC have been implicated in the activation of pro-inflammatory mediators, such as NF- κ B, connecting hyperglycemic-induced oxidative stress to inflammation. An increase in a number of pro-inflammatory cytokines and chemokines has been demonstrated in both diabetic patients and models of experimental retinopathy (Doganay et al., 2002; Sato et al., 2009). Blocking the activity of pro-inflammatory cytokines (such as TNF- α , IL-6, and IL-1) has shown beneficial effects in models of retinopathy. An IL-1 receptor antagonist reduces inflammatory responses in a rodent model of T2D (Vallejo et al., 2014) while breakdown of the BRB was completely ablated in a TNF- α knockout diabetic mouse (Huang et al., 2011). Chemokines, such as MCP-1 and IL-8, are also elevated in diabetic eye disease and contributed to neovascularization and fibrosis (Yoshida et al., 2003). However, their expression was reduced by inhibitors of VEGF, suggesting that the action of both MCP-1 and IL-8 are mediated through pathways involving VEGF. Hyperglycemic conditions also drive increased expression of a number of growth factors (including VEGF and TGF β) mediating the retinal damage associated with DR, such as BM thickening, vascular permeability and neovascularization.

TNF- α and VEGF have received particular attention for their role in the vascular lesion and neovascularization associated with late stage retinopathy. Therefore, anti-TNF α (i.e., Infliximab) (Sfikakis et al., 2005) and anti-VEGF (i.e., Avastin)

1141 (Haritoglou et al., 2006) intravitreal therapies are standard
1142 clinical therapeutic options for the treatment of DR.

1143 Many of the agents developed to target the various
1144 biochemical pathways driven by hyperglycemia have had limited
1145 effect clinically, pointing to a need for new therapeutics targets.

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1147

1148 THE ROLE OF SPMs IN RESOLVING 1149 INFLAMMATION

1150

1151 The inflammatory response consists of two phases: initiation
1152 and resolution. The initiation phase is characterized by the site-
1153 specific accumulation and coordinated activation of a host of
1154 immune effector cells in an inflammatory cytokine and pro-
1155 inflammatory lipid mediator rich environment. Inflammation is
1156 critical in the host response to infection and injury, however,
1157 timely resolution is necessary for the restoration of tissue
1158 homeostasis, thereby limiting excessive tissue injury, preventing
1159 the development of a chronic inflammatory state (Serhan et al.,
1160 2007). Non-resolving inflammation is a major driver of disease.
1161 Multiple mechanisms ensure physiological resolution toward
1162 tissue homeostasis. Cells like macrophages switch phenotypes
1163 by secreting molecules like reactive oxygen intermediates, lipids
1164 and proteins which impact a cell from displaying pro- or an
1165 anti-inflammatory behaviors (Buckley et al., 2014).

1166 Whereas inflammation and its effective outcome, i.e., a return
1167 to homeostasis, were typically considered a manifestation of
1168 the passive dissipation of pro-inflammatory stimuli, including
1169 lipids, such as prostaglandins and leukotrienes, it is now clear
1170 that the resolution of inflammation is an active and dynamically
1171 regulated process reflecting responses to endogenously generated
1172 mediators, including cytokine and lipids (Godson and Brady,
1173 2000; Maderna and Godson, 2009; Serhan, 2014).

1174 The specialized SPMs are a family of endogenously produced
1175 pro-resolving lipid mediators derived from the metabolism of
1176 PUFAs, which include LXs, resolvins (Rvs), protectins (PDs)
1177 and MaRs. They were discovered by Serhan et al. (1984). LXs
1178 (*Lipoxygenase interaction products*) were firstly isolated in a
1179 human leukocyte (Serhan et al., 1984) and classified as derivatives
1180 of the $\omega 6$ fatty acid arachidonic acid (20:4, n-6). Rvs (*Resolution*
1181 *phase interaction products*) were firstly identified in a resolving
1182 inflammatory exudate in 2000 (Serhan et al., 2000), PDs (termed
1183 neuroprotectin D1 if generated in neural tissue for its protection
1184 in neurons, glial cells, and brain stroke; or protectin D1 for other
1185 tissue in 2004 (Bazan, 2005) and MaRs (*Macrophage mediator*
1186 *in Resolving Inflammation*) in 2009 (Serhan et al., 2009). Rvs,
1187 PDs and MaRs are classified as derivatives of $\omega 3$ fatty acids:
1188 specifically, Rvs can either form from the EPA (20:5, n-3) [RVs
1189 E-series] or from the DHA (22:6, n-3) [RVs D-series]; while, PDs
1190 and MaRs only derive from DHA. As their precursors, all these
1191 derivatives are classified as PUFAs and they demonstrated potent
1192 anti-inflammatory and immunoregulatory actions (Serhan et al.,
1193 2008).

1194 Within a few hours from barrier break, tissue injury or
1195 trauma, eicosanoids are crucial in initiating the cardinal signs
1196 of inflammation (redness, heat, pain and swelling). As part of
1197 the vascular response, leukocytes traffic to the site of injury.

The prostaglandins PGE₂ and PGI₂ (involved in vasodilation) 1198
and the leukotriene LTB₄ (involved in chemotaxis and adhesion) 1199
stimulate the migration of PMN to the tissue. In parallel 1200
to the PMN–monocyte sequence, lipid mediator composition 1201
of the inflammatory exudate switches class, from eicosanoids 1202
to SPMs, marking the beginning of the end of the acute 1203
inflammatory response. LXs are the first SPM to be locally 1204
produced, highlighting its role as “stop” signal to eicosanoid 1205
production (*exudate switch*), as firstly described by the work of 1206
Levy et al. (2001). LXs and Rvs also stimulate the recruitment 1207
of monocytes. The resolving macrophages then clear apoptotic 1208
PMNs, inflammatory debris by *efferoctytosis* (stimulated by 1209
LXs, Rvs, PDs). After this has taken place, normal structure 1210
and homeostasis can be restored. “Resolution” is defined as 1211
the period between peak inflammatory cell influx and the 1212
clearance of these cells from the tissue site and the restoration 1213
of functional homeostasis. Subsequent post-resolution events 1214
involves activation of adaptive immunity B- and T-lymphocytes 1215
(Fullerton and Gilroy, 2016). 1216

Failed resolution can lead to increased levels of prostaglandins 1217
and leukotrienes, chronic inflammation and fibrosis. Ultimately 1218
SPMs reduce the magnitude and duration of inflammation (Arita 1219
et al., 2007), stimulate re-epithelialization (Hellmann et al., 2018), 1220
wound healing (Dalli, 2017) and tissue regeneration (Dalli, 2017). 1221

While most of the studies involving SPMs have been 1222
conducted on rodents models, major and recent advances have 1223
been represented by the work of Motwani et al. (2016) in 1224
humans, where a new translational model of self-resolving acute 1225
inflammatory response triggered by the intradermal injection 1226
of UV-killed *Escherichia coli* into the forearm of healthy 1227
volunteers was described. For the first time SPMs endogenous 1228
production have been identified in humans over the course of the 1229
inflammatory response. It has also been shown that resolution is 1230
an active process accelerated by addition of exogenous SPMs. 1231

The molecular mechanisms through which SPMs exert their 1232
responses include activation of distinct GPCRs and regulation 1233
of gene expression. The binding, and consequent activation, 1234
of the LX/N-formyl peptide receptor-2 (ALX/FPR2) GPCR by 1235
lipids, such as LXA₄ and RvD1 as well as Annexin-1 peptide 1236
(Krishnamoorthy et al., 2010; Maderna et al., 2010; Bena et al., 1237
2012), and the RvE1 agonist at the ChemR23 GPCR (Arita 1238
et al., 2007) are key to reduce PMN infiltration and subsequently 1239
stimulate *efferoctytosis* by macrophages, heralding the initiation of 1240
pro-resolving cascade of events. 1241

1242

1243

1244 SPMs IN ACUTE INJURIES

1245

The anti-inflammatory and pro-resolving properties of SPMs, 1246
including LXs, Rvs and their mimetics, particularly 15(R/S)- 1247
methyl-LXA₄ (Wu et al., 2013), benzo-LXA₄ (Sun et al., 2009), 1248
BDA-RvD1 (Orr et al., 2015) and have been demonstrated in 1249 Q13
several types of experimental acute renal and peritoneal injury 1250
(see below). 1251

Moreover, SPMs have recently been shown to play a key 1252
role in dampening both sterile inflammation and infection (or 1253
non-sterile inflammation). In this context, a recent advance 1254

1255 is represented by the above mentioned study on the self-
1256 resolving properties of SPMs in an acute and local *E. coli*-induced
1257 translational skin-blister model (Motwani et al., 2016).

1258

1259

1260 Biosynthesis and Functions of LXs in 1261 Acute Injuries

1262 Native LXs, LXA₄ and LXB₄, are endogenous eicosanoids,
1263 transcellularly biosynthesized by 5- and 15-LO interaction
1264 of activated leukocytes with epithelium, endothelium or
1265 platelets (Serhan et al., 1984; Serhan, 1989; Serhan and
1266 Sheppard, 1990) Acetylation of cyclooxygenase-2 by aspirin
1267 can trigger the biosynthesis of their 15R-carbon epimers, 15-epi-
1268 LXA₄ and 15-epi-LXB₄ [15-epi-LXs or aspirin-triggered
1269 LXs (ATLs)] (Serhan, 2005). Although native LXs have
1270 demonstrated potent anti-inflammatory and pro-resolution
1271 bioactions (Claria et al., 1996; Fierro and Serhan, 2001;
1272 Chandrasekharan and Sharma-Walia, 2015), their therapeutic
1273 potential is compromised for by their chemical instability and
1274 for by their rapid metabolic inactivation by prostaglandin
1275 dehydrogenase-mediated metabolic inactivation *in vivo*
1276 (Clish et al., 2000), with the growing need to synthesize
1277 their mimetics.

1278 First-generation synthetic LXA₄ analogs were designed in
1279 1995–1998 by Serhan, Petasis and colleagues to minimize
1280 metabolism of the molecule (Parkinson, 2006). These
1281 relatively stable pharmacological agents, together with
1282 myeloid-specific ALX-R-expressing transgenic mice, have
1283 provided powerful tools to explore LX functions *in vivo*.
1284 Among those, pharmacokinetic analysis of ATLa, such as
1285 methyl (5R,6R,7E,9E,11Z,13E,15S)-16-(4-fluorophenoxy)-
1286 5,6,15-trihydroxy-7,9,11,13-hexadecatetraenoate, revealed
1287 β -oxidation as a novel route for LXA₄ metabolism, prompting
1288 the development of second-generation 3-oxa-LXA₄ analogs with
1289 improved pharmacokinetic disposition (Parkinson, 2006).

1290 Second-generation 3-oxa-LXA₄ analogs, such as
1291 (5R,6R,7E,9E,11Z,13E,15S)-16-(4-fluorophenoxy)-3-oxa-
1292 5,6,15-trihydroxy-7,9,11,13-hexadecatetraenoic acid, have shown
1293 potency and efficacy comparable to ATLa in diverse animal
1294 models after topical, intravenous or oral delivery (Guilford and
1295 Parkinson, 2005).

1296 More recently, a new class of LX-analogs featuring a benzo-
1297 fused ring system have been designed and proved to be as
1298 potent as native LXA₄ in a series of *in vitro* and *in vivo*
1299 studies (O'Sullivan et al., 2007; Petasis et al., 2008). In particular,
1300 it was found to stimulate phagocytosis of apoptotic PMN by
1301 macrophages, in a zymosan-induced peritonitis murine model of
1302 acute inflammation (O'Sullivan et al., 2007). Further exploration
1303 of the mechanism of action through which PMN phagocytosis
1304 by bone marrow-derived macrophage was elicited revealed that
1305 expression, activation and internalization of ALX/FPR2 by LXA₄
1306 and the glucocorticoid-derived Annexin A1 peptide (Ac2-26)
1307 were essential (Maderna et al., 2010).

1308 In early 2000, the work from Leonard et al. (2002) suggested
1309 a framework for understanding SPMs bioactions in renal IRI
1310 and the molecular basis for renoprotection by LXs in this
1311 setting. They firstly demonstrated, in a murine renal IRI, that

the stable synthetic LXA₄ analog 15-epi-16-(FPhO)-LXA₄-
Me is reno-protective, as gauged by lower serum creatinine,
attenuated leukocyte infiltration and reduced morphologic
tubule injury. Subsequently, they employed complementary
oligonucleotide microarray and bioinformatic analyses to probe
the transcriptomic events that underpin LX renoprotection
and found that epi-LXA₄ modified the expression of many
differentially expressed pathogenic mediators, including
cytokines, growth factors, adhesion molecules and proteases.
Importantly, this LX-modulated transcriptomic response
included many genes expressed by renal parenchymal cells (such
as the Claudin family epithelial tight junctions) (Kieran et al.,
2003).

1326 Biosynthesis and Functions of Rvs in 1327 Acute Injuries

1328 Rvs are produced by 12/15-LO, p450, and/or 5-LO, in *trans*-
1329 cellular or intracellular biosynthetic systems of leukocytes or
1330 leukocytes plus endothelia/epithelia (Serhan et al., 2000). The
1331 novel lipid mediators produced from EPA were first isolated
1332 from resolving exudates that proved to contain 18R-HEPE as
1333 well as several other related bioactive compounds and were
1334 therefore collectively named 18R-E series (Serhan et al., 2000).
1335 The first bioactive product isolated from exudates, coined
1336 RvE1, reduced inflammation and blocked human PMN *trans*-
1337 endothelial migration.

1338 RvDs are derived from DHA. During inflammation,
1339 endogenous DHA is converted to 17S-HEPE which are
1340 then converted in 17S-hydroxyl-containing RvDs (RvD1–RvD6)
1341 and docosa-conjugated triene-containing PD1/NPD1, *via* 15-LO
1342 (15S-lipoxygenation)-initiated biochemical pathways (Serhan
1343 et al., 2002; Hong et al., 2003; Marcheselli et al., 2003) or to 14S
1344 hydroxyl-containing MaRs *via* 12-LO (12S-lipoxygenation)-
1345 initiated biochemical pathways. 5-LO catalyzes sequentially with
1346 15-LO or 12/15-LO, generating RvDs (Hong et al., 2003) and
1347 some MaRs (Serhan et al., 2009).

1348 RvD1 is converted by eicosanoid oxidoreductases to 17-oxo-
1349 RvD1 and 8-oxo-RvD1. The former is an inactive metabolite,
1350 while the latter is still effective in suppressing PMN infiltration
1351 (Sun et al., 2007). RvE1 is metabolized to 12-oxo-RvE, 18-
1352 oxo-RvE1, 10,11-dihydroxy RvE, 19-hydroxy RvE1, 20-hydroxy
1353 RvE1 in tissue or cells, of which the first four metabolites are
1354 inactive partially or completely in inflammation resolution, and
1355 thus are representative of RvE1 metabolic deactivation (Arita
1356 et al., 2006; Hong et al., 2008). Human PMNs convert PD1
1357 to its omega-22 hydroxy product (Serhan and Petasis, 2011).
1358 The metabolic deactivation of Rvs dysregulated in pathological
1359 conditions, may result in their deficiency, or in diminishing the
1360 pharmacological efficacy of administered resolvins. Therefore, a
1361 series of stable analogs have been successfully synthesized, such
1362 as a *p*-fluorophenoxy added to RvE1 and RvD1 ω -terminal,
1363 which blocks the critical metabolic inactivation of RvE1 or
1364 RvD1 without attenuating the anti-inflammatory pro-resolving
1365 activities (Arita et al., 2006; Hong et al., 2008; Tang et al., 2014)
1366 In particular, the RvE1 analog 19-(*p*-fluorophenoxy)-RvE1
1367 was synthesized to resist rapid metabolic inactivation and
1368

proved to retain biological activity reducing PMN infiltration and pro-inflammatory cytokine/chemokine production *in vivo*. These results established the structure of a novel RvE1 initial metabolite, indicating that conversion of RvE1 to the oxo product represents a mode of RvE1 inactivation. Moreover, the designed RvE1 analog, which resisted further metabolism/inactivation, could be a useful tool to evaluate the actions of RvE1 in complex disease models (Arita et al., 2006).

These lipids act as paracrine and autocrine mediators of leukocytes to promote resolution of acute injuries, including AKI-initiated inflammation and fibrosis and rescue of kidney functions (Zhao et al., 2016), by shortening PMN life span and promoting macrophage *efferocytosis* of ACs and the subsequent exit of the phagocytes from inflammatory tissue.

RvD1 and RvE1 also switch macrophage to the phenotype that produces pro-resolving interleukin-10. RvDs or protectin/neuroprotectin D1 (PD1/NPD1) inhibits PMN infiltration into injured kidney, blocks TLR-mediated inflammatory activation of macrophage and mitigates renal dysfunction. RvDs also repress renal interstitial fibrosis, and PD1 promotes reno-protective heme-oxygenase-1 expression. These findings provide novel approaches for targeting inflammation resolution and LMs or modulation of LM-associated pathways for developing better clinical treatments for AKI. Moreover, in LPS-induced AKI, RvD1 could decrease TNF α level, ameliorate kidney pathological injury, protect kidney function, and improve animal survival by down-regulating NF κ B inflammatory signal as well as inhibiting renal cell apoptosis (Zhao et al., 2016). Intriguingly, RvE1 counter-regulates leukocytes partially *via* increased LXA₄ biosynthesis (Levy et al., 2011). Since AKI is the major complication of renal allograft transplantation (Bellomo et al., 2012), these results further demonstrate the effectiveness of LXA₄ or RvE1 in reducing AKI. LX actions converge with the pro-resolving characteristics of RvD1, as LXA₄ and RvD1 both activate the same GPCRs ALXR/FPR2 and GPR32.

SPMs IN CHRONIC DIABETES COMPLICATIONS

Unresolved inflammation drives the development of clinically relevant chronic diseases. Here, we focus the attention on the role of SPMs, particularly LXs and Rvs, on DAA, CKD and, briefly, on DR.

As discussed previously, sustained, non-resolved low-grade inflammation, over decades, promotes formation of atherosclerotic lesions characterized by large necrotic cores, thin fibrous caps and thrombosis. In advanced atherosclerosis, there is an imbalance between levels of SPMs and proinflammatory lipid mediators, which results in sustained leukocyte influx into lesions, inflammatory macrophage polarization, and impaired *efferocytosis*. In animal models of advanced atherosclerosis, restoration of SPMs limits plaque progression by suppressing inflammation, enhancing *efferocytosis*, and promoting an increase in collagen cap thickness (Fredman and Tabas, 2017).

From a CKD-perspective, there is a clear mechanistic link between non-resolving inflammation and fibrosis. Non-resolving inflammation results in sustained secretion of pro-fibrotic cytokines and other inflammatory mediators from both resident and infiltrating cells, eliciting fibroblast proliferation and epithelial cell de-differentiation. Sustained or unresolved inflammation is recognized to be an underlying component of many chronic disease states in diverse organ systems, including CKD (Serhan, 2014; Brennan et al., 2017).

The Role of LXs and Rvs in Atherosclerosis and DAA

It is now established that the local LO-induced biosynthesis of lipid mediators, including LXA₄, RvD1 and PD1, protects against atherosclerosis. These mediators exert potent agonist actions on macrophages and vascular ECs that can control the magnitude of the local inflammatory response (Merched et al., 2008), as depicted in **Figure 1** (left).

Enhanced biosynthesis of LXA₄ in transgenic mice is associated with decreased lesion formation in models of atherosclerosis (Merched et al., 2008). Atheroprotective responses of macrophages and ECs to SPMs include enhanced *efferocytosis* of apoptotic debris and modulation of adhesion molecules expression (VCAM-1, ICAM-1, P-Sel). It has been shown that LXA₄ increases ABCA1 expression and promotes cholesterol efflux through LXR α pathway in THP-1 macrophage-derived foam cells (Sha et al., 2015). Moreover, it has been recently demonstrated that ATL signals through FPR2/ALX in vascular SMCs and protects against intimal hyperplasia after carotid ligation (Petri et al., 2015).

Over the past few years, Brennan's work focused on the role of miR in both DKD (see details below) and DAA. The let-7 miRNA family plays a key role in modulating inflammatory responses. Vascular SMC proliferation and EC dysfunction are critical in the pathogenesis of atherosclerosis, including in the setting of diabetes. The therapeutic potential of LXA₄-induced restoration of let-7 mimic levels was observed *in vitro* in SMCs, *in vivo via* tail vein injection in a 24 h murine model, and *ex vivo*, where significant changes to the secretome in response to let-7 therapy were seen. It has been proposed that restoration of let-7 expression, a mimic of response to LXA₄, could provide a new target for an anti-inflammatory approach in diabetic vascular disease (Brennan et al., 2017). Very recently, LXA₄ and the synthetic LX mimic benzo-LXA₄ have also been shown to be athero-protective in murine model of DAA (STZ-induced diabetic ApoE^{-/-} mouse). Here there was significant reduction in plaque area. The authors also demonstrated that these SPMs could attenuate vascular SMCs migration and proliferation, EC-monocytes interactions, as well as modulate the pro-inflammatory secretome signature in human carotid plaque explants. Of particular note was the finding that LX treatment reduced pre-existing plaque burden in diabetic mice (Brennan et al., 2018).

Oxidation of native LDLs plays an important role in the development of atherosclerosis. A very recent work showed that although ox-LDLs are known to be pro-inflammatory

1483 and deleterious in the context of atherosclerosis, they are also
 1484 able to induce a pro-resolution effect by self-induction of
 1485 RvD1 from HMEC (Dufour et al., 2018). Moreover, circulating
 1486 inflammation-resolving lipid mediators RvD1 and DHA are
 1487 decreased in patients with acutely symptomatic carotid disease
 1488 (Bazan et al., 2017). Similarly, RvE1 and ATL plasma levels were
 1489 found to be significantly lower in symptomatic peripheral arteries
 1490 disease than in healthy controls (Ho et al., 2010).

1491 In addition to lipid agonists, the ALX/FPR2 can also bind
 1492 peptides, such as Annexin-1 (Maderna et al., 2010). In an
 1493 advanced model of atherosclerosis, the Annexin-1 derivative
 1494 acetylated peptide (Ac2-26), was delivered using Collagen IV-
 1495 targeted nanoparticles and it showed therapeutic effect in fat-fed
 1496 LDL-R^{-/-} mice, including an increase in the protective collagen
 1497 layer overlying lesions, suppression of oxidative stress and a
 1498 decrease in plaque necrosis, thus, suggesting a new form of
 1499 therapy (Fredman et al., 2015).

1500 The Role of LXs in CKD and DKD

1502 Advances in understanding the effects of LXs in the context of
 1503 RF arose from investigating their actions on the main cell types
 1504 involved in kidney failure (mesangial cells, fibroblasts, epithelia,
 1505 adipocytes) (see details below). As outlined in **Figure 2** (right),
 1506 work from Rodgers, McMahon and Mitchell investigated the
 1507 potential of LXA₄ to regulate PDGF-induced gene expression
 1508 and the associated autocrine TGFβ1 production in human renal
 1509 mesangial cells, and found that LXA₄ is a potent modulator of
 1510 matrix accumulation and pro-fibrotic change, thus suggesting a
 1511 potential protective role in progressive renal disease (McMahon
 1512 et al., 2002; Mitchell et al., 2004; Rodgers et al., 2005). In an
 1513 experimental model of RF, i.e., unilateral ureteric obstruction
 1514 (UUO), LXA₄ and its synthetic benzo-analog attenuated injury
 1515 by inhibiting TGFβ1-induced fibroblast activation, proliferation
 1516 and gene expression (Borgeson et al., 2011).

1517 *Aging*, defined as a state of chronic, low-grade, sterile
 1518 inflammation (*inflamm-aging*) (Franceschi et al., 2017) and
 1519 *adiposity*, have recently been proposed as one of the major
 1520 risk factors underlying the pathophysiological development
 1521 of obesity-associated complications, including T2D, and its
 1522 complications DAA and DKD (Todd et al., 2015). Therefore,
 1523 of particular relevance in the diabetes context is the work that
 1524 Borgeson et al. (2011) subsequently carried out, in 2012 and
 1525 2015, on the effect of the native LXA₄ on obesity-induced adipose
 1526 tissue inflammation and related diseases. Firstly, using a model
 1527 of age-associated adipose inflammation, *inflamm-aging* it was
 1528 shown that LXA₄ attenuates adipose inflammation, decreasing
 1529 IL-6 and increasing IL-10 expression. The altered cytokine
 1530 milieu correlated with increased the insulin-regulated glucose
 1531 transporter-4 and the insulin receptor substrate-1 expression,
 1532 suggesting improved insulin sensitivity. Further investigations
 1533 revealed the ability of LXA₄ to rescue macrophage-induced
 1534 desensitization to insulin-stimulated signaling and glucose
 1535 uptake in cultured adipocytes, thus suggesting that LXA₄ may
 1536 represent a potentially useful and novel therapeutic strategy
 1537 to subvert adipose inflammation and insulin resistance, key
 1538 components of T2D (Borgeson et al., 2012). Later on, the role
 1539 of LXs in obesity-related pathologies was further explored by

1540 investigating their impact on impaired glucose tolerance, adipose
 1541 inflammation, fatty liver and CKD. In particular, LXs attenuated
 1542 obesity-induced CKD, reducing glomerular expansion, mesangial
 1543 matrix and urinary H₂O₂. These data suggested a protective role
 1544 for LXs against obesity-induced systemic disease, and supported
 1545 a novel therapeutic paradigm for treating obesity and associated
 1546 pathologies, such as TD2 and its related complications (Borgeson
 1547 et al., 2015). A role in the context of aging-related pathologies
 1548 (including obesity, atherosclerosis, renal disease and diabetes)
 1549 for SPMs has been also recently reviewed by Doyle et al.
 1550 (2018).

1551 Certain miRs have been implicated in fibrosis (both renal
 1552 and cystic). In cultured HK-2 cells, LXA₄ suppresses TGF-
 1553 1-induced RF through a mechanism involving upregulation
 1554 of the miR let-7c and downregulation of TGF R1. Expression
 1555 of let-7c targets is dysregulated in human RF (Brennan et al.,
 1556 2013). The effects of let-7 on TGF 1-mediated responses of
 1557 renal epithelia have also been shown by others, including
 1558 Cooper and Kantharidis, leading to the proposal that let-
 1559 7b miR represents a potential new target for the treatment
 1560 of RF in diabetic and non-diabetic nephropathy (Wang
 1561 et al., 2014; Kantharidis et al., 2015; Brennan et al., 2017).
 1562 Interestingly, LXA₄ demonstrated to attenuate TGF- 1-
 1563 induced fibrotic responses whereby epithelial cells express
 1564 mesenchymal markers (Brennan et al., 2013). In cultured
 1565 renal epithelia upregulation of thrombospondin and CTGF is
 1566 a well-documented fibrotic response (Crawford et al., 1998;
 1567 Liu et al., 2013). While, in cystic fibrosis, miR181b is indeed
 1568 downregulated by LXA₄ and RvD1, through ALX/FPR2
 1569 activation (Pierdomenico et al., 2015). Moreover, very recent
 1570 interesting observations showed that LXs can also reverse
 1571 established atherosclerosis (Brennan et al., 2018) and DKD
 1572 (Brennan et al., 2018).

1573 Very recently, in a DKD murine model, Brennan has
 1574 also identified a series of transcripts regulated by LXA₄ and
 1575 Benzo-LXA₄, modulating well established (TGF-β1, PDGF,
 1576 TNF-α, NF-κβ) and novel (early growth response-1) networks
 1577 in DKD, demonstrating that LXs can reverse established
 1578 diabetic complications and supporting a therapeutic paradigm
 1579 to promote the resolution of inflammation (Brennan et al.,
 1580 2018). Interestingly, a recent study from Goicoechea measured
 1581 circulating level of ATL in patients with diabetic and non-
 1582 diabetic kidney disease and found that diabetes was associated
 1583 with lower levels of the SPMs and that this could be restored
 1584 by 12-month low dose aspirin treatment (Goicoechea et al.,
 1585 2017).

1587 The Role of Rvs in Diabetic Wound 1588 Healing

1589 The work from Spite greatly deepened the knowledge around the
 1590 SPMs properties of re-epithelialization and/or re-vascularization
 1591 post ischemia, particularly focussing on Rvs bioactions. RvD2
 1592 stimulates arteriogenic revascularization in a murine model
 1593 of hind limb ischemia suggesting that resolvins may be a
 1594 novel class of mediators that both resolve inflammation and
 1595 promote arteriogenesis (Zhang et al., 2016), a mechanism
 1596

1597 which can provide protection against nephropathy and
1598 atherosclerosis.

1599 Altered resolution of acute inflammation in the context
1600 of obesity and diabetes, in which PMN apoptosis is
1601 delayed and macrophage efferocytosis is defective, cause
1602 persistent leukocyte and AC accumulation and defective
1603 wound closure (Baltzis et al., 2014). Wound healing
1604 in diabetes is enhanced by RvD1 and RvE1 *via* the
1605 promotion of macrophage-mediated AC clearance and
1606 re-epithelialization (Bannenberg et al., 2005; Spite et al.,
1607 2014). Moreover, RvD1 decreases adipose tissue macrophage
1608 accumulation and improves insulin sensitivity in obese-
1609 diabetic mice, suggesting that RvD1 could provide a novel
1610 therapeutic strategy for treating obesity-induced diabetes
1611 (Hellmann et al., 2011).

1612 **The Role of LXs and Rvs in DR**

1613 Although the anti-inflammatory (anti-TNF α and anti-VEGF)
1614 approach is still the standard therapy for DR, recent *in vitro* and
1615 *in vivo* models are shifting the attention toward a pro-resolving
1616 novel strategy (Das, 2013; Wang and Daggy, 2017).

1617 Since corneal, retinal neuronal degeneration (Srinivasan et al.,
1618 2017), conjunctivitis (Stuebiger et al., 2015) and uveitis (Sivaraj
1619 et al., 2009) have been associated with DR, the effects of LXs
1620 (Gronert, 2005; Biteman et al., 2007; He et al., 2011; Hodges et al.,
1621 2017) and Rvs (Tian et al., 2009; Settimio et al., 2012; Li et al.,
1622 2013; Lee et al., 2015) in dampening DR are of relevance.

1623 In a well established *in vivo* model of STZ-induced Diabetes,
1624 hyperglycemia induces persistent inflammation and tissue
1625 damage, due to decreased expression of heme-oxygenase (HO)
1626 in the ciliar body (Rossi et al., 2006). Recently, the effect of
1627 RvD1 on STZ-induced DR has been explored. RvD1 regulates the
1628 NLRP3 inflammasome and NF κ B signaling pathway (Yin et al.,
1629 2017).

1630 Moreover, by using an *in vivo* deletion of 12/15-LOX model,
1631 associated with exacerbated inflammation and impaired wound
1632 healing, due to a failure of HO-1 induction, it has been
1633 demonstrated that LXA₄, restored the HO synthesis and activity,
1634 rescuing the wound healing phenotype (Biteman et al., 2007).

1635 Overall, the therapeutic potential of SPMs in the treatment of
1636 DR are promising.

1637 **REALIZING THERAPEUTIC POTENTIAL**

1638 The therapeutic challenges presented by diabetes-associated
1639 complications such as DAA and DKD are well documented, and
1640 experimental evidence, as outlined above, suggests a role for
1641 SPM-based mimetics as adjuvants to current therapies. Clinical
1642 trials specifically investigating the therapeutic potentials of LXs
1643 and Rvs have been limited.

1644 In a randomized controlled trial, AT-LXA₄ and a
1645 comparatively stable analog of LXB₄, 15R/S-methyl-LXB₄,
1646 reduced the severity of eczema in a study of 60 infants
1647 (Wu et al., 2013).

1648 A synthetic analog of RvE1 is in clinical phase III testing
1649 for the treatment of the inflammation-based dry eye syndrome;
1650

1651 along with this study, other clinical trials using an RvE1
1652 analog to treat various conditions are underway, such as
1653 in a single study where inhaled LXA₄ decreased LTC₄-
1654 initiated bronchoprovocation in patients with asthma (Basil
1655 and Levy, 2016). RvE1, Mar1 and NPD1 are in clinical
1656 development studies for the treatment of neurodegenerative
1657 diseases and hearing loss (Serhan et al., 2015; Basil and Levy,
1658 2016).

1659 A clinical trial phase-I evaluating the effects of n-3 fatty acid
1660 supplementation on plasma SPMs in patients with CKD showed
1661 that endogenous production of SPMs was increased after 8-weeks
1662 n-3 fatty acid supplementation in patients with CKD, potentially
1663 impacting also patient risk of CVD complications (Mas et al.,
1664 2016).

1665 More recently, Gilroy introduced the above mentioned
1666 first translational cantharidin-induced skin blister model
1667 in healthy male volunteers, providing insights into the
1668 mechanisms of self-resolving infections in humans,
1669 identifying cells and soluble mediators that may control the
1670 resolution phase. Further use of this model will improve
1671 our understanding of the evolution and resolution of
1672 inflammation in humans, how defects in these over-lapping
1673 pathways may contribute to the variability in disease
1674 longevity/chronicity, and lends itself to the screen of putative
1675 anti-inflammatory or pro-resolution therapies (Motwani et al.,
1676 2016).

1677 **SUMMARY, CONCLUSIONS, AND 1678 FUTURE PERSPECTIVES**

1679 Aging populations, increasing urbanization and widening social
1680 inequalities are all contributing factors to the rapid rise in
1681 diabetes prevalence seen over the past 40 years worldwide.
1682 Reducing premature mortality from non-communicable diseases,
1683 including diabetes, has become a global priority. For people
1684 with either T1D or T2D, advances in clinical care, such as
1685 development of better glucose-lowering drugs and structured
1686 education programs promoting life-style changes, have led
1687 to considerable increases in life expectancy. Effectively, more
1688 people are living with diabetes for longer. Understanding the
1689 disease course, onset of complications, and comorbid
1690 conditions is critical to improving specialized care for people with
1691 diabetes.

1692 The most prevalent complications are affecting the
1693 microvascular (DKD, DR) and the macrovascular (DAA)
1694 systems. As mortality from cardiovascular complications
1695 continues to decline, attention must be turned to
1696 identifying, preventing, and treating other diabetes
1697 complications. In this context, advances in research in
1698 the molecular biology of such complications unveiled
1699 novel players and novel unified mechanisms driving
1700 different diabetes related complications. As highlighted
1701 here, inflammation is central to these processes. Evidence
1702 is accumulating that agonism of resolution of inflammation
1703 is a rational and tractable target that may be an attractive
1704 adjuvant in the context of chronic complications of
1705

1711 diabetes applying a novel therapeutic paradigm to a vast and
1712 growing unmet need.

1713
1714

AUTHOR CONTRIBUTIONS

1716

1717 MdG, EB, and CG conceived and designed the review article.
1718 MdG prepared the first draft of the manuscript. CM, AC, JH,
1719 and EB contributed to pre-publication data. All authors read and
1720 approved the final manuscript.

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