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Inflammatory Networks Linking Cardiovascular Disease, Diabetes, and Cancer

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Abstract

Cardiovascular disease (CVD), diabetes, and cancer share a spectrum of metabolic disturbances that reflect dysregulated energy homeostasis and metabolic control. According to the Centers for Disease Control and Prevention, these three entities are among the top seven causes of death in the United States, and a steady increase in disease burden is predicted for the remainder of this century. In the last 50 years, we have come to realize that changes in metabolic pathways, many of which are influenced by inflammation, are associated with CVD, type 2 diabetes, and cancer. Although a number of key regulatory molecules have been identified, their utility as therapeutic targets is limited by the magnitude and multiplicity of intersecting pathways in which they participate. Hence, the identification of yet elusive biological response modifiers may prove central to designing effective treatment modalities. This review highlights the role of inflammatory pathways and their antagonists in CVD, diabetes, and cancer.

Keywords: Cardiovascular Disease; Diabetes; Cancer; Inflammatory Pathways; Leptin

Abbreviations: ACAT: Acylcoenzyme A: Cholesterol Transferase; ACL: ATP-Citrate Lyase; AGE: Advanced Glycation End-Product; CAR-T: Chimeric Antigen Receptors/T-Cells; CC: Chemokine; CCL: Chemokine Ligand; CCR: Chemokine Receptor; COX: Cyclooxygenase; CTLA-4: Cytotoxic T-Lymphocyte Associated Protein 4; CVD: Cardiovascular Disease; CXC: Chemokine Superfamily Where X is any Amino acid; CXCL: Chemokine-X-Ligand (Formerly GRO1 Oncogene-Ligand); CXCR: Chemokine-X-Receptor; ELR-CXC: Glu-Leu-Arg Motif bound to a Chemokine; FGF: Fibroblast Growth Factor; FHS: Framingham Heart Study; GPCR: G Protein-Coupled Receptor; HMG-Coa Reductase: 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase; ICAM: Intercellular Adhesion Molecule; IGF: Insulin Growth Factor; IL-6: Interleukin-6; IRS: Insulin Receptor Substrate; LDL: Low Density Lipoprotein; LOX: Lipoxygenase; LX: Lipoxin; MALAT1: Metastasis-Associated Lung Adenocarcinoma Transcript 1; MAPK: Mitogen-Activated Protein Kinase; Metsyn: Metabolic Syndrome; MK: Mevalonate Kinase; NF-kb: Nuclear Factor-kb; NLRP3: Leucine-Rich Repeat-Containing Protein Family Pyrin Domain 3; NOS: Nitric Oxide Synthase; PD-1 Programmed Cell Death Protein-1; PI3K: Phosphatidylinositol-3 Kinase; PGI2: Prostacyclin; Ppar-γ: Peroxisome Proliferator-Activated Receptor-γ; ROS: Reactive Oxygen Species; Sirna: Silencing RNA; SIRT: Silent Information Regulator Protein; SOCS: Suppressor Of Cytokine Signaling; T2DM: Type 2 Diabetes Mellitus; TGF: Transforming Growth Factor; TLR: Toll-Like Receptor; TNF: Tumor Necrosis Factor; Txnip: Thioredoxin-Interacting Protein; VCAM: Vascular Cell Adhesion Molecule; VEGF: Vascular Endothelial Growth Factor

Epidemiological Links between Heart Disease, Diabetes, and Cancer

According to the Centers for Disease Control and Prevention, CVD, diabetes, and cancer are among the top seven causes of death (#1, #7, and #2, respectively) in the United States [1], and recent data indicate important epidemiologic links among these three entities. A major outcome of the Framingham Heart Study (FHS) was the realization that patients with type 2 diabetes (T2DM), compared with non-diabetic controls, are at increased risk for atherosclerotic cardiovascular disease (CVD) [2]. T2DM was found to confer a 2–4 - fold increased risk of myocardial infarction, as well as a significantly increased risk of congestive heart failure, peripheral artery disease, stroke, and overall mortality, with an even more robust effect for women over men. In 1981, the FHS revealed that both obesity and hyperlipidemia predicted eventual glucose intolerance, thus setting the stage for CVD [3]. These studies, and many others, established epidemiologic links between T2DM and CVD, and formally recognized the clinical constellation of abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance, and prothrombotic and proinflammatory states as defining characteristics of "metabolic syndrome" (MetSyn) [4]. As of 2009, the definition of MetSyn requires the presence of three of the five following factors: elevated waist circumference, elevated serum triglycerides, reduced high-density lipoprotein-cholesterol, elevated blood pressure, and elevated fasting blood glucose [5].

Despite these early clinical associations, MetSyn, obesity, and T2DM have grown as serious public health issue over the past several decades [6]. In the interval between the National Health and Nutrition Examination Survey (NHANES) 1999-2006 and NHANES III, the overall prevalence of MetSyn in the U.S. increased by 5 to 6 percentage points, and currently over 69 million Americans have MetSyn, with increasing representation among women. Despite public awareness, moreover, obesity rates among American adolescents dropped only slightly from 7.3% to 6.5% between 1998 and 2007, while rates among Korean youth increased from 4.0% to 7.8% over the same period [7]. Similarly, statistics from the year 2000 revealed that the worldwide prevalence of types 1 and 2 diabetes mellitus for all age groups was approximately 2.8%, and expected to rise to 4.4% by the year 2030 [8].These trends identify obesity, MetSyn, and T2DM as epidemics of the modern era.

An unexpected twist in the history of MetSyn is the finding that some medications used to treat CVD may actually induce or exacerbate diabetes. Thiazide diuretics, which are commonly used for treatment for hypertension, are linked to drug-induced diabetes, and, in some studies, an increased risk of cardiac and cerebrovascular morbid or fatal events [9]. Similarly, the JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) trial revealed a 10% increased risk of overt diabetes among subjects with prediabetes, MetSyn, or obesity when treated with rosuvastatin for prevention of CVD [10,11]. While this risk was significant, the benefits of statins, the most commonly prescribed medication worldwide, appeared to exceed the risk of new onset diabetes, prompting the recommendation for screening for glucose intolerance in patients on statins.

Another link between diabetes, CVD, and cancer is the realization that diabetes may increase the odds of developing some forms of cancer, and that co-morbid diabetes is associated with less favorable outcomes in patients with cancer [12]. Multiple meta-analyses suggest a modest to moderate, possibly causal association between T2DM and pancreatic, breast, bladder, hepatocellular, endometrial cancer, and non-Hodgkin lymphoma, with relative risk ratios ranging from 1.2 to 2.5 [13–19]. An exception to this trend is that diabetes is associated with reduced risk in prostate cancer over the long-term, particularly in subjects who exercise, suggesting a possible protective role for hypoinsulinemia [20,21]. Three additional studies, including one meta-analysis, reveal that cancer in subjects with pre-existing diabetes carries a 30-70% increase in all-cause mortality (22–24). Although intensive glycemic control alone does not appear to alter the risk of cancer in diabetes (25), evidence-based nutritional guidelines aimed at preventing cancer mirror those shown to be effective in the prevention of coronary heart disease and diabetes (26). These data suggest that factors other than hyperglycemia contribute to cancer risk in diabetes.

In addition, diabetes can be a late consequence of cancer therapy. Adult survivors of childhood cancer carry an increased risk of MetSyn and T2DM, most likely reflecting increased adiposity, sedentary lifestyle, or the late effects of radiation therapy [27,28]. Among children and young adults receiving a radiation dose of more than 10 Gray to the tail of the pancreas, for example, the incidence of diabetes at five years or more following completion of treatment was 16%. In cases where children received radiation, diabetes was unrelated to body mass index or inactivity. Thus, while pre-existing diabetes may predispose to cancer, diabetes itself may be a consequence of cancer treatment.

Heart disease, the leading cause of death in the general adult population in the United States, is also a major cause of mortality among survivors of most common cancers [20–23]. The metabolic environment in T2DM, which includes insulin resistance and inflammation, is similar to that found in several types of cancer. In one study, men with MetSyn had a 56% higher risk of cancer mortality compared with those with only one component of MetSyn, and participants with three or more risk factors had an 83% higher risk of cancer death compared to men without risk factors [29]. Factors thought to increase the risk of cancer in MetSyn include visceral adiposity and production of leptin, adiponectin, inflammatory cytokines, insulin-like growth factor-1, transforming growth factor-β, and estrogen, by adipose tissue (30). Interestingly, dietary adjustments that reduce cancer risk often have the added benefit of reversing diabetes, MetSyn, and CVD [12].

Inflammatory Mediators in CVD, T2DM, and Cancer

Inflammation is a highly organized, protective response to tissue injury, which, if unchecked or amplified, may disrupt homeostasis. Accumulating evidence suggests that dysregulation of inflammatory pathways underlies the increasingly apparent associations among CVD, T2DM, and cancer (figure 1). Evidence that inflammation is a major driver of atherosclerosis includes the observation that plasma levels of C-reactive protein (CRP), a marker of subclinical inflammation, are significantly correlated with adverse outcome [31], and that lipid-lowering treatment that reduces risk of CVD also reduces CRP. In CVD, tumor necrosis factor α (TNFα), interleukin-1β (IL-1β), and IL-6 all activate the endothelium and sustain the expression of adhesion molecules, namely vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and P-selectin, which facilitate the recruitment of monocytes and monocyte-derived macrophages that promote plaque development and plaque rupture [32,33]. Many pro-inflammatory factors involved in atherosclerosis, such as nuclear factor-kB (NF-kB), and an array of cytokines, prostaglandins, microRNAs, and angiogenic factors are also active in chronic inflammatory states that predispose to up to 20% of cancers (34). In addition, some inflammatory factors induce or exacerbate glucose intolerance, thus initiating the development of T2DM [35]. Recent advances in basic and translational research have now identified a number of substances that dysregulate inflammatory pathways in CVD, T2DM, and cancer.

One factor that links inflammation to CVD or T2DM is leptin. Leptin is a 146-amino acid polypeptide that is synthesized mainly by white adipose tissue, and signals within the hypothalamus and brain stem to control energy balance [36]. Mice deficient in leptin (ob/ob) have hyperphagia and extreme obesity [37], and exogenous leptin has anti-diabetic actions based on its ability to increase insulin sensitivity in mice and to correct hyperglycemia in insulin-deficient mice [38,39]. Interestingly, most obese humans have increased levels of circulating leptin, and are presumed to be resistant to its effects. In human obesity leptin induces estrogen biosynthesis in breast cancer cells by enhancing expression of aromatase, which converts androstenedione and estrone to estrogen [40]. In post-menopausal women, adipose tissue is a site of estrogen synthesis, and obesity is linked to increased estrogen production, stimulation of cell division, and risk for breast cancer [37]. Leptin also exerts a series of pro-inflammatory effects, including polarization of macrophages toward the M1 phenotype with increase secretion of IL-1β, IL-18, and TNFα, increased phagocytosis, and up regulation of toll-like receptor 2 (TLR2), all of which may promote CVD [41]. Overall, it appears that dysregulated leptin production predisposes to malignancy and a chronic inflammatory state that promotesT2DM and CVD in obesity.

Adiponectin is the most abundant adipokine produced by adipose tissue [42]. It is a key vasculo protective factor, exerting a spectrum of anti-inflammatory effects on the blood vessel wall. These include elaboration of the vasodilator nitric oxide (NO) through induction of endothelial NO synthase, suppression of superoxide (O_2-) generation, inhibition of endothelial cell adhesion molecule expression (ICAM1, VCAM1, E-selectin), and inhibition of macrophage class A scavenger receptor expression. Adiponectin also down-regulates acyl-coenzyme A:cholesterol acyl transferase-1 (ACAT), which catalyzes the formation of cholesteryl esters, the primary storage form of cholesterol within atherosclerotic plaques [43]. Synthesis of adiponectin is stimulated primarily by peroxisome proliferator-activated receptor gamma (PPARγ), which is indispensable for adipocyte differentiation and highly expressed in adipose tissue. Adiponectin levels are reduced in individuals with obesity or insulin resistance, most likely through the actions of pro-inflammatory cytokines such as TNFα, reactive oxygen species (ROS), and insulin itself. Through these combined effects, loss of adiponectin promotes a state of chronic low-grade inflammation, which can lead to vascular injury, endothelial cell dysfunction, and subsequent atherosclerotic arteriopathy in obesity [44].

Hyperinsulinism, characteristic of T2DM, disrupts two key pathways in cellular metabolism. Upon binding to its receptor, insulin can activate either the phosphatidylinositol 3-kinase (PI3-K) pathway, which is central to downstream metabolic and antiapoptotic pathways, or the mitogen-activated protein kinase (MAPK) pathway, which promotes non-metabolic cellular proliferation [45]. In obesity and T2DM, the PI3K pathway becomes resistant to insulin, whereas the MAPK pathway exhibits unopposed stimulation. This situation leads to unregulated mitogenesis, which may potentiate atherosclerosis and cancer. In addition, insulin resistance in obesity and T2DM can promote gluconeogenesis, deactivates glucose transport into the cell, and halts glycogen

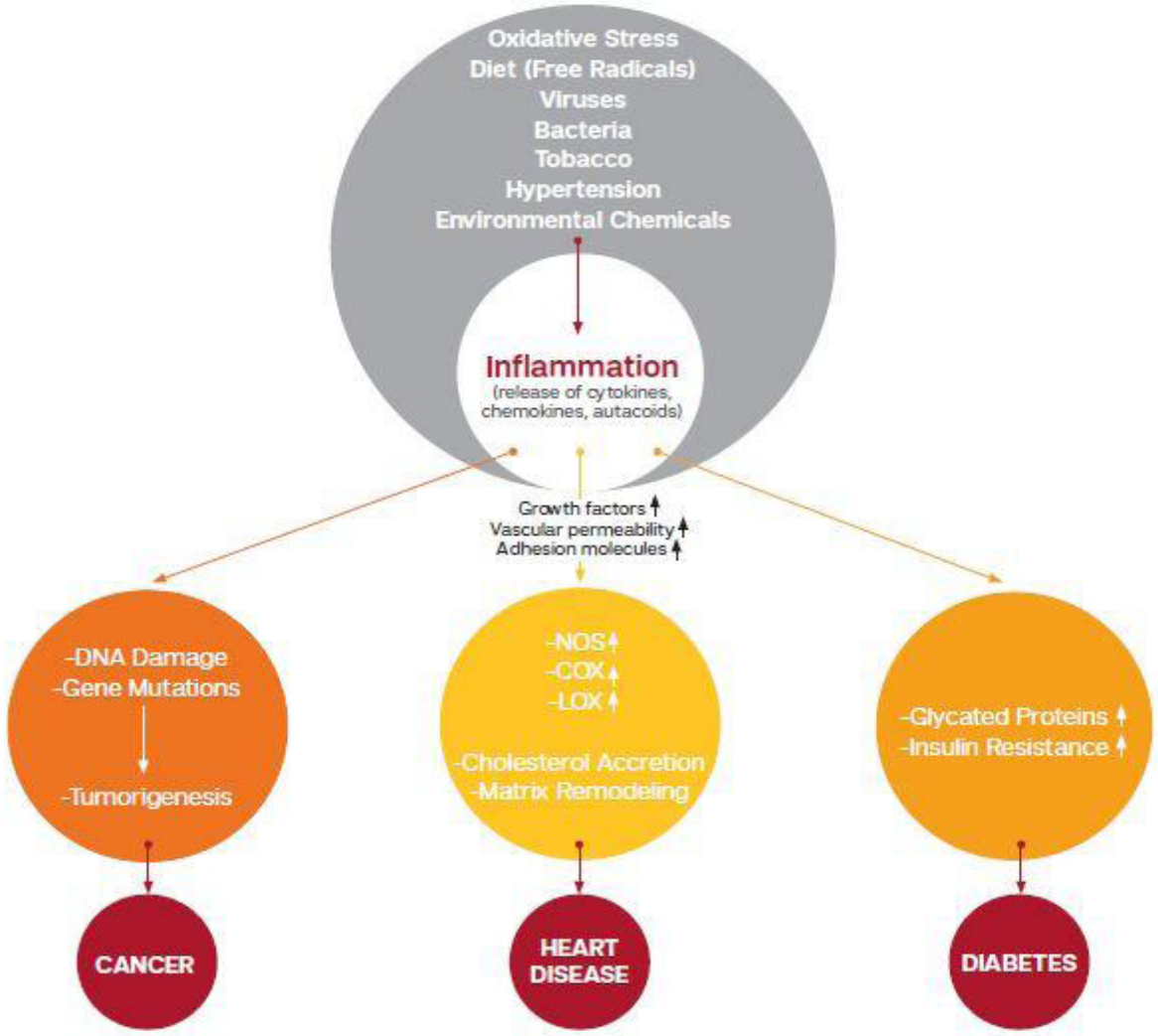

Figure 1: Some inflammatory networks common to heart disease, diabetes, and cancer. In humans, pathophysiological causes of inflammation include oxidative stress, diet-induced free radicals, DNA and RNA viruses, bacteria, tobacco product-derived nicotine, hypertension, and additional environmental factors. One important aspect of the inflammatory response is the release of cytokines/chemokines and autacoids, which can cause cell damage or cell activation, predisposing to tumorigenesis. In the pathogenesis of heart disease, inflammation can also stimulate growth factor release leading to intimal hyperplasia and/or vascular permeability changes, cholesterol accretion, tissue remodeling, activation of the nitric oxide synthase with NO production, inflammatory eicosanoid production through the COX and LOX, and adhesion molecule expression (VCAM, ICAM). The latter can facilitate the migration of macrophage scavenger cells into the vessel wall, thus exacerbating atherogenesis. Finally, inflammation can induce the production of advanced glycation end-products (AGEs) and/or insulin resistance, both of which can predispose to diabetes.

synthesis, which elevates plasma glucose and worsens the cell's energy deficit. Deficient lipolysis is due to insulin resistance, moreover, increases circulating free fatty acid levels, predisposing to further atherogenic dyslipidemia [46].

Hyperglycemia, itself, initiates another key pathway to inflammation in T2DM. Hyperglycemia generates glycated proteins and lipids known as advanced glycation end-products (AGEs), which interact with their receptors on macrophages (RAGEs), generate byproducts of oxygen metabolism called reactive oxygen species (ROS); this pathway activates nuclear factor-kB (NF-kB), which facilitates transcription of inflammatory cytokine genes [47]. ROS, such as nitric oxide radical, superoxide anion radical, peroxides, and hydroxyl radicals are highly reactive, can damage membrane lipids, proteins, and carbohydrates, and may induce DNA strand breaks, thus increasing the demand on DNA repair mechanisms [47]. Thus, ROS induce inflammation as well as cellular injury and DNA damage, all of which predispose to CVD, T2DM, and cancer.

Silent information regulator proteins, or sirtuins (SIRTs), represent a seven-member family of highly conserved histone deacetylases that forestall the development of cancer, cardiovascular disease, and T2DM, thereby promoting longevity [48,49]. SIRT1 is the most critical sirtuin in modulation of vascular function, and regulates endothelial cell physiology by promoting vasodilatory and regenerative functions of the vascular wall. SIRT1 prevents ROS-induced apoptosis of vascular endothelial cells by deacetylating p53, rendering it susceptible to ubiquitination and degradation. SIRT1 also stimulates production of NO through deacetylation of lysine 496 and 506 on eNOS, and blocks expression of plasminogen activator inhibitor, a prothrombotic, anti-fibrinolytic serine protease inhibitor. In the presence of hyperglycemia, oxidative stress, and inflammatory cytokines, endothelial cell SIRT1 expression is depressed, suggesting a contribution to the accelerated cardiovascular disease of T2DM. The role of p53 deacetylation vis a vis other post-translational modifications in carcinogenesis is an area of active investigation.

Non-coding RNAs include both long non-coding RNAs (lncRNAs) and microRNAs. LncRNAs, which are defined as 200 or more nucleotides in length, are highly expressed in endothelial cells [50]. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), for example, promotes proliferation of ECs in response to VEGF, and elevated levels are associated with adverse outcomes in cancer. Levels of MALAT1 increase in hypoxia and in response to high glucose, providing a possible link between T2DM and cancer. In addition, several of the more than 1000 sequence-specific, ~21-nucleotide inhibitors of messenger RNA translation, known as microRNAs (miRs), have been shown to regulate cholesterol and fatty acid metabolism [51]. miR-122, for example, increases expression of cholesterol synthesis genes, and reprograms glucose metabolism in the breast cancer premetastatic niche to promote metastasis [52]. In addition, miR-33 targets the ABCA1 cholesterol efflux pump, thereby increasing intracellular cholesterol. Finally, oxidized LDL can down-regulate miR-125a-5p in monocytes, increasing intracellular cholesteryl esters in macrophage foam cells. miRs are an emerging and potentially druggable group of intracellular modulators.

Obesity is a common, predisposing link between diabetes and atherosclerosis [32]. Adipose tissue produces the pro-inflammatory cytokines IL-1β, IL-6, TNFα, and IL-18, an effect that is accentuated in the obese individual [35]. One way in which chronic inflammation contributes to insulin resistance is by increasing suppressor of cytokine signaling (SOCS) proteins that attenuate insulin receptor signaling [53,54]. As mediators of cytokine-induced insulin resistance, SOCS1 and SOCS 3 reduce phosphorylation of insulin receptor substrate 1 (IRS1) and IRS 2, adapter proteins that transmit insulin signals to the PI3K and MAPK pathways in adipocytes. Therefore, as stimulators of SOCS, cytokines contribute critically to the development of insulin resistance.

Through the action of phospholipase A2, mechanical trauma, cytokines, and growth factors stimulate the release of membrane-associated arachidonic acid (20:4ω6), making it available to cyclooxygenases (COXs), lipoxygenases (LOXs), and the cytochrome P450 pathway for production of bioactive eicosanoids (figure 2) [55]. Prostaglandin products of COX enzymes are released from cells by facilitated transport, and interact with up to nine different, widely expressed cell surface receptors, all members of the G protein-coupled superfamily of seven-transmembrane spanning proteins (GPCRs). Leukotrienes are produced by the action of neutrophils, macrophages, and mast cells when activated by immune complexes or bacterial products, and also interact with GPCR receptors.

Constitutively expressed COX-1 produces prostaglandin E2 (PGE2) and PGI2, which interact with GPCRs, and often have opposing biological actions [55]. Inducible COX-2 is expressed by macrophages, leukocytes, and endothelium in response to inflammatory cytokines [56]. The disparate (patho) physiologic roles of COX-derived products may be governed by their coupling to individual downstream isomerases [55]. Non-steroidal anti-inflammatory drugs, such as aspirin, target COX-1 and COX-2 in the treatment of inflammation, tumorigenesis, and fever.

Particularly relevant to the inflammatory response to injury, LOX isoforms are constitutively present in monocytes, and inducible in macrophages. Lipoxins, the products of LOX activity, possess both pro-inflammatory and pro-resolving capabilities, whereby

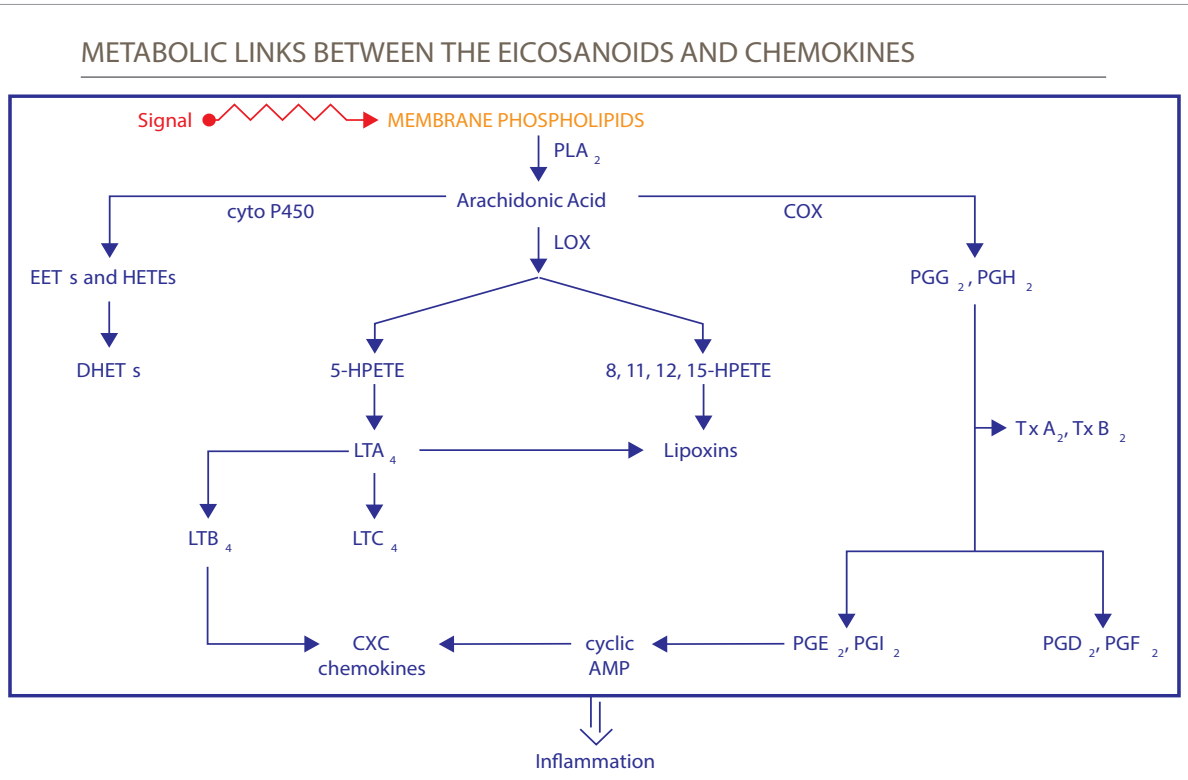

Figure 2: Metabolic links between eicosanoids and chemokines. Arachidonic acid is released from membranes by the action of phospholipase A2 on membrane phospholipids. Through the cytochrome P450 pathway, arachidonic acid can be converted to EETs and HETEs. Alternatively, it can be converted into prostaglandins (PGs) by cyclooxygenase (COX), via endoperoxide intermediates, PGG2 or PGH2. Thromboxane (TxA2) is produced in platelets while PGE2, PGI2, PGD2, and PGF2 are synthesized by vascular cells and inflammatory cells, such as macrophages. Arachidonic acid is also converted into HPETEs through the action of lipooxygenase LOX). HPETEs can be used to make leukotriene A4 (LTA4), a precursor for for the production of the lipoxins or other leukotrienes, namely LTB4 and LTC4. In the presence of cAMP, LTB4 is also a substrate for the synthesis of chemokines. Elevation of these biological response modifiers contributes to inflammation, which predisposes to CVD, T2DM, and cancer.

they can not only initiate or amplify, but also resolve inflammatory responses. In the synthesis of lipoxins, 15S-hydroxyeicosatetraenoic acid (15S-HETE), formed by15-LOX in monocytes, is absorbed by neutrophils and converted to lipoxin A4 (LXA4) in a 5-LOX-catalyzed reaction [56,57]. In addition, lipoxins can serve as anti-angiogenic factors, potentially curtailing tumor angiogenesis and vascular intimal hyperplasia.

Toll-like receptors (TLRs) are transmembrane receptors that recognize a spectrum of pathogen- and damage-associated molecular pattern (DAMP and PAMP) molecules, generally leading to activation of innate immune cells [58]. TLR4, for example, interacts with bacterial lipopolysaccharide to activate NF-κB, thus inducing expression of TNFα, IL-1β, and IL-6. TLR4 activation also induces expression of the nucleotide-binding domain, leucine-rich repeat-containing, pyrin domain-3 containing protein (NLRP3), which is central to the formation of the inflammasome. The assembled inflammasome activates caspases that convert pro-IL-1β and pro-IL-18 to their cleaved, secretable forms [35]. TLR2, is increased in endothelial cells overlying atheromata, and is particularly important in the accumulation of atherosclerotic burden, in LDL receptor-deficient mice. TLR4, on the other hand, is central to the recruitment of activated macrophages to the lesion, and appears to play a role in plaque rupture and formation of occlusive thrombi [58]. In the setting of a high-fat diet, TLR4, which is highly expressed in the adipocyte, responds to excess free fatty acids by dampening insulin action, thus connecting diet to T2DM [59–61]. In most tumors, expression of TLR4 is associated with a poor outcome; TLR4 is expressed on many lung, prostate, colon, and breast tumor cells, where its stimulation increases expression of factors, such as VEGF, GM-CSF, and IL-6 and IL-8, which are pro-inflammatory and trophic for tumor growth [62]. Thus, TLRs link the metabolism of dietary fat with metabolic inflammation, insulin resistance, T2DM, CVD, and cancer.

The inflammasome is a cytoplasmic complex that forms within innate immune cells and consists of a nucleating receptor protein (e.g., NLRP3), an adaptor protein such as apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and an inflammation-associated protease, such as caspase-1 [35]. When NLRP3 assembly is activated, ASC oligomerizes and caspase-1 is activated, allowing cleavage of pro-IL-1β and pro-IL-18 into their mature, secretable forms. Microbial products, toxins, and environmental substances can all activate the NLRP3 inflammasome.

In atherosclerosis, the NLRP3 inflammasome can be activated by either ROS or lysosomal perturbation in both mouse and human macrophages [63]. Phagocytosis of cholesterol crystals may lead to lysosomal membrane damage and release of lysosomal enzymes, such as cathepsins, into the cytoplasm causing inflammasome activation and apoptotic cell death [64]. In hyperglycemia, thioredoxin-interacting protein (Txnip) is the single most-highly up-regulated transcript in pancreatic islet cells [65]. Txnip is a direct ligand for NLRP3, and thus provides a potential explanation for the role of elevated glucose in inflammasome activation [35]. Increased ROS, which can emanate from damaged mitochondria, can induce conformational changes in Txnip, suggesting that mitochondrial dysfunction may contribute to inflammasome activation in T2DM [66]. In diabetes, insulin resistance increases production of amyloid, which, upon phagocytosis, can also activate the inflammasome. It appears that the precise role of the inflammasome in neoplasia is less clear and likely variable among disparate tumor types, but several recent studies suggest that inflammasome activation may drive progression of certain malignancies, such as breast cancer [67,68].

Chemokines, or chemotactic cytokines, are biological response modifiers that facilitate cell migration in wound repair in inflammatory states [69]. In atherosclerosis, CXC superfamily chemokines (chemokines where X is any amino acid), such as CXCL (chemokine X ligand) 1, CXCL2, CXCL3, and CXCL8, recruit inflammatory cells that release pro-angiogenesis factors, including basic fibroblast growth factor (bFGF) and vascular endothelial cell growth factor (VEGF), thus promoting atheroma development. This class of chemokines also promotes tumor cell survival and growth [52,53]. The altered chemokine and chemokine receptor expression profile in tumor cells may recruit inflammatory cells that release tumor-enhancing angiogenic factors [70], whereas ELR (Glu-Leu-Arg motif bound to a chemokine)−CXCs may attenuate tumor angiogenesis and metastasis [71,72]. Some chemokines promote tumor cell adhesion to the vessel wall and tumor cell migration [73], and may explain why certain inflammatory disorders, such as prostatitis, hepatitis, and pancreatitis, predispose to cancer [69,74]. Neutralizing antibodies directed against chemokines or their receptors have been used successfully to block tumor cell growth [69]. Antibodies to CCL (chemokine ligand) 2 can significantly reduce tumor burden in prostate cancer-bearing mice, and reduce breast cancer [69,75,76]. Inhibition of the CXCL12-CXCR4 signaling pathway can block cancer cell migration and invasion [69,76].

In diabetic patients, chemokine expression is stimulated byoxidative stress [77], amyloid deposition [78], glucotoxicity [79], and lipotoxicity [80], and leads to recruitment of T cells to adipose tissue [69,81]. Similarly, obese patients have elevated levels of CCL2 in their adipose tissue and blood [69,82], and CCL2 and CXCL10 levels are also elevated in patients with diabetic retinopathy, suggesting a role in macrophage recruitment to the retina [69,83]. Individual polymorphisms in the CX3CL1 receptor, CX3CR1, may either predispose to or protect against coronary artery disease and acute coronary syndrome [69,84]. Eicosanoid production appears to be linked to production of chemokines, which can stimulate inflammation (figure 2), which is common to CVD, T2DM, and cancer.

Inflammation-Based Treatments for CVD, Diabetes, and Cancer

In atherosclerosis, lipid-lowering statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis, have become a mainstay in the primary and secondary prevention of CVD. At the same time, new links between statins and inflammation have emerged (35). For example, two hydrophobic statins, lovastatin and simvastatin, have been reported to increase release of IL-1β and decrease release of the IL-1 receptor antagonist by peripheral blood mononuclear cells in a dose-dependent manner [85]. These effects may reflect a block in the isoprenoid biosynthetic pathway that is normally driven by mevalonate kinase (MK) and generates steroids, cholesterol, and vitamins A and E; individuals deficient in MK develop a hyper inflammatory disease known as hyperimmuno globulinemia D with recurrent fever (HIDS), and benefit from treatment with IL-1 receptor antagonist [35]. Several clinical trials are currently evaluating the efficacy of anti-inflammatory drugs for the treatment of atherosclerosis; these include to cilizumab for inhibition of IL-6, anakinra to block the IL-1 receptor, and MLN-1202, a CCR2 antagonist [86].

Data from animal models strengthen the postulate that inhibition of the inflammasome pathway may have utility in diabetic cardiovascular disease. For example, caspase-1inhibitorinterleukin converting enzyme 1 significantly reduced cardiac dysfunction and left ventricular inflammation in streptozotocin-treated diabetic rats

[35], while blockade of TNFα reduced cytokine levels, expression of leukocyte adhesion molecules, and myocardial inflammation [87]. Thus, several pro-inflammatory pathways implicated in diabetic atherosclerosis offer novel strategies for prevention of CVD in T2DM [35]. These include IL-1β-neutralizing antibodies from Novartis, Lilly, and Xoma, namely canakinumab, Ly2189102, and Xoma 052, respectively [35]. NLRP3 inhibitors are also under consideration as anti-inflammatory agents for diabetic CVD [35].

ATP-citrate lyase (ACL) is an enzyme that links glucose and lipid metabolism with cancer progression, and provides another potential target for MetSyn and cancer therapy [88]. ACL catalyzes the formation of acetyl-coenzyme A (CoA) and oxaloacetate from citrate produced during glycolysis in the presence of ATP and CoA. In adipose tissue, cytosolic acetyl-CoA is carboxylated in the first step toward fatty acids and, eventually, triglyceride synthesis. ACL expression levels correlate inversely with tumor stage and differentiation, and ACL serves as a negative prognostic marker in many forms of cancer [88]. For the control of several forms of cancer as well as the hyperlipidemia of MetSyn, several small molecules, as well as hydroxycitrate, an active component of Garcinia cambogia, are being used to target ATP-citrate lyase with promising early results [88].

Targeting inflammation directly is another effective strategy in some, but not all, forms of cancer [34]. For example, inhibition of COX-2 with NSAIDS reduces the incidence of colon cancer related to premalignant polyposis [89]. In addition, blocking inflammatory signals emanating from angiotensin II type 1 receptor signaling in fibroblasts has shown promise in a mouse model of desmoplastic pancreatic ductal adenocarcinoma [90]. Inflammation is also a consequence of radiation therapy, whereby damaged tissue recruits bone marrow-derived myeloid cells, which can then stimulate regrowth of the tumor [91]. Whether the inflammatory response generated by RT enhances tumor ablation or promotes relapse is not yet clear, as analysis of RT data may be complicated by variability in delivery mechanism and dosing schedule. Clearly, this is an area ripe for further research.

Even more promising are recently developed strategies that target immune "checkpoints" to relieve the immunosuppression that frequently accompanies cancer. Cytotoxic T lymphocyte-associated protein 4 (CTLA4) is a receptor that is highly expressed in activated regulatory T cells and functions to diminish immune responses. Efforts to disinhibit T cell responses by blocking the action of CTLA4 have led to a new class of drugs called immune checkpoint inhibitors [92]. CTLA-4 functions by outcompeting CD28 binding to the co-stimulatory molecule B7, thereby creating the "checkpoint" that prevents T cell proliferation [93]. Humanized anti-CTLA-4 antibodies, such as ipilimumab (Bristol-Myers Squibb), allow activation of effector T cells, and are showing impressive clinical efficacy against melanoma and other tumors [94–96]. Checkpoint inhibitors are also being used to target the programmed death 1 pathway that limits T cell response in cancer [92,97]. Expressed primarily during the late phase of T cell activation, the programmed death 1 protein (PD-1) and its ligand PD-L1 protect tumors by inducing T cell apoptosis [97]. Pembrolizumab and nivolumab are humanized monoclonal antibodies that block ligand binding to PD-1, permitting T cell activation [92]. These drugs appear to be effective against melanoma, non-small cell lung, and renal carcinoma [98,99]. We have summarized the inflammation-based treatments for CVD, diabetes, and cancer including the primary targets of the drugs and their side effects in table 1.

Summary

An increasing number of inflammatory pathways link CVD, diabetes, and cancer through the production of cytokines, lipid autacoids, chemokines, and other factors. Although inflammation is a highly organized, protective response to cellular trauma, it can, when dysregulated, exacerbate the progression of disease. Characterization of the inflammatory pathways linking CVD, diabetes, and cancer has helped identify potential targets for which new drugs may minimize or even reverse disease. In the near future, an improved understanding of inflammatory pathways will stimulate the development of new, testable drugs, which are likely to include long-acting monoclonal antibodies, small molecule therapeutics (perhaps nanoparticles), and a new generation of anti-inflammatory statins to modulate the metabolic linkage points common to CVD, diabetes, and cancer.

Disease Area	Drug Class / Example	Primary Target	Relevant Pathways	Side Effects (e.g)	Impact on Inflammatory Pathways
CVD	Statins	HMG-CoA reductase	Cholesterol biosynthesis, decrease in ROS, NFkB, IL-1ß, IL-1ra secretion	Muscle pain; diabetes risk; liver damage	Anti-inflammatory
CVD	Immunosuppressive drugs	e.g. IL-6, IL-1 receptor, chemokine receptors	Cytokine and chemokine signaling	Various immunosuppression (infection, metabolic, GI)	Anti-inflammatory
CVD	PCSK9 inhibitors	Proprotein convertase subtilisin/kexin type 9	Cholesterol homeostasis, innate immune response	Neurocognitive, further data needed	Anti-inflammatory
Diabetes	Caspase-1 inhibitors	Caspase-1/Interleukin-1 converting enzyme	Inflammasome	Further data needed	Anti-inflammatory
Diabetes	Immunosuppressive drugs	e.g. TNF, IL-1β	Cytokine feedback loops	Further data needed	Anti-inflammatory
Cancer	Checkpoint Inhibitors	CTLA-4 PD1, PDL-1	T cell-mediated tumor kill	Pruritus, rash, diarrhea, pneumonitis	Pro-inflammatory
Cancer	ATP citrate lyase inhibition	ATP-citrate lyase	Macrophages, NOS, Prostaglandins	glucose and lipid metabolism	Anti-inflammatory
Cancer	Immunosuppressive drugs	e.g. COX-2, angiotensin II type 1 receptors	Prostaglandin synthesis, pro-inflammatory ARB signaling	Mild immunosuppression	Anti-inflammatory

Table 1: This table summarizes some examples of drugs specific for CVD, diabetes and cancer where we indicate some of their primary targets, relevant metabolic pathways, side effects and their general impact on inflammation.

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