Review

Oxidative Stress and ROS Linking Diabetes and Cancer

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Simple Summary: Globally, Diabetes Mellitus is the sixth leading cause of death, whereas Cancer is the second leading cause of death in the US and is the most prevalent disease worldwide - a major public health problem worldwide, both diseases extract enormous financial and societal costs. Both diseases share risk factors of obesity and sedentary lifestyles. Diabetic patients have been shown to be at increased risk for several types of cancers. This review seeks to explore the influence of oxidative stress and oxygen free radicals on the molecular and signaling pathways occurring in diabetes that result from metabolic hyperglycemia, because of obesity, that ultimately lead to oxygen free radical activation of cell regulatory mechanisms, inflammatory reactions, and immune responses that result in cancer expression.

Abstract: Type 2 diabetes mellitus (T2DM) accounts for one-sixth of deaths, globally, whereas cancer is the second leading cause of death in the U.S. T2DM is a known risk factor for many cancers. This review examines the link of Reactive oxygen Species (ROS)-altered metabolic and signaling pathways in T2DM to cancer. These reprogrammed metabolic and signaling pathways are activated that contribute to diabetic complications, impact redox balance (Oxidative Stress), and have differential roles in early and late stages of cancer. If the respiratory chain is highly reduced (as under hyperglycemic conditions) or if reduced cofactors accumulate, ROS are greatly elevated. ROS may cause mutations in mitochondrial DNA (mtDNA) that result in further ROS elevation. Amplification of ROS results in activation of PKC, an overarching signaling pathway that activates MAPK with subsequent regulation of several factors that result in pathophysiological manifestations of T2DM and cancer. Upregulation of PKC leads to deregulation of NF-kß that regulates the PKB/P13/Akt pathway that orchestrates cell survival, growth, proliferation, and glucose metabolism manifested in cancer. It also affects Insulin Receptor Substrate (IRS-1), decreasing insulin stimulated glucose transport and glucose uptake, disrupting subsequent cell signaling pathways contributing to the development of T2DM. Dyslipidemia is a hallmark of T2DM and cancer. ROS-induced lipid peroxidation leads to systemic inflammation, producing inflammatory prostaglandins, cytokines and chemokines that result in tumor proliferation, rapid tumor growth, and modulation of immunity. The dual role of ROS in early and late stages of cancer make antioxidant therapy precarious and may be responsible for controversial results. A system that delivers an antioxidant directly to mitochondria may be useful in inhibiting formation of ROS early during the pre-diabetic stage whereas antioxidant therapy must be halted in later stages to retard metastasis.

Keywords: Cancer; Diabetes; ROS; Oxidative stress; Signaling pathways; Antioxidants' dual role in cancer

1. Introduction

Diabetes Mellitus (DM) accounted for 6.7 million deaths globally in 2021 and was the sixth leading cause of death worldwide. [1, 2]. Thirty-seven million people in the US suffer from DM. The annual cost incurred by this disease in the US is approximately $379 billion USD [3]. The American Diabetes Association lists three main types of diabetes – Type 1 results from autoimmune destruction of beta-cells in the pancreas that produce insulin. Type 1 DM requires insulin therapy for survival. Type 2 DM (T2DM) results from an insulin secretary defect, insulin resistance or insensitivity and accounts for about 90-95% of

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people in the US with DM [4, 5]. T2DM is the fastest growing disease globally and the mortality rate is expected to rise nearly 10-fold by the year 2030 [1]. Type 3 is gestational diabetes that develops in pregnant women who have not been previously diagnosed as diabetic, and while this type of DM usually subsides after birth of the baby, both mother and child are predisposed to T2DM later in life [4].

Although cancer death rates have declined from a peak in 1991 through 2018, due largely to reductions in smoking, improved disease management, and breakthroughs in treatment and therapies, cancer remains the second leading cause of death in the US with over 600,000 cancer deaths projected in 2021 [6-8]. On a global basis, approximately 22 million new cancer cases are projected in 2030 – based on population ageing and growth. This represents a 54% increase on the 14.1 million new cases in 2012 [9]. According to WHO, cancer is a major leading cause of death globally, accounting for 1 in 6 deaths in 2018 [10]. The economic and societal burden of cancer is great, ranging from 1.8% of gross domestic product (GDP) in the US in 2017 to 1.07% of GDP for the European Union [11].

T2DM has been associated with increased risks for various cancers [12] Among those cancers in which the increased risk with T2DM have been reported are pancreatic [13], colorectal [14], hepatocellular carcinoma (liver) [15], bladder [16], breast (postmenopausal) [17, 18], endometrial [19], and non-Hodgkin's lymphoma [20]. And although an inverse association was observed for prostate cancer [21], T2DM did not reduce aggressive forms of the cancer and mortality rates were higher in diabetic patients [22]. T2DM was associated with a 23% increased risk of prostate cancer death and a 25% increased risk in all-cause mortality [23].

Obesity and sedentary lifestyle are risk factors shared by both T2DM and 13 types of cancer [24]. A report that 77% of pediatric T2DM patients exhibit obesity does not portend well for future cancer risk [25]. Obesity in individuals afflicted with insulin resistance (T2DM) leads to a hyperglycemic condition linked to higher risk of cancer and in which up to 10-fold higher levels of oxygen radicals (ROS) may be produced as a result of increased flux of glucose through normal metabolic pathways [26-28]. As a result, a number of metabolic and signaling pathways are activated that contribute to diabetic complications, impact redox balance (Oxidative Stress), and have differential roles in early and late stages of cancer [28,29].. It is the intent of this review to examine the link of these ROS-altered pathways in T2DM to cancer expression.

2. Oxidative Stress and Reactive Oxygen Species (ROS)

2.1. Background.

Major atmospheric oxygenation events, occurring about 2.4 to 1.8 billion years ago and again, 800-500 million years ago, resulted in fundamental redox evolutions that impacted elemental composition of the biosphere [30]. It is believed that the first ROS appeared on Earth with the first atmospheric oxygen, about 2.4-3.8 billion years ago [31]. Indeed, ROS have played a pivotal role in the evolutionary reactions of life.

The concept of "Oxidative Stress" has evolved from early studies in which it was observed that, in the presence of oxygen (O_2), the lethal dose of X-ray radiation was about one-third that required to produce an equivalent lethality under anoxic conditions [32]. This so-called "oxygen effect" was the result of radicals from O_2 and hydrogen peroxide (H_2O_2) that attacked DNA [33], although ROS also attack proteins and lipids and are implicated in the causal etiology of T2DM [28], and cancer [29].

Oxidative stress, as a consequence of excessive ROS production, is characterized by an imbalance between the generation and removal of these species. Redox imbalance results in insulin resistance, beta-cell dysfunction, and impaired glucose intolerance that are found in T2DM [34]. ROS may be generated exogenously and endogenously. Exogenous sources of ROS may be air pollutants, metals, asbestos, tobacco, or radiation, including UV [34, 35]. Oxidative stress can arise from excess food intake, and it has been shown that an intake of excessive calories can lead to a 5-10-fold increase in ROS, resulting from loss

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of normal respiratory chain regulation [36]. Redox imbalance has been shown to be one of the most important fundamental reasons for cancer development, progression, and metastasis [34, 37]. Among those mechanisms that exhibit potential for creating a prooxidant state, or oxidative stress, are modulation of the cytochrome electron transport chain (ETC); inhibitors of antioxidant defenses; membrane active agents; and inflammatory agents [38]. All are interdependent manifestations of T2DM that link to cancer.

2.2. *ROS and endogenous reactive species*

Molecular oxygen, polyunsaturated fatty acids, sulfhydryl compounds, quinones, and related compounds that can easily transfer single electrons tend to be the major endogenous sources of reactive species [39, 40]. The primary ROS, superoxide anion [28], is formed by the univalent reduction of molecular oxygen. Superoxide anion is reduced to hydrogen peroxide (H_2O_2). Normally the subsequent reaction yielding the highly damaging hydroxyl radical (•OH) proceeds slowly unless catalyzed by a heavy ion, e.g., iron. Iron-sulfur clusters are found in the Mitochondrial Complexes that facilitate the transfer of electrons in the ETC. The reductive pathway of molecular oxygen is depicted in **Figure 1.**

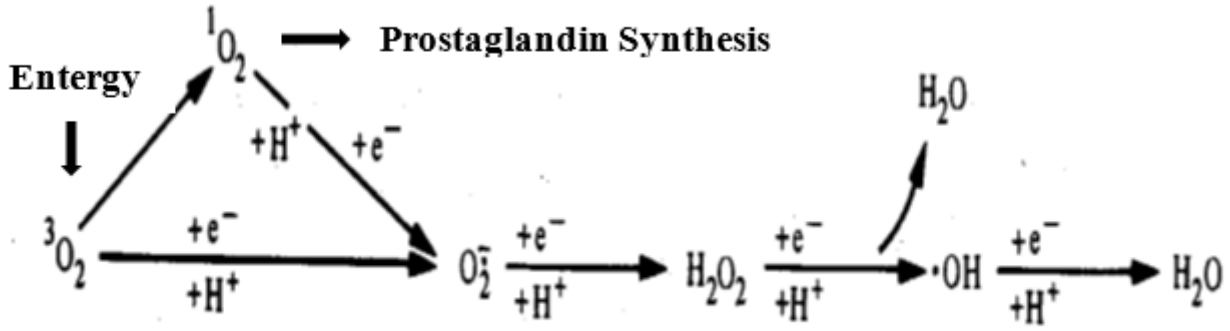

Figure 1. Major ROS are derived from the mono-, di-, and trivalent reduction of molecular oxygen. An alternative path to superoxide anion formation is through formation of singlet oxygen ($^1O_2$). Singlet oxygen is not a free radical, albeit, an excited state species created by absorption of energy that lifts an electron to a higher energy orbit. It is highly reactive and produces biological effects similar to other ROS [41]. Evidence supports the thesis that singlet oxygen is the initial oxidant formed in the initial peroxidative steps of prostaglandin synthesis [42].

2.3. Antioxidant defense in maintaining Redox balance.

Redox imbalance is a ROS-initiated manifestation of T2DM. Although ROS are generated in normal euglycemic, insulin-regulated glucose metabolism, the levels are controlled by factors that regulate cellular respiration. These factors include NAD-linked substrates, succinate, oxygen, and antioxidant enzymes that maintain the redox balance. The major endogenous antioxidant enzyme, super oxide dismutase (SOD) dismutes superoxide anion to H_2O_2. Hydrogen peroxide is reduced to water by Catalase and Glutathione Peroxidase. The oxidized glutathione (GSSG) is re-reduced to GSH by glutathione reductase in the presence of NADPH (35, 39). These reactions are depicted in Figure 2. Overwhelming of this natural defense system occurs under hyperglycemic conditions, when the respiratory chain is highly reduced, reduced cofactors accumulate, and up to 10% of the respiratory oxygen consumed is lost as ROS [27]. This sets the stage for examining the T2DM link to cancer.

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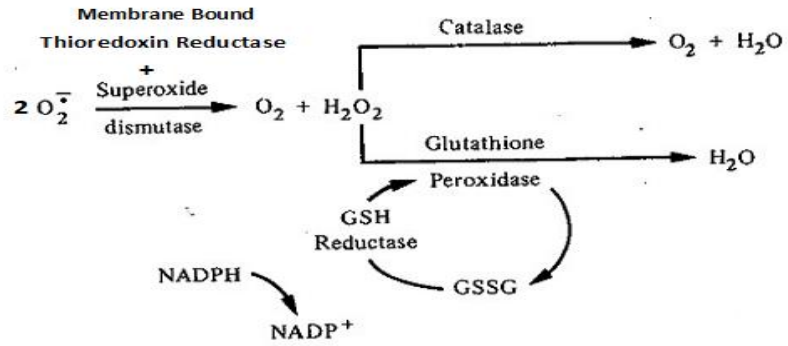

Figure 2. Simplified schema of major antioxidant enzymes that maintain Redox balance. These antioxidant defense enzymes include epidermal membrane-bound thioredoxin reductase and endogenous superoxide dismutase – both are involved in the dismutation of superoxide anion to hydrogen peroxide. The latter may be reduced to H_20 and O_2 by either catalase or glutathione peroxidase.

Antioxidant supplementation to maintain or restore redox balance and prevent cancer has largely either failed or been controversial [43-45]. Some antioxidants, e.g., ascorbic and uric acids, promote autoxidation by reducing oxygen activators i.e., transition metals and quinones, resulting in free radical formation, thus acting as a pro-oxidant. Ascorbic acid, in the presence of a metal complex and oxygen (as might occur in the respiratory ETC) can undergo a redox-induced homolysis that leads to formation of perhydroxyl radical or superoxide anion [46]. An adverse side effect of high vitamin C supplement intake has been associated with an increased risk of cardiovascular disease (CVD) mortality in diabetic postmenopausal women [47]. A water-soluble analog of vitamin E, Trolox, has been shown to increase melanoma metastasis in experimental animals [48]. A small clinical study, in which subjects were supplemented with vitamin E, found that the antioxidant significantly reduced skin malondialdehyde levels but did not affect other measures of oxidative stress in human skin [49].

Resveratrol, (3,4',5-trihydroxystilbene) is a polyphenol derived primarily from red grape skin, peanuts, and berries. that has shown some promise as an anti-cancer agent [50]. The polyphenol was shown to have beneficial effects on T2DM, e.g., increased insulin sensitivity, decreased blood glucose levels, and positively regulate several other biomarkers. However, the effects on cancer were dependent upon the type of cancer. It produced beneficial effects on breast cancer while causing severe adverse effects in multiple myeloma patients. The polyphenol affects all carcinogenic stages, i.e., initiation, promotion, and progression, as well as inducing the apoptotic pathway [50]. Specific flavonoids, secondary polyphenol metabolites, have been shown to have beneficial effects on T2DM by targeting cellular signaling pathways in specific tissues, influencing ß-cell function, insulin sensitivity, glucose metabolism, and lipid profile [51]. Other phytochemicals, e.g., those found in green tea, have been shown to have beneficial effects on certain human cancers, although conflicting results have also been reported [52, 53]. Other flavonoids that have antioxidant properties and have been shown to have anti-neoplastic properties include curcumin (found in turmeric) and Epigallocatechin gallate (GCG, found in green tea) [54, 55]. Dietary supplementation in clinical trials with Resveratrol have, generally, been ambiguous and some even detrimental [50].

ß-carotene (a tetraterpenoid, C40 compound consisting of eight isoprenoid residues) is known to quench singlet oxygen and to have strong antioxidant activity. Indeed, increased ß-carotene intake has been inversely associated with T2DM risk [56]. A study in which diet quality score, plasma carotenoids (both total and ß-carotene), and lipid

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peroxidation was employed to monitor oxidative stress, found that ß-carotene significantly reduced lipid peroxidation, associated with the oxidative status [57]. ß-carotene has been shown to have effects on adipogenesis, lipolysis, insulin resistance and obesity – all hallmarks of metabolic diseases and T2DM [58-60]. A seminal 1981 study found that individuals that consumed greater quantities of green, leafy and yellow vegetables exhibited a lower risk for cancer and it was proposed that ß-carotene, because of its singlet oxygen quenching and antioxidant activity, might be responsible [61]. Epidemiological studies found inverse relationships between cancer risks and ß-carotene intake and blood levels. However, clinical trials failed to support these findings and ß-carotene supplementation was found to actually increase lung cancer by 18% [44]. The conflicting clinical data for several types of cancers have been previously reviewed [45]. Experimentally, dietarily supplemented ß-carotene was shown to provide photoproduction against UV-induced skin tumors [62]. However, in 1998, a study reported that dietarily supplemented ß-carotene exacerbated UV-carcinogenesis [63]. A closed-formula diet was employed in the studies in which photoprotection occurred whereas a semi-defined diet was employed in the study in which exacerbation of carcinogenesis occurred [64]. A dietary study in which various levels of ß-carotene and vitamins C and E were added to the semi-defined diet failed to ameliorate the exacerbating effect of the carotenoid [65]. It became apparent that other dietary components present in the closed-formula diet (other carotenoids, their isomers, or other phytochemicals) not present in the semi-defined diet were responsible for potentiation of the carcinogenic response to ß-carotene. The carotenoid has been shown to exhibit either limited antioxidant protection or to behave as a pro-oxidant under oxidative stress conditions [66] and several pathways have been proposed by which these responses might occur [45].

A synthetic phenol, 2,6-di-tert-butyl-*p*-cresol, or butylated hydroxytoluene (BHT) was shown to provide dramatic photoprotection against UV-carcinogenesis [67, 68]. The mechanism of action of BHT is compatible to action mediated *via* UV dose diminution, perhaps by altering the keratin cross-links of the stratum corneum [69, 70]. As with the ingestion of any chemical agent, other physiological effects are induced and BHT induces hepatomegaly, accompanied with induction of hepatic Phase I and II microsomal detoxification enzymes (mixed function oxidases) [71, 72]. Employing a modified Ames test, the influence of antioxidant supplementation (containing BHT) was assessed for activation of N-2-fluorenylacetamide, a potent hepatocarcinogen [73]. Mutation frequencies in antioxidant supplemented animals increased twofold, creating a risk to the host it was intended to benefit. Indeed, BHT has been shown to induce cell proliferation of lung epithelia [74] and to act as a tumor promoter in promotion-sensitive mice [75].

NAC (N-Acetylcysteine) is a stable form of l-cysteine that is a necessary precursor for glutathione synthesis. Glutathione (GSSG) is a major antioxidant as depicted in Figure 2. NAC was reported to be effective in diminishing T2DM complications, inferring that glucose homeostasis was maintained and that ROS production was diminished [76]. However, NAC supplementation of hyperglycemic T2DM patients exhibited no benefit on markers of glucose metabolism, ß-cell response, or oxidative status and it was concluded that NAC supplementation was unlikely to represent an effective therapeutic prospect [77]. Further, NAC supplementation has been shown to increase melanoma metastasis in experimental animals [78], a consequence of the differential role that ROS play in the early and late stages of cancer [29]. However, when glycine was added to the NAC supplement, (GlyNAC) and supplemented to T2DM patients, it improved mitochondrial dysfunction, insulin resistance, increased glutathione synthesis, and lowered oxidative stress [79]. GlyNAC, if proven effective and safe, may circumvent the disappointing results that have questioned the use of antioxidant supplementation as a means to reduce cancer risk in the general public. It approaches the catalytic antioxidant that Brownlee [80] posited that would act continuously to reduce ROS. GlyNAC would act endogenously to regenerate glutathione, a major antioxidant, and restore and maintain the redox balance. This appears to be a promising avenue for future research.

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The safety and effectiveness of antioxidant supplementation was questioned after several reports of nominal or adverse effects of antioxidant supplementation appeared [43, 44, 63, 77, 78]. A review and meta-analysis reported a significant (16%) increase in all-cause mortality in trial participants receiving ß-carotene and vitamins A and C treatments [81]. Antioxidant supplementation was reported to negate some of the health-promoting effects of physical exercise [82[. When vitamins C and E were supplemented to T2DM patients, blocking exercise-dependent formation of ROS, health-promoting effects of physical exercise, i.e., promoting insulin sensitivity and antioxidant defense was negated. The disappointing and conflicting results of large doses of vitamins C, E and ß-carotene should not be too surprising {29]. Supplementing the highly complex and intricate natural antioxidant defense system with a high level of one antioxidant may alter the stoichiometry of the antioxidant pathways and push the pathway from an antioxidant to a pro-oxidant state or through other pro-oxidant paths [45,83] As a result of these reports of adverse effects of antioxidant supplementation on cancer risk and incidence, the World Cancer Fund/American Institute for Cancer Research and the IARC withdrew recommendations for dietary antioxidant supplementation as a means for cancer prevention [84, 85]. This should not deter efforts to seek endogenously metabolized agents that maintain redox balance and thus have the potential to prevent T2DM complications and cancer. It may require a reassessment of our current methods and the development of new algorithms for safety testing and overall risk/benefit analysis, weighing the risk of one form of cancer to other forms and adverse pathophysiological responses [86]. The application of new methods, e.g., liquid biopsy, might be employed for T2DM patients to determine when antioxidant therapy must *cease* to avoid antioxidant-ROS inhibition, leading to cancer development and metastasis [87]. Timing of antioxidant therapy is important to the oxidative stress/ROS link of T2DM and cancer. The reduction of ROS and oxidative stress, however, remains a fertile avenue of investigation to prevent and ameliorate both T2DM conditions and the cancers that are linked.

3.0. Mitochondria, the Electron Transport Chain (ETC) and Respiration.

3.1. Mitochondria and ROS

Mitochondria are the primary source of endogenous ROS. Usually, ROS are formed in the normal (euglycemic, insulin-regulated glucose metabolism) oxidation of foodstuffs, primarily glucose, accounting for about 1-2 % of oxygen consumed, and are essential for regulating cell development and normal cellular processes, cellular signaling, and cell death. However, under hyperglycemic, insulin-resistant glucose metabolism as manifested in T2DM, about 10% of the consumed oxygen may be lost as ROS [27]. Under these conditions, the respiratory chain is highly reduced, and ROS are shown being formed at the starred sites of glucose metabolism depicted in Figure 3, although the ROS are formed as the electrons are transferred from the reduced cofactors through the ETC. Figure 3 also shows that under persistent hyperglycemic conditions, the Polyol Pathway is activated through which about 30% of the body's glucose is metabolized [88]. This pathway, and related NAD depleting pathways ultimately result in a NADH/NAD+ imbalance and Oxidative stress in T2DM [28]. The resulting increased ROS also increase flux through the Hexosamine pathway that produces the precursor of all amino sugars for the synthesis of proteoglycans, glycolipids, and glycoproteins [89].

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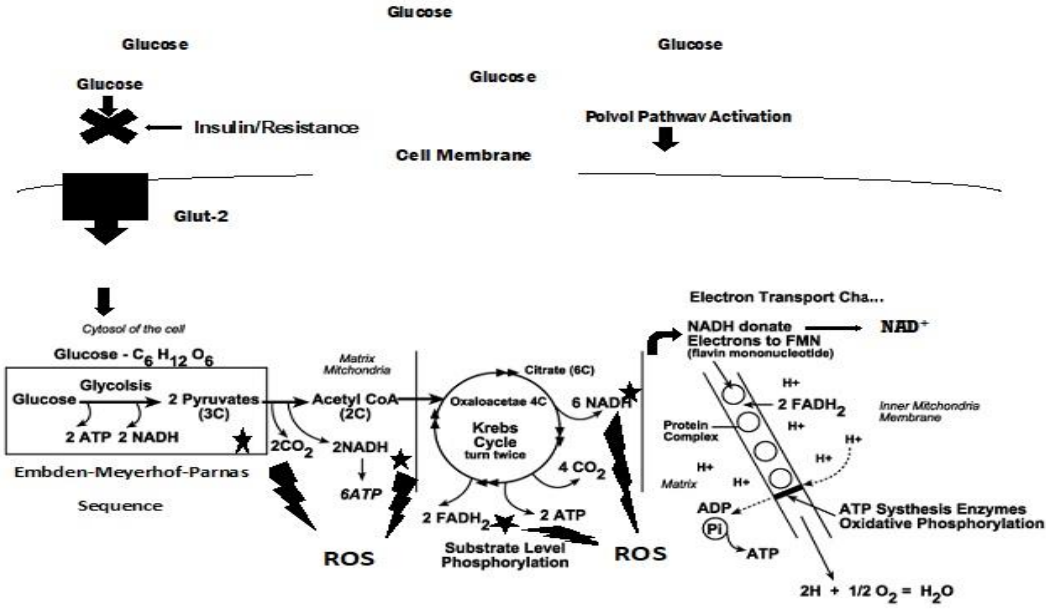

Figure 3. Hyperglycemic, insulin-resistant glucose metabolism and formation of ROS [28]. Starred sites represent where cofactors have been reduced. The reduced cofactors donate electrons through the ETC to produce superoxide anion as depicted in Figure 4.

3.2. Electron Transport Chain.

The chain of proteins through which the electrons flow are categorized as Complex I, II, III and Q cycle, and IV [90]. The ETC, embedded in the mitochondrial membrane, is depicted in Figure 4.

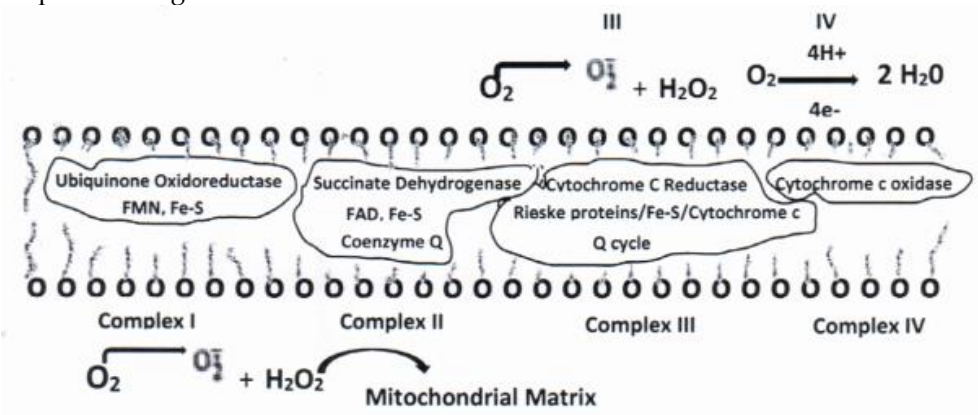

Figure 4. Electron Transport Chain is composed of protein complexes I, II, III, and IV.

Complex I, ubiquinone oxidoreductase and containing NADH dehydrogenase, transfers two electrons from NADH to FMN, Fe-S clusters and finally coenzyme Q, with the ultimate production of superoxide oxide anion and H_2O_2, moving into the mitochondrial matrix. In this process, four hydrogen ions pass from the mitochondrial matrix into the intermembrane space, increasing the proton motive force (Δp) [91, 92].

Complex II. Succinate dehydrogenase accepts electrons from succinate oxidation and transfers these electrons to FAD, Fe-S clusters, and coenzyme Q. No protons are translocated across the mitochondrial membrane, resulting in less ATP being produced as compared to Complex I.

Complex III. Cytochrome C reductase. The cytochrome c component can only accept a single electron at a time and the process occurs in two steps in the Q cycle. [90]. The second step of the Q cycle is a repeat of the first with Complex III releasing four protons

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into the intermembrane space that contributes to the Δp, and transferring the electrons, one at a time, to Complex IV. It is the Q cycle that produces superoxide anion [93].

Complex IV. Cytochrome c oxidase is the final electron carrier of aerobic respiration and catalyzes the transfer of electrons to dioxygen to produce water [90].

4. Diabetic versus Cancer Metabolism and Antioxidants

4.1. Diabetic metabolism

It should be noted that the pathophysiological responses in T2DM are cell and tissue specific, whereas the description of diabetic metabolism are synthesized herein, to present a general, comprehensive overview. Nevertheless, persistent hyperglycemia leads to repeated, acute changes in cellular metabolism initiating four metabolic pathways induced by ROS production that, in turn, lead to higher levels of ROS and oxidative stress. These pathways are activated by increased ROS levels that elevate PARP (poly (ADP-ribose) polymerase) levels and downregulate GADPH (glyceraldehyde-3-phosphate dehydrogenase) levels. The latter activate the Polyol pathway, the Hexosamine pathway, the Protein Kinase C pathway, and the formation of advanced glycation products [28, 80], as depicted in Figures 5-9.

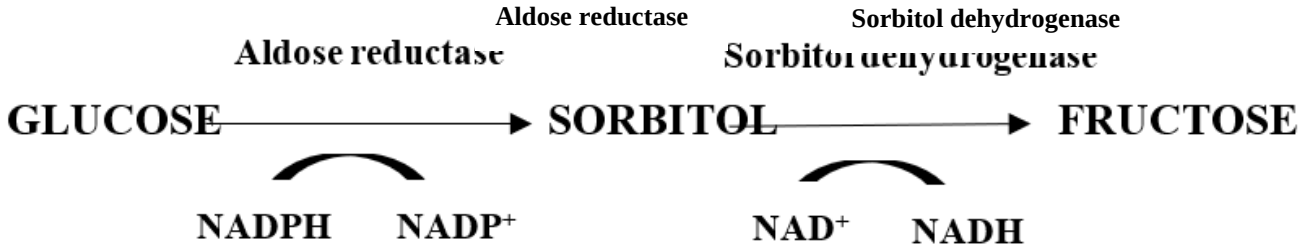

Figure 5. Polyol Pathway. It is estimated that under persistent hyperglycemic conditions, the Polyol pathway is activated by elevated ROS levels that, in turn, elevates PARP levels and downregulates GADPH levels. The latter activates and upregulates Polyol and Hexosamine pathways, accelerates the formation of AGE and activates PKC as depicted below, (reprinted from Reference 28).

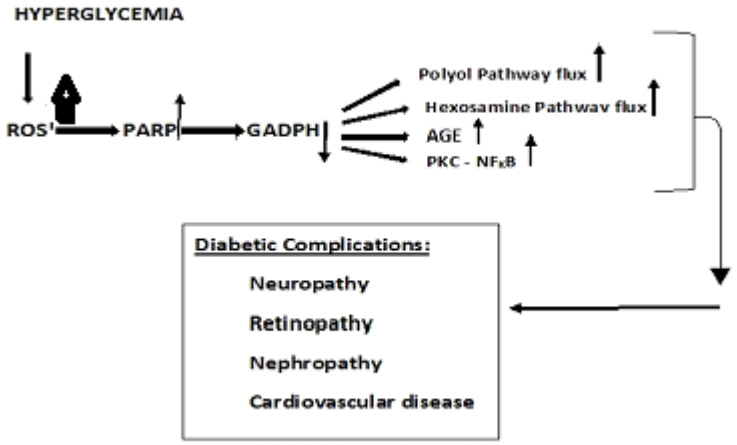

Figure 6. Hyperglycemic mediated elevation of ROS level and activation of the Polyol and Hexosamine pathways, advanced glycation end products, and the PKC pathway leading to tissue damage and diabetic complications. .

As the high levels of intracellular glucose are reduced by aldose reductase to sorbitol, the reaction consumes NADPH, a cofactor critical for regeneration of the natural antioxidant, reduced glutathione (Refer to Figure 2). Decreasing the level of reduced glutathione increases intracellular oxidative stress (94). Two NAD+ degradative reactions, a mitochondrial family of signaling proteins (Sirtuins), a histone deacetylase and an ADP ribosyl

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transferase are NAD+ dependent, the latter consumed in the formation of nicotinamide, thus contributing to the NADH/NAD redox imbalance (95, 96). Thus, the Polyol pathway plays a critical part in pathophysiology that contributes to diabetic complications and is initiated by formation of ROS.

Fructose-6-phosphate is metabolized either through the Embden-Meyerhof-Parnas pathway, or under conditions when the rate of reoxidation of NADPH is limited, may be produced when glucose metabolism is diverted through the Pentose Phosphate shunt. Nevertheless, fructose-6-phosphate is the initial point of both the Hexosamine and PKC pathways. The Hexosamine Pathway is depicted in Figure 7 (reprinted from Reference 28).

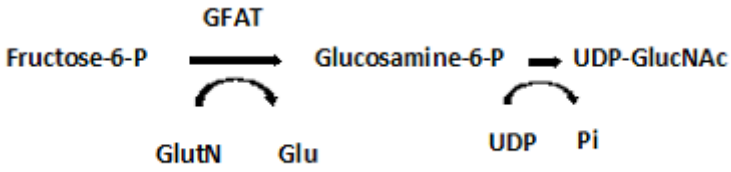

Figure 7. Hexosamine Pathway. GFAT, glutamine: fructose-6-phosphate-aminotransferase; UDP-GlucNAc, Uridine-5-diphosphate-N-acetylglucosamine; GlutN, Glutamine; Glu, Glutamic acid; UDP, Uridine 5′-diphosphate; Pi, inorganic phosphate. Glutamine fructose—phosphate-aminotransferase. .

GFAT regulates the flux through the Hexosamine pathway and is involved in the etiology of diabetic nephropathy (97). Uridine-5-diphosphate-N-acetylglucosamine (UDP-GlucNAc) is the precursor of amino sugars required for the synthesis of proteoglycans, glycolipids, and glycoproteins.

The PKC pathway, depicted in Figure 8 and reprinted from reference 28, is a signaling pathway that not only results in pathophysiological manifestations of T2DM, but is also a direct link to cancer.

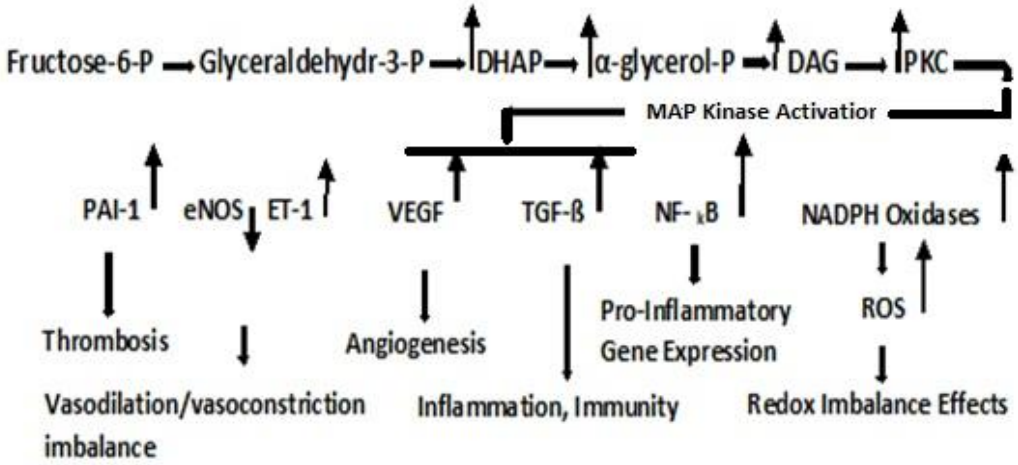

Figure 8. Protein Kinase C (PKC) Pathway. Metabolism of Fructose-6-phosphate results in the up-regulation of dihydroxyacetone phosphate (DHAP), α-glycerol-phosphate and diacylglycerol (DAG). PKC activation, although cell type and isoform specific, is generally activated by DAG [98].
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The activation of PKC leads to activation of a cascade of kinases, including MAP kinases that regulate a number of factors that are not only important to T2DM but to cancer, as well. **PAI-1**, Plasminogen activator inhibitor-1 (serpin E1) is a risk factor for thrombosis

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and atherosclerosis [99]. The downregulation of **eNOS**, nitric oxide synthase results in vasodilation and upregulation of ET-1, Endothelin-1, a vaso-constrictor [100]. Vascular Endothelial Growth Factor (**VEGF**, a glycoprotein) mediates Retinopathy and Nephropathy in T2DM [101]. VEGF-D plays a role in lymph angiogenesis and promotes lung metastasis by regulating prostaglandins produced by the collecting lymphatic endothelium [102, 103]. Transforming growth factor-beta (**TGF-ß)**, a multifunctional cytokine, is a pro-inflammatory that is important in host immunity [104]. TGF-ß signaling is known to play a role in a large number of human cancers [105-107]. Over 40 TGF-ß proteins have thus far been identified and this family of ligands exert their activities as homodimers or heterodimers that are covalently linked by disulfide bonds, the latter a product of oxidation (ROS?) [108] of two sulfhydryl groups and a vulnerable target for antioxidant action. TGF-ß manifests dual faces in a complex signaling system with respect to ROS. The signaling pathway exerts an anti-tumorigenic function during early stages of cancer formation and a pro-tumorigenic effect at later stages, promoting metastasis [107, 108]. This dual function for ROS has **also** been reported in pancreatic cancer [108]. Downregulation of insulin receptor substance by ROS favors premalignant tumor formation whereas elevated ROS levels enhances metastasis. The specific response to TGF-ß during tumor progression has been attributed to a range of definitive factors, among which are changes in receptor expression, downstream signaling, evasion of immune response, stimulation of inflammation, and recruitment of cell types that favor tumor growth or promote angiogenesis [106]. **NF-kß**, nuclear factor-kappa B, is a DNA binding protein factor required for transcription of pro-inflammatory gene expression [109**]**. NF-ķß is a central mediator of the inflammatory response and a major participant in innate and adaptive immune responses [110]. Thus, it plays a major role in the link between inflammation and cancer [111]. Importantly, NF-ķß regulates the ability of preneoplastic and malignant cells to avert apoptosis-mediated tumor surveillance. The complexity of the NF-ķß signaling pathways are now becoming apparent and, as in T2DM, it is clear that various effects of NF-κB on cancer initiation, promotion, and progression are cell-type, tissue and context specific [112]. **NADPH Oxidase,** nicotinamide adenine dinucleotide phosphate oxidase (a flavocytochrome B heterodimer), is a major source of ROS in T2DM [113]. Increased ROS results in a decrease of glyceraldehyde-3-phosphate dehydrogenase (**GADPH**) and an increase in methylglyoxal, a strong glycating agent that is a source of advanced glycation end-products (**AGE**). The latter contribute to diabetic complications [80]. An additional burst of ROS are generated when AGE are bound to their receptor sites **(RAGE)**. The overall effect of NAPDH Oxidases has been Redox imbalance. Nevertheless, the discovery of a family of NADPH oxidases (NOXs 1-5 and dual oxidases DUOX1/2 has provided a mechanism for ROS formation in tumor cells. Evidence suggests that these oxidases produce ROS in the G.I. tract under chronic inflammatory stress and may contribute to colorectal and pancreatic carcinomas in patients with inflammatory bowel disease and chronic pancreatitis [115]. The NOX5 isoform is highly expressed in melanoma, prostate cancer, and Barrett's esophageal adenocarcinomas. Deregulation of these NADPH oxidases, leading to elevated ROS levels, has been recognized as a potential target for clinical therapy. An inhibitor, VAS2870 [3-Bezyl-7-(2-benzoaxozolyl) thio-1,2,3-triazolo(4,5-d) pyrimidine], has been shown to block ROS production, decrease cell proliferation and enhance the apoptotic response induced by TGF-beta in Hepatic cell carcinoma [116].

4.2. Dyslipidemia and Cell Signaling

It is known that hyperglycemia, as occurs in T2DM, results in elevation of circulating triglycerides and free fatty acids (FFA). This condition denotes serious dysfunction in lipid dynamics and leads to severe diabetic clinical complications [117]. Dyslipidemia is also a

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major risk factor for cardiovascular disease (CVD) [118]. Indeed, CVD and cancer share several similar risk factors. e.g., obesity, T2DM, dyslipidemia, chronic inflammation, oxidative stress, and cytokine production - all mediators that contribute to the connection of T2DM/CVD and cancer [119- 121]. Although conflicting evidence of CVD and cancer lipidomic risk profiles have been observed [122], other studies have demonstrated that elevated levels of lipid biomarkers are independently associated with all-cause mortality as well as CVD risk [123]. Further evidence of a CVD and cancer link was found when study participants who met 6-7 of Life's simple 7 ideal health ASCV (Atherosclerotic cardiovascular) metrics [124], exhibited a 51% lower risk for cancer incidence and those at high CV risk having a >3-fold increased risk of cancer compared with low CV risk subjects [119]. Thus, a link runs from T2DM to CVD, and Cancer, although the complexity of this link is multifaceted.

Type 2 Diabetes Mellitus-associated dyslipidemia may partially be a consequence of systemic FFA flux secondary to insulin resistance [125. 126]. At least 35% of gluconeogenesis in T2DM patients is FFA dependent. Efforts to explain the competitive oxidation between glucose and FFA resulted in what became known as the Glucose-Fatty Acid cycle, or the Randle cycle [127]. Fatty acids are first transported across the cell membrane by Fatty Acid transport protein 1 (FATP1) where a FA acyl-CoA synthetase yields acetyl- CoA in the cytosol or a carnitine palmitoyl transfers acyl-CoA across the mitochondrial membrane. The initial reactions occur in the cytosol. Acyl-CoA is transported across the mitochondrial membrane by carnitine palmitoyl transferase 1 (CPT1) (see Figure 9). Although the Randle cycle has been discussed previously, with respect to T2DM [28], a recapitulation is necessary to place the importance of these reactions in perspective to the link between T2DM and cancer. Acyl-CoA formation, in both the cytosol and mitochondria, induces ß-oxidation of FA [128]. In the mitochondria, this results in formation of Acetyl-CoA that feeds into the Krebs cycle, increasing citrate that, in turn, inhibits hexokinase and pyruvate dehydrogenase activities. Inhibition of hexokinase results in the downregulation of glucogenesis. Elevated Krebs cycle activity results in increased formation of $FADH_2$ and NADH that yield ROS as electrons are passed down the ETC [129]. The Acyl-CoA formed in the cytosol stimulates ß-oxidation in the peroxisome and upregulates the glyoxylate cycle by which glucose is synthesized.

Dyslipidemia, with respect to insulin resistance and T2DM, has been shown to be complex and cell specific. The influence of cell signaling may not only hold the key to varied results observed from the Randle cycle [128], *but the convergence of cell signaling pathways represent a direct link of T2DM and Cancer.* A comparison of Figures 8 and 9 demonstrate this link. Whereas signaling pathways are extremely complex with downstream paths involving isoforms of signal molecules, oncologic and tumor suppressor molecules, transcription factors, cell types, etc., it is the intention of this review to focus on the *overarching*, initiating pathways that link T2DM and Cancer.

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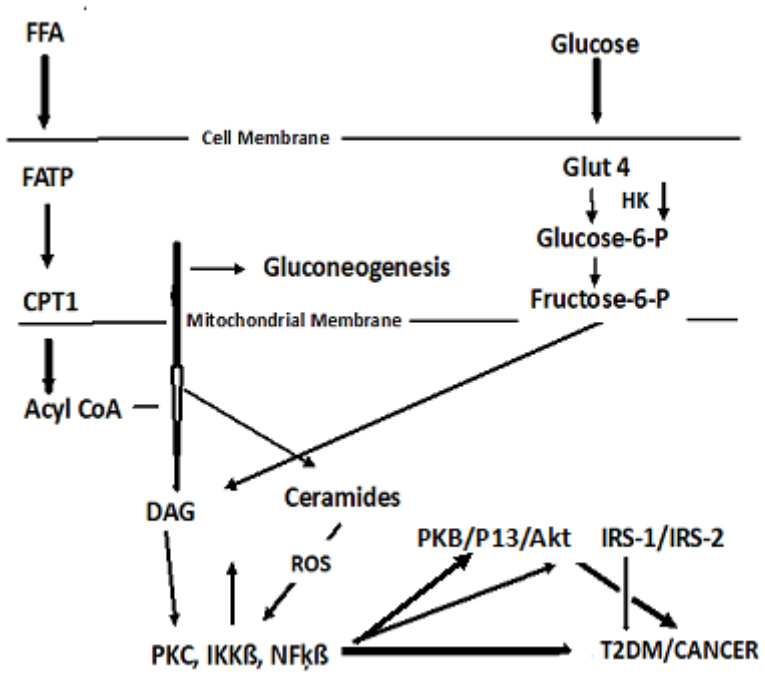

Figure 9. A simplified schema depicting confluence of Glucose and Free Fatty Acid ROS-induced signaling that links T2DM and Cancer.

A major convergence of signaling pathways involves Protein Kinase C (PKC) activation. Under hyperglycemic conditions in T2DM, incoming surplus energy from obesity is stored in adipocytes in the form of lipids or triacylglycerides (TAG). TAG is converted to diacylglyceride (DAG) by triglyceride lipase (TGL) [130]. Upregulation of DAG occurs through metabolism of Fructose-6-P (Figure 8). Convergence of these pathways to produce DAG is depicted in Figure 9. PKC upregulation is generally activated by DAG [98].

PKC isozymes, phospholipid dependent serine/threonine kinases, signal through multiple transduction pathways and, in cancer cells, are implicated in angiogenesis, cell proliferation, tumor promotion, invasion, migration, metastasis, and apoptosis (cell survival) [131-133]. PKCs role in normal cell function and that in cancer is complicated in that, based upon their structural and activation properties, three subfamilies are classified as: classic PKC isozymes that require DAG as activator and Ca^{2+} as cofactor; non-classic, regulated by DAG with no Ca^{2+} requirement; and atypical PKC that is not activated by DAG [131, 134]. Thus, the various isoforms may exhibit different responses dependent upon their target proteins and their subsequent signaling responses, with some isoforms even acting as tumor suppressors [133]. Generally, however, it is recognized that PKC are associated with a number of types of cancer, including breast [11,135], bladder [136], colon [137], gastric 138], glioma 139,140], head and neck [141,142], lung [143. 144], melanoma [145,146], and some types of leukemia [131, 147-150]. The most widely studied isozymes, in relation to cancer, have been PKCα, β, ε, and δ [131]. However, the theta isozyme, PKCϴ, is classified in a novel PKC subfamily and its expression is limited to only a few cell types. However, it controls T-cell activation, survival, and differentiation [151]. PKCϴ is highly expressed in T-cell immune responses, playing a critical role for the T-helper (Th2 and Th17) mediated responses while the cytotoxic T-cell driven responses remain relatively intact. Although the function and mode of action of this isoform is different, depending on the type of cancer, in most cancers the presence of an elevated PKCϴ leads to abnormal proliferation, migration, and invasion of cancer cells and, thus, promotes tumor aggressiveness [151].

IKKß (inhibitory kß phosphorylase) is a serine/threonine kinase that is upregulated either through the conversion of triacylglycerides (TAG) to diacylglyceride (DAG) in the FFA arm of the Randle cycle or upregulation of DAG through metabolism of Fructose-6-

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P in the glucose arm of the cycle [152] [**Figure 9**]. IKKß phosphorylates and deregulates NF-ķß, a serine/threonine kinase nuclear transcription factor that has critical roles in inflammation, immunity, cell proliferation, and apoptosis [153]. NF-ķß may also be activated by proinflammatory cytokines, e.g., tumor necrosis factor, (TNF)-α [154]. Most known hallmarks of cancer are affected by NF-ķß activation [155]. Some of these are depicted in Figure 8 after PKC activation induces a cascade of kinases, including mitogen-activated serine/threonine proteins (MAP Kinases) that regulate cell differentiation, proliferation, and apoptosis [156]. Although the downstream secondary signaling cascades are numerous and complex, one, depicted in Figure 9, has particular importance with respect of T2DM and cancer, i.e., NFķß suppression of IRS, PKB/Akt. Protein kinase B (**PKB**), serine/threonine-based proteins that are also known as **Ant** as the widely expressed isoforms of PKB, **α, ß**, and **γ,** are also known as **Ant1**, **Ant2**, and **Ant3** [157].

IRS-1, Insulin Receptor Substrate, phosphorylation and dysregulation reduces GLUT4 translocation to the cell surface, decreasing insulin stimulated glucose transport, and glucose uptake. It also disrupts subsequent cell signaling pathways, contributing to the development of T2DM [128, 158]. NF-ķß targets P13 (Phosphatidylinositol 3-kinase) that plays a central role in a complex, multi-armed signaling network that orchestrates cell response including cell survival, growth, proliferation, angiogenesis, migration and glucose metabolism [159, 160]. PI3K is presumed to activate most of its downstream targets *via* Akt, a serine/threonine kinase, that affects the aforementioned cellular responses [161].

Contributing to an already intricate and complex picture, is the formation of ceramides (Figure 9). Ceramide is a core Sphingolipid and generally produces antiproliferative responses, e.g., cell growth inhibition, apoptosis induction, and cell invasiveness – thus acting as a tumor suppressor [162, 163]. However, ceramide metabolism involves its glycosylation to produce AGE that reacts with receptor sites to 0form RAGE that, in turn, releases ROS (Figures 6, 8). Tumor suppressor function is lost, and ROS activates the PKC signal transduction pathway. Ceramide glycosylation is closely linked to drug resistance, and this has become a high interest area of investigation for therapeutic targets for cancer [164].

Dyslipidemia is a hallmark of T2DM. FFA flux yields acyl-CoA that induces ß-oxidation in the mitochondria that results in the formation of $FADH_2$ and NADH that, in turn, yields ROS as electrons are passed through the ETC. ROS attack of PUFA leads to increased lipid peroxidation that aggravates systemic inflammation. The relationship between inflammation and cancer was recognized in the mid-1800s when Virchow theorized that cancers originated at sites of chronic inflammation. The causal relationship between inflammation, innate immunity, and cancer is now recognized [165]. Cytokines, and this includes "chemokines" that are chemotactic cytokines, are the messengers for most of the biologic effects of the immune system, e.g., cell mediated immunity and allergic responses [166- 168]. The major source of cytokines/chemokines are T lymphocytes. Chemokines play a central role in the development and homeostasis of the immune system and are involved in all protective or destructive immune and inflammatory responses [168]. T lymphocytes are characterized by the presence of cell surface molecules, CD4 or CD8. Those lymphocytes expressing CD4 are known as helper T-cells and are prolific cytokine producers and are further subdivided into subsets Th1 and Th2. Th1 produces pro-inflammatory responses. The pro-inflammatory cytokine, Tumor Necrosis Factor—α, (**TNF-α**) a proinflammatory cytokine, regulates inflammatory cell populations but once homoeostasis is imbalanced and both Th1 and Th2 arms produce an overabundance of proinflammatory cytokines, rapid tumor growth and proliferation occurs [165]. (**Figure 10**). Indeed, in studies of particulate lung carcinogenesis it has been shown that chronic inflammation, alone, can initiate tumor growth without direct interaction with DNA [169].

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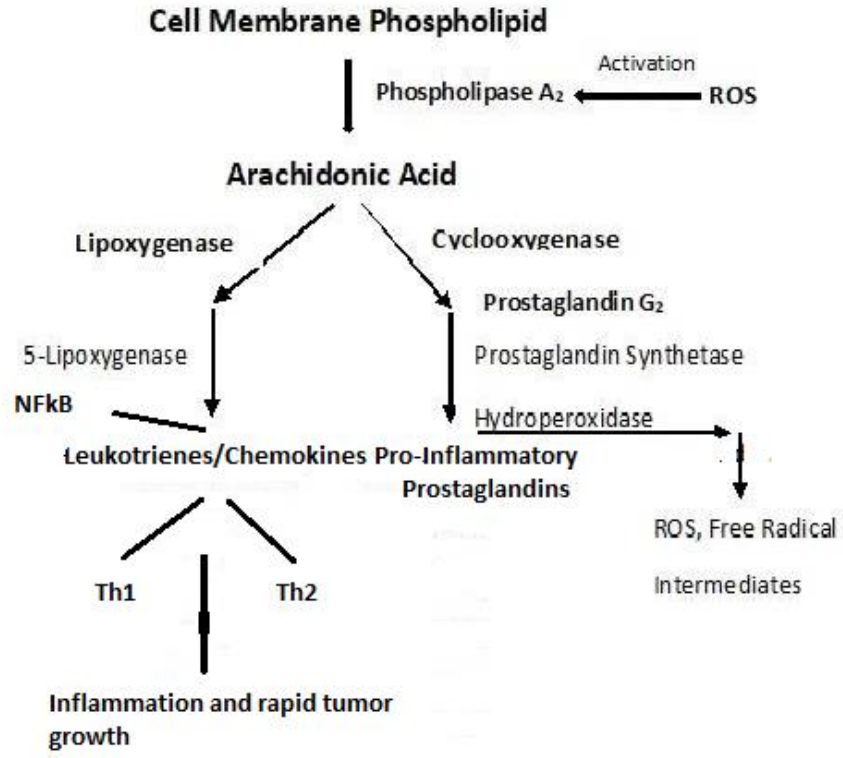

Figure 10. Pro-Inflammatory Schema Leading to Inflammation and Rapid Tumor Growth.

Irrespective of the actions of various isoforms and downstream transduction signaling, the activation of PKC is an overarching and primary signal transduction node for the linkage of T2DM and cancer. Under hyperglycemic conditions, ROS levels are elevated and initiate the reactions leading to PKC activation and to T2DM complications (Figures 6, 8). A convergence of PKC pathways from glucose and FFA metabolism, and the role of ROS, is depicted in Figure 9. This convergence links T2DM and cancer. Finally, ROS are known to promote a chronic state of inflammatory cytokines that result in tumor cell proliferation and rapid tumor growth [167] (Figure 10).

4.3. Cancer Cell Metabolism

Otto Warburg first observed, in 1922, that cancer cells exhibited a specific metabolic pattern – one characterized by a shift from aerobic respiration to anaerobic fermentation (the Warburg Effect) [170]. The aerobic respiratory metabolic pattern of normal cells and anaerobic fermentation of cancer cells is depicted in Figure 11.

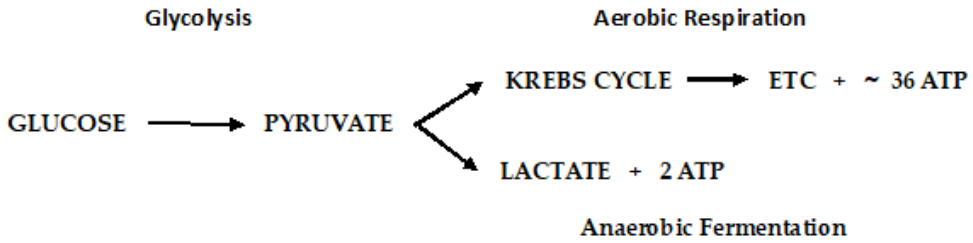

Figure 11. Metabolic pathways of glucose metabolism of normal (Aerobic Respiration) and cancer cells (Lactic acid Fermentation).

The Warburg Effect raises a number of questions that have been systematically addressed [171]. First, how does a switch to a much lower yielding ATP pathway as

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fermentation sustain tumor growth? Using mouse ascites (cancer) cells that obtain ~100% of their energy from fermentation, it was determined normal mouse cells consumed an average of seven mm3 of oxygen.mg/hr. whereas fermentation produced 60 mm3 of lactic acid/mg/hr. Converted to energy equivalents, cancer cells obtain approximately the same amount of energy from fermentation as normal cells do through aerobic respiration. A second question, recognizing that respiration of all cancer cells is irreversibly damaged (irreversible damage occurs as restoration of oxygen does not restore cells' normal respiration), is how this damage is induced without killing the cells? Warburg postulated that damage to the respiratory system could be induced by decreasing oxygen consumption, consequently decreasing yield of ATP or, uncoupling of respiration and ATP production with undiminished oxygen consumption, Injury to respiration is irreversible and this is common to all cancer incitants. Calculation of metabolic quotients demonstrated that the first phase of carcinogenesis (the irreversible damaging of respiration) need not involve a decrease in the respiratory quotient but entail uncoupling of oxidative phosphorylation without undiminished oxygen consumption. Warburg provided striking confirmation of his main conclusions from metabolic studies of the C3H/He mouse cell lines developed at the NCI. Two cell lines, developed from a single cell, demonstrate a high and low malignancy rate when injected into C3H/He mice. The anaerobic glycolysis quotient for the high malignancy line was $Q_M{}^{N_2}$ =60-80, that of the low malignancy rate was 20-30. The aerobic glycolysis values, $Q_M{}^{O_2}$, was 30 *vs* 10, for the high and low malignancy lines, respectively. They were of lower magnitude because of the Pasteur Effect which was greater in the high malignancy cell line. The Pasteur effect is the inhibiting effect of oxygen upon fermentation. As oxygen is increased, the accumulation of fermentation products is repressed and there is a decline in the rate of carbohydrate dissimilation. Conversely, the rate of oxygen consumption (Q^{O_2} = 5-10) in the high malignancy line was less than that of the low malignancy line (QO_2 = 10-15), corresponding to a greater level of respiratory damage in the high malignancy line. *In toto*, there is strong evidence consistent with the Warburg Effect but the question of how this irreversible damage is induced remains open and a very active area of investigation.

Some critics of Warburg's hypothesis, i.e., that the "driver of tumorigenesis is defective cellular respiration" have proposed alternative possibilities, particularly the activation of oncogenes and inactivation of tumor suppressor genes [172]. It is posited that damaged mitochondria are not the root cause of the aerobic glycolytic lesion exhibited by most tumor cells but results from oncogene-directed metabolic reprogramming required to support anabolic growth [173]. It is argued that most tumor mitochondria are not defective in their ability to conduct oxidative phosphorylation and that anabolic growth is the result of oncogene-directed metabolic programming and that the metabolites can be oncogenic by altering cell signaling and blocking cellular differentiation. In this scenario, activation of the P13/Akt pathway leads to enhanced glucose uptake, glycolysis, increased glucose transporter expression, and activation of hexokinase. Increased nutrient intake, glucose and glutamine, support the anabolic requirements of cell growth whereas proliferating cells use strategies to decrease their ATP production. The overall hypothesis is that reprogramming of the cells metabolism towards macromolecular synthesis is critical for maintaining cell mass and reaching G_2 phase in preparation for cell division. In this reprogrammed metabolism, the need is greater for reduced carbon and nitrogen and NADPH for reductive biosynthetic reactions. However, with respect to a link between T2DM and cancer, it should be noted that hyperglycemia leads to activation of the Hexosamine pathway that would limit glutamine availability [28]. Further, in insulin-resistant cells, mitochondrial respiration, glycolysis, and ATP levels decreased (in part due to changes in glucose transporter, GLUT4)- all conditions associated with cancer cells.

Seeming contradictory to the argument that most tumor mitochondria are not defective in their ability to carry-out oxidative phosphorylation, control of the latter's metabolic machinery resides in the mitochondrial DNA (mtDNA) and there have been extensive studies to examine the mitochondrial genome [172]. It is posited that long term consequences induced by ROS are the result of alterations in mtDNA and indeed, mutations in

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Complex 1, ubiquinone oxidoreductase, of the ETC are derived from mutations in mtDNA[174]. Although mutations in mtDNA occur at high frequency, the question of whether these mutations alter tumor behavior has been difficult to discern. Using the mtDNA from two tumor cell lines, one highly metastatic, the other of low metastatic potential, transfer of the mtDNA into recipient tumor cells conveyed the metastatic potential of the transferred mtDNA. The mutations produced a deficiency in respiratory Complex I and produced an overabundance of ROS. Experimental results indicated that mtDNA mutations contributed to tumor progression by enhancing metastatic potential of tumor cells [175]. A commentary to this study suggested that, using the methodology employed, the researchers failed to show evidence for formation of superoxide and hydrogen peroxide that was presumed to be generated from Complex I deficiency associated with mtDNA mutations [176]. Nevertheless, all of the mutations that affect Complex I have similar consequences, i.e., they promote an increase in ROS, increase succinate, and inhibition of mitochondrial pyruvate dehydrogenase (reducing the flux of pyruvate into the Krebs cycle), and stabilization of Hypoxia-inducing factor 1-α (HIF-1α) [172, 174].

Hypoxia (low oxygen tension) is thought to be one of the main elements in the switch between glycolysis and respiration [172,174]. Hypoxia induces a complex of intracellular signaling pathways including P13/Akt, MAPK, NFkß, and HIF – all of which are involved in cell proliferation, apoptosis, glucose metabolism, metastasis, and inflammation [177]. Low oxygen availability inhibits oxidative phosphorylation. Adaption of a cell to hypoxia is partially dependent on the expression and stabilization of Hypoxia-inducing factor 1-α (HIF-1α), a transcription protein that when overexpressed is implicated in promoting tumor growth and metastasis. Overexpression of HIF-1α in tumor cells and rapidly growing normal cells stimulates glycolysis and restricts mitochondrial respiration. Inadequate regulation of hypoxia is an important contributor to the malignant phenotype. Hypoxia also leads to immune-resistance and immune suppression that aid tumor cells to escape immune surveillance [178].

Considering the second possibility for transition to the Warburg phenotype, i.e., uncoupling of respiration and oxidative phosphorylation, mitochondrial uncoupling proteins (UCP) catalyze a regulated proton leak across the inner mitochondrial membrane without the generation of ATP [179]. ROS (superoxide) and long chain fatty acids activate UCP-1 which can be inhibited by purine nucleotides, e.g., ATP [180]. There are five isoforms of UCP that have been identified thus far, each with specific functions [181]. Increased expression of UCP-1 has been shown to play a relevant role in immune infiltration by regulating oncogene levels in ovarian cancer [182]. Based on cancer single cell sequencing data, tumor functional status analyses suggest that UCP-1 may down regulate invasion, epithelial-mesenchymal transition, metastasis, DNA repair, and angiogenesis. UCP-2 inhibits ROS production that results in reduced ADP yield and reduced insulin secretion [182]. UCP-2 also catalyzes an exchange and transport of intramitochondrial C4 intermediates (e.g., oxaloacetate) that negatively controls oxidation of acetyl-CoA-producing substrates through the Krebs cycle. This lowers the redox pressure on the mitochondrial respiratory chain, the ATP:ADP ratio, and ROS production [183]. Employing a UCP-2 knockout mouse, the first *in vivo* evidence was reported that UCP-2 significantly reduced the chemically induced formation of papilloma and malignant squamous cell carcinomas of the skin while not affecting apoptosis [184]. Lactate generation was significantly increased in the carcinogen-treated wild-type mice, but there was no difference between carcinogen-treated and vehicle-treated UCP-2 knockout mice. Upregulation of UCP-2 is known to promote aerobic glycolysis and increase lactate levels.

Seeking the "switch" that turns normal cells into the cancer phenotype seems inexpedient considering the cacophony of biological responses that may occur simultaneously within an indeterminate time span. As example, cell signaling pathways, including P13/Akt, MAPK, NFkß, and HIF, and their myriad of secondary responses; oxygen tension and overexpression and stabilization of HIF-1α; mutations in mtDNA, especially those affecting Complexes in the respiratory chain; and the uncoupling of respiration from oxidative phosphorylation, are all involved in the reprogramming of the metabolism of

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the cell. If there is a single "switch", ROS must be considered the prime candidate. Through a somewhat tortuous journey of possibilities, the conclusion remains the same, i.e., "reprogrammed metabolism should now be considered as a core hallmark of cancer" [173], and cancer joins T2DM, Metabolic Syndrome, and CVD, as a metabolic disease.

4.4. ROS' role in early and late stages of cancer

Mitochondrial damage and resulting dysfunction of respiratory components that are induced by ROS, lead to malignant transformation [35]. These organelles are essential for energy metabolism, apoptosis regulation, and cell signaling [185]. Overproduction of ROS, as occurs in hyperglycemia, induces cancer development by causing genomic instability (mtDNA), inducing signal transduction pathways that modify gene expression (tumor proto-oncogenes and tumor suppressor genes), and impairs oxidative phosphorylation. The latter results in production of more ROS that aggravates physiological and metabolic dysfunction. These elevated levels of ROS can cause cell apoptosis. ROS levels critically determine whether ROS augment tumorigenesis or terminate tumorigenesis *via* apoptosis [29]. Thus, a homeostatic balance of ROS must be maintained for normal cell survival [29, 35,186].

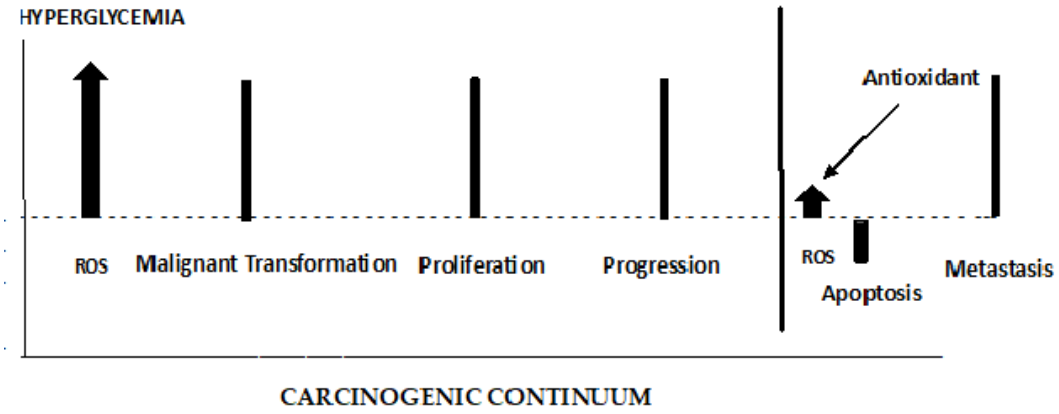

Figure 12. The differential role of ROS and Antioxidants in the early and late stages of cancer.

The role of ROS in initiating the early stages of carcinogenesis is depicted in **Figure 12**. ROS are elevated from Hyperglycemic metabolism. Elevated ROS result in malignant cell transformation. High ROS levels can lead to apoptosis; therefore, any effective antioxidant therapy should be administered prior to cancer cell proliferation. When antioxidants are administered late in the carcinogenic continuum, ROS levels are suppressed, apoptosis is lowered. The cancer cells lose their polarity, cell-cell adhesion, and gain mobility. This epithelial to mesenchymal transition is a major cause of tumor metastasis [186]. As seen in **Figure 12**, antioxidant therapy at this late stage of carcinogenesis results in a boost in metastasis. The timing of antioxidant therapy is obviously important and should be initiated as early as possible. If dietary interventions are not successful in addressing dietary risks leading to hyperglycemia, the antioxidant therapy should begin in the pre-diabetic phase of T2DM. Discontinuation of antioxidant therapy should take place before the later stages of carcinogenesis and metastasis. Unfortunately, up to this point, antioxidant supplementation, in clinical trials, in order to maintain or restore redox balance and prevent cancer ha**ve** largely either failed or been controversial for reasons given previously [43-45]. GlyNAC has shown some promise if it is shown to avoid the detrimental effects of NAC supplementation [77-79]. A recent report describes a mitochondrial targeting nanoparticle that delivers an antioxidant directly to mitochondria, the major source of endogenous ROS [187]. Perfection of these targeting systems hold promise for targeted antioxidant therapy.

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5. DISCUSSION AND CONCLUSIONS

Globally, the combined incidence of both T2DM and Cancer accounts for a significantly high mortality rate and exacts an enormous financial and societal burden. T2DM is a known risk factor for many forms of cancer, and both manifest a reprogrammed glucose metabolism, the latter leading to the "Warburg cancer phenotype".

Altered glucose metabolism provides the link of T2DM to cancer. This is the first point at which this link could be addressed – through dietary interventions to reduce the major risk factors for T2DM. Once insulin resistance and hyperglycemia occur, the altered metabolism associated with these conditions results in elevated ROS. ROS not only impact the cell's redox balance (Oxidative Stress), but can attack DNA, proteins, and lipids. ROS may have direct effects on mtDNA, resulting in mutations in the respiratory Complexes I-IV with further elevation of ROS levels. ROS may create hypoxic conditions by overexpression of HIF-1α that results in stimulation of glycolysis; restricts mitochondrial respiration; and promotes tumor growth and metastasis. A further complecting response to ROS is the activation of mitochondrial uncoupling proteins (UCP). These proteins catalyze a regulated proton leak across the inner mitochondrial membrane without the formation of ATP. There are five known isoforms of UCP, some exerting counter responses. Upregulation of the isoform, UCP-2, is known to promote aerobic glycolysis and increase lactate levels. Overall, ROS regulation of HIF-1a and UCP must be important contributing factors that drive cells to anaerobic fermentation and the Warburg cancer phenotype.

Hyperglycemia-mediated elevation of ROS levels lead to activation of the Polyol and Hexosamine pathways; advanced glycation end products; and the PKC-NF-kß pathways. The PKC signal transduction pathway leads to MAPK activation, and a downstream cascade of kinases that regulate a number of factors, e.g., VEGF, TGF-ß, NF-kß, and NADPH oxidase, that are important to the clinical symptoms and pathophysiologic manifestations of both T2DM and cancer. As example, VEGF mediates Retinopathy and Nephropathy in T2DM and promotes lung metastasis by regulating prostaglandins produced by the collecting lymphatic endothelium; TGF-ß is a pro-inflammatory cytokine that is important in host immunity and TGF-ß signaling is known to play a role in a number of human cancers; NF-kß plays a major role in the link between inflammation and innate and adaptive immune responses and regulates the ability of preneoplastic and malignant cells to avert apoptosis-mediated tumor surveillance; NADPH Oxidase deregulation leads to redux imbalance (Oxidative Stress) and to elevated ROS levels with its inherit consequences in T2DM and cancer. It should be emphasized that many of these effects are cell-type, tissue, and context specific and that we are addressing very complex pathologies in T2DM and cancer.

PKC activation can also result from dyslipidemia – a major hallmark of both T2DM and cancer. Secondary to insulin resistance, elevated systemic FFA results in a competitive oxidation between glucose and FA in adipose cells – known as the Randle cycle. FFA flux yields acetyl-CoA that is oxidized in the mitochondria and results in the formation of $FADH_2$ and NADH (also products of ROS-induced ß-oxidation of FA). The electron carriers yield ROS as they are carried through the ETC. ROS attack of PUFA leads to increased lipid peroxidation that results in systemic inflammation, producing pro-inflammatory prostaglandins, cytokines and chemokines, particularly IL-6, IL-1, and TNF-α, that result in modulation of immunity, tumor proliferation, and rapid tumor growth. ROS also activate phospholipase A_2 that cleaves Arachidonic acid that is oxidized through the lipoxygenase and cyclooxygenase pathways through which these pro-inflammatory products are produced. It is evident that ROS-induced effects on cell signaling, lipid oxidation/peroxidation, chronic inflammation, and immunity are etiologic factors in manifestation of both T2DM and cancer.

Although the rational approach to controlling redox balance and ROS levels would be antioxidant therapy, the differential role of ROS in early and late stages of cancer make such therapy precarious. Indeed, the safety and effectiveness of antioxidant supplementation was questioned after several reports of nominal or adverse effects of antioxidant

supplement appeared. Thus, the World Cancer Fund/American Institute for Cancer Research and the ARC withdrew recommendations for dietary antioxidant supplementation as a means of cancer prevention. Nor has antioxidant supplementation of T2DM patients been encouraging. It was proposed that to reduce direct oxidative damage, the amount of superoxide anion must be reduced and that conventional antioxidants were unlikely to do so effectively. Nevertheless, a recent report of a system that delivers and antioxidant directly to the mitochondria may be useful in inhibiting formation of ROS (particularly to inhibit superoxide anion) early in the pre-diabetic stage that then would break the link to cancer. Antioxidant therapy should be halted in later stages to retard metastasis. Timing of antioxidant therapy is important to the oxidative stress/ROS link of T2DM and cancer and may be responsible for some of the controversial results obtained earlier. Nonetheless, the reduction of ROS and maintenance of redux homeostasis remains a fertile investigative approach to prevent and ameliorate T2DM and the cancers that are linked.

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