

Significant Dietary Changes during Human Evolution and the Development of Cancer: From Cells in Trouble to Cells Causing Trouble

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Abstract

In all western societies, mortality rates from cancer are high and even increasing. In striking contrast, cancer rates are very rare and even non-existent in primitive cultures, like hunter-gatherer (HG) populations. HGs are free of disease as long as they adhere to their traditional low-insulinemic "Paleolithic" nutrition. With acculturation and transition to current high-carbohydrate/high-insulinemic "Western" diets (HCHIDs), cancer develops in high rates. This paper follows the question of how significant nutritional changes, brought about by the Agricultural revolution, may cause development of cancer. The evidence presented shows that the switch from a Paleolithic to a Western nutrition has brought about significant metabolic perturbations, like an abnormally increased activation of the insulin-like growth factor system, the sympathetic nervous system and the renin-angiotensin-system, an increased expression of HIF-1 α and other more, all of which are deeply involved in cancer development through promotion of proliferation, angiogenesis, inflammation, macrophage infiltration, metastasis and inhibition of apoptosis.

In addition, HCHIDs generate oxidative stress which may cause mitochondrial damage and genomic instability, and may interfere with normal stem cell development. Faulty redox signaling is suggested to play a significant role in cancer development: hydrogen peroxide, generated at low concentrations, represents an important chemical mediator in the regulation of various cellular signal transduction processes, including stem cell development. Oxidative stress may be sensed by cells as redox signaling. Faulty "redox signaling" is proposed to affect normal stem cell development by sustained activation of uncoupling protein 2, leading to inhibition of differentiation ("maturation arrest"), sustained uncontrolled proliferation, and glycolysis with high expression of hexokinase II, typical features of cancer. In summary, an abnormal diet-related activation of various metabolic systems, together with faulty redox signaling, is suggested to play a pivotal role in cancer development.

Keywords: Carcinogenesis; High-carbohydrate nutrition; Insulin resistance; Oxygen reactive species; Uncoupling protein; Redox signaling

Abbreviations

ANG II: Angiotensin II; AT1R: Angiotensin II receptor type 1; CSC: Cancer stem cell; FADH: Flavin adenine dinucleotide; FFA: Free fatty acids; H₂O₂: Hydrogen peroxide; HCHID: High-carbohydrate/high-insulinemic diet; HG: Hunter-gatherer; HIF-1 α : Hypoxia-inducible factor 1 α ; HOMA: Homeostasis model assessment; hPSC: Human pluripotent stem cell; IGF: Insulin-like growth factor; IR: Insulin resistance; LCLID: Low-carbohydrate/low-insulinemic diet; LGA: Large-for-gestational-age; NADH: Nicotinamide adenine dinucleotide hydrogen; NE: Norepinephrine; NOX: NADH oxidase; OXPHOS: Oxidative phosphorylation; RAS: Renin-angiotensin system; ROS: Reactive oxygen species; SC: Stem cell; SGA: Small-for-gestational-age; SNS: Sympathetic nervous system; UCP: Uncoupling protein

Introduction

In all western societies, mortality rates from cancer are high and even increasing. At present, cancer is second only to cardiovascular disease as a cause of death [1]. In striking contrast, historical records of explorers, adventurers and frontiersmen as well as medical and anthropological reports indicate that cancer rates are very rare and

even non-existent in primitive cultures [2-14]. Several reports and studies on the Inuit show that—prior to acculturation and adoption of a „Western” diet—people were virtually free of cancer [6-8]. Vilhjamur Stefansson [9] reports about the search of George Leavitt, a physician, for cancer among the Inuit of Canada and Alaska. It took him nearly 50 years, from 1884 to 1933, to find a case of cancer. Similarly, an article on Eskimo health in The Canadian Medical Association Journal from May of 1936 reports: "In the Western Arctic Dr. Urquhart has as yet not met with a single case of cancer in the seven years of his practice. Cancer must be extremely rare in the Eastern Arctic also" [10].

The reported absence of cancer in hunter-gatherer societies is not restricted to the Inuit. Several other have reported on an astonishing low incidence or absence of cancer in "primitive" cultures, like the Australian aborigines and the aboriginal peoples of Africa and the Melanesian Islands [4,11-14]. The famous medical missionary, Dr. Albert Schweitzer, is quoted in Berglas [11] as follows: "On my arrival in Gabon, in 1913, I was astonished to encounter no cases of cancer. I saw none among the natives two hundred miles from the coast. I cannot, of course, say positively there was no cancer at all, but, like other frontier doctors, I can only say that if any cases existed they must have been quite rare".

Cancer (as well as other diseases of civilization, including coronary heart disease, obesity, hypertension, type 2 diabetes, autoimmune disease, osteoporosis, and other more) are rare or absent among

hunter-gatherer (HG) societies, as long as these peoples adhere to their traditional diet. However, with transition to a high-carbohydrate/high-insulinemic “Western style” diet (HCHID), whether by migration or acculturation, invariably leads to a dramatic increase in this disease(s) [14-18]. In the Inuit, cancer incidence increased steadily through the 20th century; meanwhile the circumpolar Inuit and Athabaskan/Dene have rates for several cancer sites that exceed all other regions in the world [15,17,19]. Similar developments apply to many other hunter-gatherer societies [15,20].

The notion that Stone Agers usually didn't live long enough to get cancers is not accurate. Average life expectancy in hunter-gatherer societies is lower than in most acculturated societies today, which largely is attributed to higher rates of infant and child mortality and a lack of medical assistance. But once these people reach adulthood, their life expectancy is comparable to that of affluent nations. A conspectus of data on hunter-gatherer societies suggests that modal age of adult death is about seven decades (adaptive life span of 68-78 years). In contrast to most westerners, these people tend to be healthy up to old age. Causes of death are predominantly infectious diseases, while chronic degenerative disorders are rare [21].

Etiology and pathomechanism of cancer development are still under debate. While the somatic mutation theory has been the prevailing one in cancer research for the last 50 years, a body of evidence has accumulated showing that cancer is not only a genetic disease of uncontrolled cell proliferation, but also a metabolic disease [22-24]. Several risk factors for cancer development have been identified, most important smoking [25], age [26] and obesity (including comorbidities like type II diabetes and cardiovascular diseases) [27].

This paper presents evidence that fundamental dietary change during human history cause significant metabolic perturbations, related to the malignant process. A novel hypothesis is postulated that links carcinogenesis to HCHIDs.

Human Evolution and Nutrition

During the Paleolithic Period, from approximately 2,5 million years ago until the Agricultural Revolution about 10,000 years ago, our ancestors subsisted on diets containing large amounts of protein and varying amounts of fat (depending on the latitude), and relatively small amounts of (digestible) carbohydrate. Their diet was based chiefly on wild game, fish and uncultivated plant food high in fiber, like tubers, wild herbs, roots, berries, nuts, vegetables, fruits (and occasionally some honey), but not on cereals.

One of the major differences between hunter-gatherer diets and our “modern” nutrition concerns the Glycemic and Insulinogenic Index [28]: wild plants are fibrous and are therefore slowly digested, much of the carbohydrate is unavailable, and the carbohydrate content is therefore lower than that of their cultivated equivalents [29]. Hence, carbohydrates, consumed during this period were low-glycemic in effect [30], eliciting a low insulin response only [31]. Since the effect of protein and fat on insulin production is small too [32], postprandial glucose and insulin levels were low during a very long time of human evolution.

Living organisms thrive best on the diet to which they are evolutionarily adapted. The human genome has formed during a period of several million years and the DNA has remained largely unchanged during the past 10,000 years [33], thus, human metabolism

is still adapted to the low-glycemic and low-insulinogenic diet of our Paleolithic ancestors.

The Agricultural Revolution about 10,000 years ago brought about a significant increase in dietary carbohydrate in the form of cereals and legumes. Progresses in food processing during the Industrial Revolution about 250 years ago resulted in a significant increase in the Glycemic and Insulinemic Index of refined cereals. In addition, cow milk (and other dairy products) also produce high postprandial insulin levels (despite a low-glycemic effect), not significantly different from the Insulinemic Index of the reference bread [34,35]. The switch from a low-carbohydrate/low-insulinemic “Paleolithic” diet (LCLID) to HCHIDs has brought about substantial adverse metabolic alterations and perturbations that may promote malignant transformation.

HCHIDs and Insulin Resistance

Insulin resistance (IR), obesity and the metabolic syndrome have risen dramatically in all westernized populations during the last decades [36], and the syndrome meanwhile is increasing also in developing countries [37]. Furthermore, peripheral insulin sensitivity as well as glucose tolerance decreases in westernized populations with advancing age. Both, fasting and postprandial glucose concentrations are higher in elderly than in young subjects [38,39].

In contrast, low serum insulin levels and a persisting excellent insulin sensitivity is characteristic of HGs, and diseases of IR are rare or absent, as long as they adhere to their traditional low-carbohydrate diet and their ancestral life style [14,16,40-43]. But with acculturation and transition to a westernized lifestyle, especially to high-insulinemic diets, these populations develop high prevalence rates of hyperinsulinemia, IR and the metabolic syndrome [31,41,44-46]. Otherwise, a reversion to traditional low-insulinemic nutrition is accompanied with marked improvement of IR and fasting insulin levels [44,47,48].

There is a widespread acceptance in the literature that obesity causes IR and compensatory hyperinsulinemia, but this assumption is not convincing [49]. In this regard, it also has to be considered that not all obese individuals are insulin resistant while IR has been shown to exist also in a significant proportion of the normal weight population [50].

Meanwhile, substantial evidence has accumulated indicating that hyperinsulinemia represents the driving force in the development of IR and precedes the development of IR as well as of obesity [35,51-53]. As shown by a whole range of experimental studies in animals [54-56] and in humans [35,57-60], a sustained elevated level of insulin, immaterial of its origin, represents the key factor for the development of IR [61]. Hyperinsulinemia was shown to impair insulin-stimulated glucose uptake and its cellular signaling in a dose-dependent manner [62,63]. Moderate hyperinsulinemia decreases insulin receptor numbers, with development of moderate IR; severe IR has been suggested to result from a combination of decreased insulin receptor numbers and a post-receptor defect [63]. An (insulin-induced) increased gene expression of proinflammatory cytokines in adipocytes [64], as well as metabolic inflexibility [65], ectopic lipid accumulation [65] and increased reactive oxygen species (ROS) production [65,66] have been implicated in the developmental process. Depending on the individual texture of the β cells, hyperinsulinemia and insulin resistance may develop rapidly, or increase gradually with increasing age.

Hyperinsulinemia also appears to be involved in the development of obesity by overstimulating white adipose tissue and liver metabolic activity [52-54,67-71]. Several studies provide evidence that weight gain occurs prior to the development of IR. Postprandial hyperinsulinemia has been shown to represent the very first metabolic abnormality in developing obesity, while fasting insulin levels and insulin sensitivity are normal [35,52-54]. In a study by Sigal et al. [70], high rates of weight gain occurred in individuals who presented with a high acute insulin response to glucose, and this effect was particularly manifested in insulin-sensitive individuals. Similarly, a study in Pima Indians revealed that the relatively most insulin sensitive individuals had a greater tendency towards weight gain than the most insulin resistant ones [71]. IR (with compensatory hyperinsulinemia) develops later during the course of chronic obesity [52,70] and limits further weight gain [53,71,72]. HCHIDs elicit a high postprandial insulin response. Along with a “Western dietary pattern” of frequent snacking and frequent consumption of sucrose-containing soft drinks, insulin levels are elevated for most part of the day [37]. Pancreatic β -cells, genetically not adapted to this high insulin demand, may react with hypertrophy, functional dysregulation, and finally overresponsiveness and hyperinsulinemia [73,74]. Further, it is important to consider that high-carbohydrate diets are less satiating, while a higher protein intake increases satiety and leads to a reduced subsequent energy intake [75]. Consequently, restriction of carbohydrate intake has been shown to spontaneously reduce caloric intake and decrease hunger [76].

Insulin Action during Pregnancy: Early Onset of IR and Cancer Risk

Birth weight has been positively correlated with cancer risk [77]. Maternal diet composition has a significant impact on birth weight, as the following lines will prove.

During the course of pregnancy, beginning around the tenth week, a physiologic (transient) profound IR develops. Following delivery, IR abates [78-79]. Brand-Miller and Colagiuri [80] proposed that IR during gestation represents a genetic adaptation to the inherent low glucose content of LCLIDs our ancestors subsisted on during a very long period of human evolution, in order to reduce glucose consumption of the maternal tissues and spare glucose for the developing fetus.

Current HCHIDs “collide” with this hereditary adaptation. Diets high in rapidly digested and absorbed foods induce high maternal blood sugar levels. While glucose uptake by insulin-dependent maternal tissues is diminished, glucose can freely cross the placenta. Since insulin is not able to cross the placenta, the fetal pancreas is forced to produce large amounts of insulin. The degree of maternal IR as well as of its compensatory hyperinsulinemia mainly determines nutrient flux from mother to fetus and therefore influences birth weight. This has been confirmed in several studies, for instance in a retrospective observational study evaluating the association between the degree of maternal IR and neonatal birth weight in uncomplicated pregnancies: in non-diabetic, non-obese pregnant women, postprandial insulin levels as well as HOMA-IR were found to be positively correlated with birth weight and the risk of giving birth to a large-for-gestational-age (LGA) infant [81]. Also, a longitudinal study on nondiabetic, non-obese pregnant women revealed a significant correlation of postprandial blood glucose levels with fetal growth [82]. The metabolic alterations described are especially pronounced in maternal obesity [83] and gestational diabetes [84,85].

According to Pedersens hyperglycemia-hyperinsulinism hypothesis [86], excessive maternal glucose crossing the placenta causes fetal hyperglycemia and hyperinsulinemia. Fetal hyperinsulinemia, plus a large supply of glucose substrate greatly enhances protein, lipid and glycogen synthesis, thereby promoting growth and adiposity [83,87,88] and may cause β -cell hyperplasia [88], development of intrauterine IR [89-91] and IR during childhood [92]; increased IR and oxidative stress are already present in prepubertal normal-weight, small-for-gestational-age (SGA) and LGA infants [92]. In addition, high plasma norepinephrine values were found in infants of diabetic mothers [93].

An interesting finding was reported by Neufeld et al. [94,95]: monocytes [94] as well as liver cells [95] of infants of diabetic mothers showed a significant increase in insulin receptor numbers as well as a greater binding capacity compared with normal infants, suggesting that the development of insulin receptors in embryonic cells/tissues is positively related to insulin levels, in contrast to downregulation in adult hyperinsulinemia.

Birth Weight and Stem Cells—A Link to (Childhood) Cancer?

Birth weight has been positively correlated with subsequent risk of childhood cancer as well as several cancer types in adults [77]. According to a “stem cell burden theory” [96], the in utero environment and perinatal factors may influence the size of the overall stem cell pool as well as birth-weight. The greater the stem cell pool size, the greater the risk that one of the stem cells will undergo malignant transformation in later life. The size of the stem cell pool in the developing fetus as well as birth weight are determined by the level of in utero/perinatal levels of growth factors and hormones, especially insulin and insulin-like growth factor 1 (IGF1); IGF1 is thought to increase the size of the stem cell pool; further, insulin itself is a growth-promoting hormone as well as the main regulator of fetal IGF 1 production [97,98]. It increases the bioactivity of IGF1 by directly enhancing hepatic IGF1 production [97] and by decreasing levels of IGFBP1 and IGFBP3 [98] which results in increased tissue availability of IGF1. In support of the theory, the umbilical cord blood concentrations of various hematopoietic stem and progenitor populations were shown to correlate with cord blood plasma levels of particular mitogens, especially IGF-1 [99], as well as with birth weight: a positive U-shaped correlation with high as well as low birth weight was noted [77].

Interestingly, a U-shaped relationship has also been observed between birth weight and IR in utero [89-91] and IR in childhood [92,100].

In summary, diet composition influences the microenvironment of the fetus. High-insulinemic nutrition during pregnancy has the potential to exert significant influence on birth weight, insulin resistance in utero as well as in early childhood, the stem cell pool and cancer risk of the offspring later in life. In contrast, low-glycemic/insulinemic diets are accompanied by lower insulin levels and lower birth weight [83,101,102]. Intriguingly, mean birth weight increased in the United States during the second half of the 20th century [103]. This may reflect the increase in consumption of sucrose and high-insulinemic food during this period.

Insulin and Cancer

The IGF system exerts a fundamental role in the regulation of cell growth and metabolism in response to nutrients and affects nearly every organ system in the body. The IGF system consists primarily of two ligands (IGF1 and IGF2, two cognate cell-surface receptors (IGF1R and IGF2R) and six IGF-binding proteins (IGFBP1 to IGFBP6). In addition to their endocrine properties, IGFs function also as paracrine (IGF1 and IGF2) and autocrine hormones (IGF1) and are produced by tumor cells [104]. The insulin receptor is activated by insulin, IGF-I and IGF-II. It has two isoforms, IR-A and IR-B. IR-A, predominantly expressed during prenatal life, enhances the effect of IGF-II during embryogenesis and fetal development. IR-A is often aberrantly expressed in cancer cells [105].

Suspicion about a possible role of insulin and the IGF system in carcinogenesis was raised by epidemiological studies that reported that obese individuals, especially those with type 2 diabetes, are at a higher risk of dying from cancers when compared with lean individuals without diabetes. In addition, the metabolic syndrome has been shown to be a major risk factor for cancer [106]. Hyperinsulinemia and IR have been implicated as a possible causal factor linking obesity and the metabolic syndrome to cancer [107]. Involvement of insulin, in particular hyperinsulinemia, as well as of the IGF system in malignancies is well documented [108]. Insulin itself is a growth-promoting hormone with mitogenic effects [97]. IGF1 as well as IGF2 are potent mitogens that play important roles in the promotion of cell proliferation, differentiation, metastasis and inhibition of apoptosis [109-113].

Furthermore, insulin and IGF1 inhibit hepatic synthesis of sex-hormone binding globulin, while both hormones stimulate ovarian synthesis of sex steroids, which may promote cellular proliferation and inhibit apoptosis in breast tissue and endometrium [114].

Finally, IR and hyperinsulinemia are increasingly recognized as a low-grade inflammatory state associated with elevation of interleukin-6, adiponectin, leptin, tumor necrosis factor- α , plasminogen activator inhibitor-1, monocyte chemoattractant protein and free fatty acids, which can play a role in malignant transformation and/or cancer progression [108]. The level of these inflammatory mediators has been shown to correlate with the degree of hyperinsulinemia [115]. Low-grade inflammation is widely prevalent in human cancer and may be a driver for p53 mutagenesis [116].

Epidemiological studies corroborate the adverse role of high-insulinemic nutrition, insulin and IR in the malignant state: high intake of sugar and refined carbohydrates and elevated blood glucose were found to be strongly associated with the risk of cancer [117] and with poorer survival after diagnosis for early breast cancer [118]. Also, chronic exogenous insulin therapy significantly increases the risk of colorectal cancer among type 2 diabetes patients [119]. In a clinical trial on breast cancer patients, IR was associated with a significantly worse prognosis [120].

Sympathetic Nervous System (SNS) and Cancer

The SNS is involved in the regulation of the microenvironment of virtually every major organ system of the body by releasing two catecholamine neuroeffector molecules, norepinephrine (NE) and epinephrine. NE is released primarily from the sympathetic nerves, while epinephrine is mainly secreted from the adrenal medulla. Both catecholamines act as neurotransmitters as well as circulating

hormones. Adrenergic receptors are expressed on virtually every cell type in the body, including cancer cells [121].

It is well established that SNS activity is influenced by food ingestion: among dietary substrates, carbohydrate (starch and sugars) ingestion activates the SNS, characterized by a significant increase in plasma NE levels caused by spillover from sympathetic nerve endings [122,123], while protein or fat ingestion exert minimal effects on NE levels only [124,125]. In feeding studies, high carbohydrate/protein diets were associated with a significant increase in NE levels, while high fat/protein diets did not alter SNS activity [124,125].

Insulin proved to be the link between carbohydrate intake and SNS activity [126,127] and was shown to increase plasma NE levels in a dose-dependent fashion in normal man [127]. The reason for this diet-induced SNS activation is thought to be due to the vasodilatory effect of insulin: in normal humans, carbohydrate ingestion with its attendant physiologic insulinemia causes dilatation of the skeletal muscle vasculature, mediated chiefly by stimulation of nitric oxide release [128]. Activation of the SNS may then occur to offset an excessive fall in blood pressure as a result of generalized vasodilatation [123,129].

In consideration of these facts there can be no doubt that the introduction of high-insulinemic food into human nutrition has brought about a new deleterious metabolic situation: a diet-related unphysiologically increased activity of the SNS [130], especially pronounced in obesity, where a sustained sympathetic activation, related to chronic hyperinsulinemia, has been detected [131].

At present, a growing body of evidence suggests that NE plays a pivotal role in the progression of malignant tumors by modulating proliferation, angiogenesis, inflammation, macrophage infiltration, metastasis and inhibition of apoptosis, mediated to some extent through activation of various growth factors and cytokines [132-135].

Renin-Angiotensin-System (RAS) and Cancer

The renin-angiotensin system (RAS) plays an important role in normal physiology as well as in pathologic conditions. Angiotensin II (ANG II) is the major effector peptide of the RAS. Insulin as well as IGF-I stimulate angiotensinogen production [136,137]. In addition, NE has been shown to stimulate renin secretion, thereby activating ANG II, while circulating ANG II interacts with the SNS at various sites and appears to amplify sympathetic activity [138]. It is meanwhile well established that in addition to the "classic" hormonal circulating system, a local RAS exists in various organs and tissues, leading to production of ANG II, with autocrine and paracrine effects [139].

ANG II has been recognized as a potent mitogen, and tumor cells frequently overexpress angiotensin II receptor type 1 (AT1R) [140,141]. Local expression of several components has been revealed to be involved in various cancer cells and tissues, including brain, breast, prostate, skin, lung, cervix and pancreatic carcinoma and glioblastoma [142]. Increasing evidence suggests that the RAS is linked to cancer through its ability to promote cell proliferation, tissue invasion, inflammation, angiogenesis and metastasis, immune suppression and pro-survival signaling [140,142-144].

Furthermore, the RAS is a key mediator of inflammation: the activation of AT1R has a powerful pro-inflammatory effect, promoting the expression of many pro-inflammatory mediators such as cytokines, chemokines and adhesion molecules [141]. The invasiveness and

immunosuppression of many cancers appear to depend on inflammation and the upregulation of AT1R.

Also noteworthy, NE [145], the IGF system [146,147] as well as the RAS [148] increase the expression of the oxygen-responsive hypoxia-inducible factor 1 α (HIF-1 α) which is deeply involved in cancer development, specifically in areas of vascularization and angiogenesis, energy metabolism, cell survival, and tumor invasion and metastasis [149].

In summary, the switch from LCLIDs to HCHIDs is associated with an abnormally increased activation of several metabolic systems related to the development of cancer (as well as other pathological processes). HCHIDs produce a metabolic situation that—inter alia—promotes proliferation and inhibits apoptosis. The next section shows that in addition, a (diet-induced) increased production of ROS (in especially hydrogen peroxide (H₂O₂)) and an increased activation of uncoupling protein 2 (UCP2) may play a central role in carcinogenesis.

Mitochondria, Oxidative phosphorylation (OxPhos) and ROS Production

The primary role of mitochondria is the generation of energy through OxPhos, and to regulate cellular metabolism. The tricarboxylic acid cycle oxidizes nutrients, yielding electrons in the form of reduced carriers NADH and FADH₂ to the mitochondrial electron transport chain. The sequential transport of electrons from complex I or II to III and IV pumps protons across the inner membrane, thereby generating an electrochemical gradient. The final acceptor of electrons in the electron transport chain is reduction of molecular oxygen at complex IV, yielding water and ATP. ROS are an inevitable byproduct of the mitochondrial respiratory chain activity: some of the electrons transferred along the electron transport complex escape and reduce molecular oxygen to form a superoxide anion (O₂⁻) which is rapidly converted to H₂O₂ by superoxide dismutase [150]. In addition, ROS, produced by various sources, play a central role in cell signaling.

Oxidative Stress and Counter Measures

Significantly increased ROS production (“oxidative stress”) may have deleterious effects on cells and mitochondria through damage of cellular macromolecules, including mitochondrial DNA (mDNA), protein and lipid. Mitochondria are protected by several countermeasures to mitigate oxidative stress, including glutathione- and thioredoxin-reducing system and carnitine acyltransferase enzymes [150], but these defenses are not perfect. Considering the fact that the mitochondrial genome, which encodes several OxPhos genes, is situated in close proximity to the electron transport chain, increased ROS production, overriding mitochondrial antioxidant defense, may cause mDNA mutations [151]. Since mDNA lacks the protective shields of histones and has limited DNA-repairing systems, mDNA damage may lead to a higher degree of mitochondrial dysfunction and, in turn, to higher ROS production, initiating a vicious cycle of ROS amplification [152] which may cause nuclear genomic instability [23,153,154]. Oxidative stress, with accumulation of damaged macromolecules, is considered the cause of mitochondrial dysfunction of aging [155].

In addition to the countermeasures described above, activation of UCPs has been implicated in decreasing ROS production [156]. At present, 5 UCP homologues (UCP1-5) have been identified in humans,

with UCP2 being the most ubiquitous. While the main function of UCP1, situated in brown adipose tissue, is driving nutrient oxidation towards heat production instead of ATP generation, more recently identified homologs (UCP2-5) are not involved in thermogenesis but decrease the formation of mitochondrial ROS [152]. Expression of UCP2, the most ubiquitous protein, increases greatly in response to increased ROS production (in particular H₂O₂) [156-160]. Further, UCP2 is upregulated by hyperglycemia [161] and ANG II [162]. Expression levels of UCP2 are therefore often increased in pathological processes associated with oxidative stress, like obesity, diabetes, lipotoxicity, atherosclerosis, chronic inflammation, etc. [163].

Stem Cell Metabolism and the Role of UCP2

It is now largely clarified that UCP2 decreases ROS production by modifying mitochondrial substrate utilization. According to Bouillaud [164], UCP2 decouples OxPhos from glycolysis by inhibiting pyruvate (glucose) mitochondrial oxidation, and induces a metabolic shift that promotes glycolysis and therefore indirectly lowers the mitochondrial production of ROS. Consistent with this notion, a study on UCP2^{-/-} cells suggests that UCP2 promotes free fatty acid (FFA) and/or glutamine oxidation while limiting glucose-derived pyruvate oxidation in mitochondria [165] and is necessary for efficient oxidation of glutamine [166]. These findings are well in line with studies on the role of UCP2 in human pluripotent stem cells (hPSCs) [167,168]. Consequently, UCP2 is deeply involved in the regulation of energy metabolism, proliferation and differentiation of hPSCs. It is well established that stem cells heavily rely on glycolysis and use FFA and glutamine as the main energy source for OxPhos [165,169,170]. In stem cells, UCP2 inactivates the pyruvate dehydrogenase complex, thereby shunting substrates such as pyruvate away from glucose oxidation while promoting glycolysis, mediated by expression of high levels of hexokinase II [167,170], and promotes oxidation of alternative substrates such as glutamine and free fatty acids (FFA) [165,170]. Inhibition of pyruvate entry into mitochondria, compensated by FFA and glutamine usage, prevents a non-reversible degradation of pyruvate to acetyl-CoA, thereby keeping the door open for utilization of pyruvate for anabolic purposes. With regard to high proliferation rates of stem cells, glycolysis may therefore be advantageous to provide intermediate metabolites like ribose and nicotinic adenine dinucleotide reduced form (NADPH) from the pentose phosphate pathway to synthesize macromolecules, such as nucleic acids, lipids and proteins, required for anabolic metabolism and proliferation [171,172].

With early differentiation, UCP2 is repressed and hPSC proliferation slows, glycolytic flux decreases dramatically and mitochondrial OxPhos, fueled by glucose and fatty acids, increases, indicating that glycolysis represents the preferred metabolic state of rapidly proliferating cells. UCP2 repression is necessary for full differentiation potential [167]. Ectopic UCP2 expression perturbs this metabolic transition, impairs hPSC differentiation, blocks glucose oxidation and promotes glycolysis and proliferation. Otherwise, UCP2 knockdown shifts hPSC bioenergetics towards glucose oxidation inhibits proliferation and promotes differentiation [165,167].

UCP2 seems to play an important role in carcinogenesis. UCP2 is well known to be overexpressed in cancer [152] and has been suggested to promote tumor development [157]. Overexpression of UCP2 was found in a variety of cancers, like in leukemia, ovarian, bladder, esophagus, testicular, colorectal, kidney, pancreatic, lung and prostate tumors [157]. Several studies have shown that UCP2

overexpression is associated with increased proliferation, decreased ROS production [157,173,174] and resistance to apoptosis [173], whereas UCP2 silencing led to the induction of apoptosis and cell differentiation [152,175].

Embryo-Fetal Characteristics of Cancer

Striking similarities exist between the energy metabolism of cancer cells and stem cells. As noted earlier, stem cells rely heavily on glycolysis, with high expression of hexokinase II, and use fatty acids and glutamine as the main energy source for OxPhos [169,176]. Similarly, cancer cells take up glucose and glutamine at high rates and convert glucose to lactate through aerobic glycolysis in the presence of oxygen ("Warburg effect"), with high expression of hexokinase II [177]. Glutamine as well as FFA oxidation is a major means of ATP production in transformed mammalian cells [178,179]. Like in stem cells, glycolysis may be advantageous for cancer cells by shunting glycolytic intermediates into amino acid, lipid and nucleotide synthesis for anabolic metabolism and proliferation [171,172]. While Warburg originally proposed that glycolysis in cancer cells was due to a permanent impairment of mitochondrial OxPhos, more recent investigations found that mitochondrial function is largely retained or at least not completely compromised in most cancers [171], and a majority of ATP is produced by oxidative phosphorylation [178]. It seems that the Warburg effect represents a physiologic genetic program that enables stem cells to provide large amounts of metabolites for proliferation, and (stem cell-derived) cancer cells use the same mechanism [180]. Ayyasami et al. [157] recently concluded that "the Warburg effect is mediated by UCP2 and UCP2 over-expression promotes tumor development".

A striking resemblance also exists between neoplastic and embryonic tissues as well as between several hallmarks of cancer and embryo-fetal development, including sustained proliferative signaling, self-sufficiency in growth signals, resistance to cell death, replicative immortality, angiogenesis and activation of invasion [181]. Significant similarities between embryonic stem cells and various cancers were found to also exist concerning gene expression as well as expression of alpha-fetoprotein [reviewed in 181].

For these and other reasons, like their ability to self-renew indefinitely and to differentiate into a variety of specialized cell types, stem cells (SCs) have been linked to cancer development already in the late 1970's; more recently, it has been suggested that cancer stem cells (CSC) (also called "tumor initiating cells") may be the driving force behind neoplastic transformation, cancer recurrence and metastasis [182,183]. The "cancer stem cell hypothesis" suggests that cancer is a stem cell disease and is based on the finding of cancer cells with the characteristics of adult stem cells in many human malignancies.

Stem Cells or Retrodifferentiation of Differentiated Cells?

While the CSC hypothesis suggests that CSC derive from the neoplastic transformation of normal stem cells from different origin [182], it does not imply that cancer is always caused by stem cells. Accordingly, CSC may arise from a stem cell, a progenitor cell, or a fully differentiated cell undergoing retrodifferentiation back to a stem-like state. Retrodifferentiation of differentiated cells has been defined as "a process of stepwise cell reversion (retrodifferentiation or retroprogramming) leading, by division, mature or stem cells to progressive immaturity" [181]. Evidence for retrodifferentiation was

provided by Chaffer et al. [184], studying cultures of normal and neoplastic mammary epithelial cells. They could demonstrate that normal, differentiated cells can spontaneously convert to a stem-like state without genetic manipulation. Increased activation of the IGF system, the SNS and the RAS supports the conversion of differentiated cells into stemlike cells, for instance through p53 inactivation [185] which makes cell reprogramming more efficient, or through increased expression of HIF-1 α which plays a critical role during the induction of pluripotency by initiating a gene expression program which leads to a switch from OxPhos to glycolysis [186].

Hydrogen Peroxide as Signaling Molecules

While the majority of ROS are generated *via* the respiratory chain cascade as an inevitable byproduct, ROS are also generated intentionally (predominantly by NADH oxidases (NOX), but also by mitochondria [187,188] as part of a signal transduction pathway in cellular response to various stimuli, like cytokines and growth factors, insulin, and ANG II [187]. Thus, in addition to the well-known pathophysiological effects of oxidative stress, ROS, produced at low concentrations, act as important chemical mediators in the regulation of signal transduction processes. In contrast to the superoxide anion and hydroxyl radical, the less reactive H₂O₂ is involved in various signal transduction pathways in normal as well as in cancer cells, including proliferation and differentiation [189,190,reviewed in 191] as well as inflammation, phagocytosis and apoptosis [192]. The mechanism of "redox signaling" involves the H₂O₂-mediated reversible oxidation of specific amino acids in enzymes and transcription factors, thereby altering their activities [187,193].

Under normal conditions, the generation of H₂O₂ is tightly controlled through an elaborate cellular antioxidant system, and the expression of these antioxidant enzymes is also tightly regulated, suggesting that the levels, localization, and/or activities of cellular antioxidants are important in determining biological responses to hydrogen peroxide [187]. Recent studies in mammalian cells have revealed that cell signaling depends on both, the concentration as well as on the mode of mitochondrial H₂O₂ production: in stem cells, increases in ROS production cause stem cell proliferation, differentiation, senescence, and apoptosis in a dose-dependent manner; low levels of ROS are required to maintain quiescence, a moderate increase may promote proliferation/differentiation, and a further increase can induce stem cell senescence or apoptosis [194]. Different levels and modes of H₂O₂ production can therefore induce distinct responses within a cell by activating different pathways [reviewed in 187]. As an example, the role of H₂O₂ in cardiovascular differentiation of embryonic stem cells is antagonistic: continuous exposure to ROS results in inhibition of differentiation, while pulse-chase exposure to low-level ROS enhances differentiation [190]. Similarly, gene expression of the tumor suppressor p53 is different in response to different amounts of hydrogen peroxide: at low concentrations of hydrogen peroxide, the p53 transcription factor activates antioxidant genes that induce antioxidants, while higher amounts stimulate the expression of pro-oxidant target genes [195].

A body of evidence has accumulated demonstrating that, compared with their normal counterparts; many types of cancer cells are associated with increased levels of ROS. In addition to mitochondrial ROS production, growth factors and cytokines as well as inflammatory cells stimulate the production of ROS (in particular H₂O₂) in cancer (microenvironment) [196,197]. H₂O₂ is involved in various signal transduction pathways in cancer cells [190,191]. Furthermore, tumor

cells express increased levels of antioxidant proteins to detoxify from ROS, suggesting that a delicate balance of intracellular ROS levels is required for cancer cell function [197].

Increased ROS levels may play a significant role in cancer development by activating various signaling pathways [193,198]. Simply put, increased H₂O₂ values may be perceived as "redox signaling". It is tempting to assume, that abnormal "signaling" may interfere with normal stem cell development (which comprises proliferation, followed by differentiation). Activation of UCP2 plays a central role in this process by promoting glycolysis and proliferation ("stemness"), and inhibition of hPSC differentiation. As noted before, expression of UCP2 was found to increase greatly in response to elevated ROS production (in especially to H₂O₂) *in vitro* [157-160]. It is tempting to assume that continuous exposure of stem cells to (certain levels of) H₂O₂ may induce sustained UCP2 activation, resulting in inhibition of differentiation ("maturation arrest"), sustained uncontrolled proliferation, and glycolysis with high expression of hexokinase II, typical features of cancer. Maturation arrest has been implicated into cancer development before [199]. Based on the fact that malignant tumors frequently consist of a mix of undifferentiated cells and cells with a varying amount of differentiation (contributing to the well-known heterogeneity of cancer), the author suggested that the degree of differentiation of a carcinoma may depend "on the proportion of undifferentiated tumor stem cells, the stage of maturation arrest of the majority of cells in the tumor, and on the ability of some cells to escape arrest and to differentiate" [199]. Further, embryonic, fetal and neonatal antigens have been found in numerous malignant tumors, indicating that most, if not all, tumor-associated antigens are related to transitional stages of cell differentiation [183]. Varying levels of UCP2 expression may cause varying amounts of differentiation, thus contributing to heterogeneity of cancer.

Increasing evidence corroborates these hypothetical considerations: persistently upregulated H₂O₂-dependent signaling pathways have been shown to be involved in cell differentiation, growth and survival, as well as cell cycle arrest or apoptosis in many cancer cells. Several hallmarks of cancer can be directly linked to an increased ROS production, such as sustained proliferative signaling, activation of invasion and metastasis, induction of angiogenesis and resistance to cell death. Depending on its intracellular concentration and localization, H₂O₂ exhibits either pro- or anti-apoptotic activities [193,198]. Furthermore, neoplastic transformation is not an irreversible event: in experimental studies, carcinoma cells were induced to differentiate into normal mature cells and tissues [181,199,200], supporting the notion that maturation arrest plays a pivotal role. In addition, alterations in redox signaling have been identified as a contributor to many disease processes, like IR, aging etc. [188].

In summary, ROS exert both positive and negative effects on cellular structures and metabolism. While low levels of hydrogen peroxide play an important role as signaling molecules involved in the regulation of many different biological processes including stem cell development, increased ROS production may cause damage to lipids, proteins and mDNA, and genomic instability, and may additionally interfere with normal stem cell development by abnormal activation of UCP2. The next section shows that HCHIDs may cause oxidative stress, and that oxidative stress may derive from several other sources, all of which represent well-known risk factors for cancer.

Dietary Related Oxidative Stress

It is well established that IR and obesity are associated with oxidative stress [201,202]. Excess supply of energy substrates in obesity and IR is believed to cause mitochondrial dysfunction and increased ROS production [156,201,203,204]. HCHIDs may be causally related to the production of oxidative stress, as the following section shows.

Glucocentric and Adipocentric Metabolism

The macronutrients carbohydrate, fat and protein are the primary catabolic substrates which provide humans with the bulk of energy. They are broken down into glucose, fatty acids and amino acids. Glucose and fatty acids serve as main fuels which can be oxidized in mitochondria for ATP production. Amino acids are used in body cells to form new proteins, or may be converted into glucose or stored as fat [205].

Dependent on diet composition, a "glucocentric" or an "adipocentric" metabolism develops, with significant differences regarding cell fuels and metabolic consequence. Low-carbohydrate diets, like the traditional diets of many hunter-gatherer societies, are associated with an adipocentric metabolism, while current "Western" high-carbohydrate diets are associated with a glucocentric metabolism. In an adipocentric metabolism, fatty acids serve as main fuel, while glucose is provided for glucose-dependent tissues only; in a glucocentric metabolism, glucose and fatty acids both serve as main fuels in a diurnal oscillating way [76].

LCLIDs are metabolically "uncomplicated". Since only one of the two main cell fuels is ingested in significant amounts, a clear-cut separation of cell fuels is sustained during feeding and fasting, 24 h/day. FFA or ketones serve as main fuel during the fed as well as the fasted state and are easily stored and released into circulation on demand. Glucose-dependent tissues (brain, red blood cells, retina, lens and renal medulla) receive glucose from ingested carbohydrate, supplemented, if necessary, through gluconeogenesis and glycogenolysis on demand. Diurnal oscillations in mitochondrial fuel selection between glucose and fatty acids are unnecessary. Postprandial insulin production is low and serves solely the fine tuning of blood sugar levels. Proteins serve as building blocks as well as energy sources. Very low carbohydrate diets as a variant (like the Inuit diet or ketogenic diet) lead to production of ketone bodies. These serve as the sole source of cellular energy production (except for red blood cells). Necessary amounts of glucose are provided through hepatic gluconeogenesis.

Human metabolism has (and still is) genetically adapted to this smoothly functioning and well balanced fuel utilization, with energy supply matched to demand.

In contrast, HCHIDs, containing high amounts of carbohydrates as well as substantial amounts of fat and protein are metabolically "demanding" because of a steady influx of competing fuels. Both, glucose as well as lipids, serve as cell fuels, competing for mitochondrial oxidization. Basically, mitochondria are able to switch freely between glucose and fatty acid oxidation in order to adjust fuel oxidation to fuel availability (termed as "metabolic flexibility"), but function smoothly only as long as acetyl-CoA is produced from one fuel at a time. Hence, this situation requires nutrient partitioning in order to avoid mitochondrial indecision and metabolic "gridlock" [203].

Nutrient partitioning is accomplished on a hormonal level through a temporary switch between glucose and fat utilization, mediated by the counter-regulatory hormones insulin and glucagon, both of which exert a strong influence on fat metabolism. During the fed state, a high insulin/glucagon ratio promotes lipid storage, while in the fasted state a high glucagon/insulin ratio stimulates lipolysis as well as hepatic glucose production to provide glucose supply to glucose-dependent tissues. Hence, during the fed state, glucose serves as the main fuel and fat is stored, while during the fasted state, fatty acids serve as main fuel and glucose is preserved for glucose-dependent tissues [76].

In addition, regulation of fuel selection occurs on a cellular level independent of hormonal mediation: The Randle Cycle adds an additional layer of metabolic “fine tuning” to the relative coarse hormonal regulation of nutrient utilization and storage. In 1963, Randle and coworkers [206] proposed a “glucose-fatty acid cycle” which describes the interplay between carbohydrate and lipid fuels in relation to the requirement for energy utilization and storage. According to the Randle cycle, utilization of one nutrient inhibits the use of the other directly, such that, on a cellular level, glucose consumption is suppressed when fat oxidation increases (and vice versa).

From an evolutionary perspective, a switch from a “one main fuel only” metabolism to a mix of competing fuels with necessity for a fed-to-fasted fuel switch represents a new and potentially problematic situation, the human organism is not adapted to genetically. It needs well-functioning fuel partitioning to organize adequate mitochondrial fuel choice in response to nutritional circumstances.

As insulin controls systemic flux, storage and disposal of glucose, fatty acids and amino acids, insulin sensitivity is a prerequisite for this task [203]. Therefore, development of IR causes significant metabolic perturbations. With onset of IR, insulin-mediated suppression of fatty acid oxidation and of gluconeogenesis during the fed state is impaired and the genetic program, human metabolism has adapted to, retakes control: fatty acids are not stored sufficiently anymore and even released into circulation during the absorptive state, augmented by increased lipolysis, mediated by elevated norepinephrine levels [207]. β -oxidation in muscle increases in the fed state in spite of sufficient or even increased amounts of glucose [208], accompanied by hepatic gluconeogenesis despite high glucose levels. Hence, the combined effect of HCHIDs and IR confronts all types of body cells with an increased mix of fuels, competing for mitochondrial oxidation.

IR, Nutrient Excess, Mitochondrial Inflexibility and ROS

At present, human physiology is characterized by overeating [203,209], with a steady influx of cell fuels, aggravated by metabolic perturbations described above. Large amounts of fuels, taken up by cells and competing for mitochondrial oxidation, may lead to a faulty fuel choice and aberrant nutrient partitioning of various organs and cell types, a phenomenon termed as “metabolic inflexibility” [203]. Basically, OxPhos is a demand driven process where energy supply corresponds to energy demand. In a state of metabolic inflexibility, however, the overfed mitochondria continue to degrade an everlasting flood of different incoming carbon substrates (glucose, fatty acids and amino acids), with increased production of electron transfer donors (NADH and FADH₂). When electron supply exceeds demand for ATP, proton re-entry through ATP synthase decreases and mitochondrial membrane potential rises, leading to an increased production of

superoxide anions (O₂⁻), followed by its rapid conversion to hydrogen peroxide by superoxide dismutase [150,156]. At high membrane potential, a small increase in membrane potential gives rise to production of significant amounts of ROS [210,211]. Nutrient excess and metabolic inflexibility are a major cause of increased mitochondrial ROS production and oxidative stress [156,203,212]. These perturbations of blunted fuel switching and distorted nutrient sensing have been described in a variety of clinical settings, including obesity and diabetes, as well as in various organs and cell types, like adipose tissues, macrophages and monocytes [203].

In addition, nutrient excess has the potential to cause mitochondrial dysfunction and increased ROS production through adverse effects on the mitochondrial life cycle which is characterized by continuous transitions between elongation (connected state) and fragmentation (separated state). Disabling these brief transitions between connected and separated mitochondria arrests the life cycle, compromises mitochondrial quality control and may lead to accumulation of damaged mitochondria that cannot be segregated [156,213]. Prolonged nutrient excess leads to fragmentation and inhibition of the mitochondrial life cycle and autophagy, and ultimately to mitochondrial damage and an increase in ROS generation. Hyperglycemia, as an example, has been shown to cause increased production of mitochondrial ROS, associated with dynamic changes in mitochondrial morphology in the form of rapid fragmentation [214]. According to Liesa [156], these alterations may explain different reports, demonstrating mitochondrial dysfunction in pathologies associated with an imbalance in nutrient supply and demand, like obesity and diabetes.

The opinion that cancer could be a diet-related disease has already been expressed earlier: Wellen et al. [215] proposed that nutrient excess may play a role in carcinogenesis through hyperinsulinemia, chronic low-grade inflammation and ROS-mediated mutagenesis of DNA.

Cancer Risk Factors and Related Metabolic Alterations

Intriguingly, the most important risk factors for cancer development are associated with increased ROS production and frequently with insulin resistance.

Ageing: Advancing age is a high risk factor for cancer, with persons over 65 accounting for 60% of newly diagnosed malignancies and 70% of all cancer deaths [26].

Aging is associated with a whole series of metabolic alterations related to the development of cancer, like increased ROS production and damage to mitochondria with mitochondrial dysfunction (including stem cells) [155,212,216], insulin resistance and hyperinsulinemia including activation of the IGF system [39], glucose intolerance [38], increased SNS activity [217], and a progressive increase in total body fat in the general population with advancing age [218].

Obesity: Obesity is associated with systemic oxidative stress [201,202], mitochondrial dysfunction [204], expression of UCP2 [219], IR and hyperinsulinemia [54,70,73], and increased SNS activity [220].

Smoking: Smoking has been implicated in cancer development through its mutagenic effects.

However, smoking is also associated with systemic oxidative stress [202], mitochondrial damage and dysfunction, increased SNS activity

and NE turnover [222], and has been suggested to cause IR and hyperinsulinemia [223,224].

Inflammation: Many cancers arise from sites of chronic irritation, infection, or inflammation which also represents sites associated with increased stem cell activity. The finding that chronic inflammation is accompanied by the copious production of ROS supports the concept that oxidative stress induced by chronic inflammation could mediate neoplastic transformation of stem cells [193].

Growth factors and cytokines as well as inflammatory cells like neutrophils and macrophages stimulate the production of ROS [197]. In addition, inflammation induces cell proliferation, and this inflammation-induced cell proliferation potentiates DNA damage-induced mutations [225]. Inflammation is frequently associated with IR [64,226], like for instance in chronic bowel disease [226].

Viruses: Viral infections may be associated with mitochondrial dysfunction and increased production of ROS [227,228]. Hepatitis C virus, for instance, has been reported to cause hepatocellular carcinoma, at least in part through oxidative stress, inflammatory response and insulin resistance-related mechanisms [108].

Summary and Suggested Pathomechanism (Figure 1)

The evidence presented shows that the switch from a Paleolithic to a “Western” nutrition has brought about significant metabolic perturbations that may cause malignant transformation, like an abnormal activation of metabolic systems like the IGF system, the SNS and the RAS, an increased expression of HIF-1 α , and other more, all of which are deeply involved in cancer development and well known to promote proliferation as well as angiogenesis, inflammation, macrophage infiltration, metastasis and inhibition of apoptosis.

Furthermore, HCHIDs generate oxidative stress which may cause mDNA damage and genomic instability, and may interfere with normal stem cell development. Faulty redox signaling is suggested to play a significant role in cancer development. Hydrogen peroxide, generated at low concentrations, represents an important chemical mediator in the regulation of various cellular signal transduction processes including stem cell development. Oxidative stress may be sensed by cells as redox signaling. This abnormal “signaling” may interfere with normal stem cell development through sustained UCP2 activation, resulting in inhibition of differentiation (“maturation arrest”), sustained uncontrolled proliferation, and glycolysis with high expression of hexokinase II, typical features of cancer. Faulty signaling may also affect other aspects, like for instance aberrant p53 expression. While it is likely that most of the transformed cells will undergo apoptosis, some will not.

As far as the findings of Neufeld et al. [94,95] are concerned – the number of insulin receptors correlated positively with the insulin level during fetal development - it is tempting to assume that receptor expression in the developing embryo (and in stem cells?) generally correlates positively with ligand levels. If this were the case, it could provide an explanation for the well-known receptor upregulation in cancer (including upregulation of the antioxidant system?).

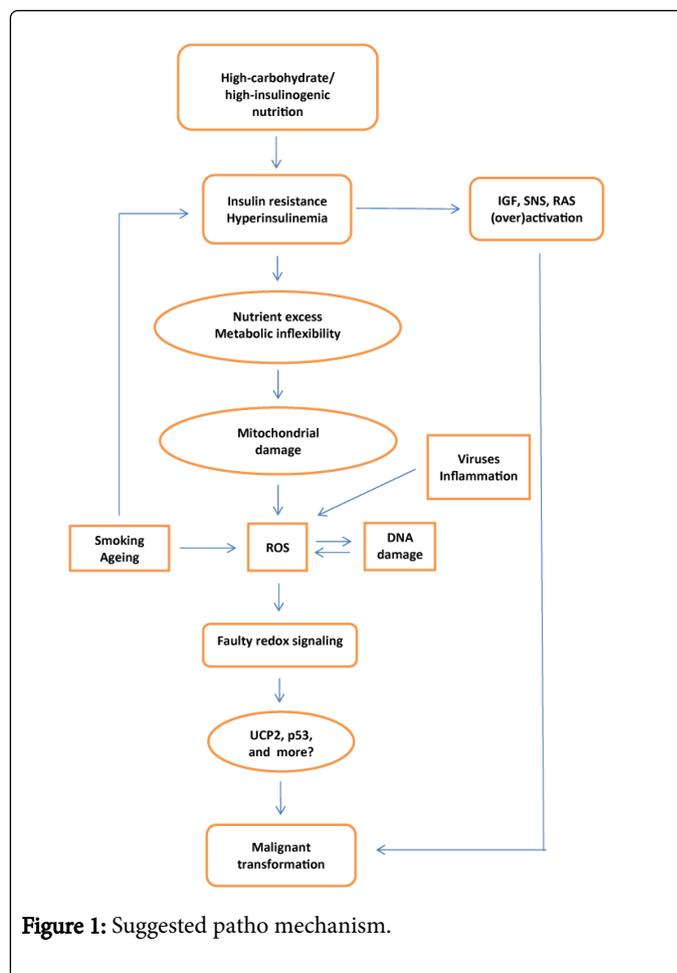


Figure 1: Suggested pathomechanism.

In summary, an abnormal diet-related activation of various metabolic systems, together with faulty redox signaling, is suggested to play a pivotal role in cancer development. The proposed pathomechanism is able to elucidate several characteristics of cancer development which currently do not have a sufficient explanation, like for instance the association between cancer and the metabolic syndrome, the increasing prevalence of cancer during the past century, and the Warburg effect.

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