Additional File 1: Detailed Descriptions of Biological Mechanisms

Mechanism 1: Hyperglycemia induces Cell Hyperproliferation

Oversupply of energetic resources, especially serum glucose, fuels the cell hyperproliferation that drives oncogenesis. In computer simulations of oncogenesis, nutrient excess directly drives cell hyperproliferation and thus oncogenesis (1). Substantial evidence empirically confirms this model's prediction (2). For example, *in vitro* experiments showed that in the presence of endothelin-1, high glucose concentration mimicking hyperglycemia caused hyper-proliferation by vascular smooth muscle cells (3).

Hyperglycemia increases cell proliferation and cancer risk not only through oversupply of glucose to cells, but also through elevated levels of mitogenic signals including IGF, insulin, leptin, adiponectin, steroid hormones, and sirtuins (4).

Mechanism 2: Cell Hyperproliferation induces Cancer Risk

One of the best-established principles of experimental cancer biology is that certain exposures, termed 'cancer promoters', increase cancer risk by increasing cell proliferation. This early experimental result remains consistent with the modern understanding of oncogenesis through somatic cell evolution (5); (6) , and has been confirmed for human cancer through large sets of clinical data (7); (8); (9).

Moreover, experimentally, reduction in cell hyperproliferation mediates many of the anti-cancer effects of caloric restriction (10). Animal studies have demonstrated reduced cell proliferation resulting from interventions that reduce cancer risk through metabolic dysfunction. For example, caloric restriction reduced cell proliferation and cancer incidence in murine models of metabolically induced colon carcinogenesis (11).

Mechanism 3:Hyperglycemia induces Hyperlipidemia, and reverse

Under conditions of imbalance, the liver can either convert glucose to lipid through lipogenesis, or convert lipids to glucose through gluconeogenesis.

Thus, high-carbohydrate dietary intake can induce lipogenesis, and dyslipidemia frequently disappears with reduced calorie intake (4). Furthermore, low glycemic diets can alter lipid metabolism in ways that inhibit tumor growth (12).

Mechanism 4: Hyperlipidemia induces Visceral Adiposity

Visceral obesity is a response to a high flux of free fatty acids through the visceral circulation (4).

More than other adipose tissues, visceral adiposity is strongly associated with metabolic pathology. Increased visceral adiposity is an important mediator of metabolic disease and lipotoxicity. This is at least partly because proinflammatory cytokine and chemokine production is higher in visceral than subcutaneous adipose tissue (13). Therefore, despite high body fat mass, metabolically healthy obesity is characterized by low visceral fat accumulation (14).

Mechanism 5: Visceral Adiposity induces Metabolic Inflammation

Metabolic inflammation (or metaflammation) is chronic, low-grade systemic inflammation, as distinct from the classical transient and acute inflammatory responses of the innate immune system (15). It is strongly associated with overnutrition and obesity (16), and many mechanisms of its causes and effects have been described (Figs. 1 & 2). Chronic

metabolic inflammation has been blamed by some authors for as much as 90% of all human cancer (17), although other estimates are lower.

Different fat depots differ in their contributions to metabolic inflammation, and visceral adiposity is an especially important contributor. Metabolically healthy obesity is characterized by low visceral fat accumulation (14). Mechanistically, visceral adipose produces more proinflammatory cytokines than does subcutaneous adipose tissue (13). Consequently, visceral adipose tissue contains more pro-inflammatory macrophages and T cells (18), and is a key driver of inflammation in metabolically unhealthy obesity (19).

Another mechanism by which visceral adiposity drives metabolic inflammation is its accumulation of senescent SIPS cells (Mechanism 23). These senescent cells are primarily located in visceral adipose tissue (13). However, through pro-inflammatory signaling, senescent SIPS cells can spread their phenotype in an endocrine manner to distant organs, causing systemic effects (13).

Mechanism 6: Metabolic Inflammation induces Cell Hyperproliferation

Acute local inflammation, including attendant cell proliferation, is normally self-limiting. In contrast, chronic systemic inflammation has pathologically extended pro-mitogenic effects (20).

Chronic inflammation induces cell hyperproliferation through vascular oversupply of energy and mitogenic signals to affected tissues (1). It also increases proliferation and survival of emerging malignant cells, promotes angiogenesis and metastasis, subverts adaptive immune responses, and alters responses to hormones and chemotherapeutic agents in tumor-supportive ways (21).

Mechanism 7: Metabolic Inflammation induces Genetic Instability

Chronic low-level systemic inflammation mechanistically links metabolic syndrome to cancer. Proinflammatory cytokines and resulting inflammation stimulate reactive oxygen species (ROS), resulting in oxidative DNA damage. This is a critical step to cancer because oxidative DNA lesions can result in genetic instability (22).

Inflammation and ROS also induce epigenetic modifications and epigenetic instability (23), which can act analogously to genetic instability in fueling oncogenesis (24).

Consequently, inflammatory conditions increase the risk of cancer. Well-understood molecular and cellular pathways link inflammation to carcinogenesis, and these pathways also suppress effective antitumor immunity (21).

Mechanism 8: Genetic Instability induces Cancer Risk

Oncogenesis results from Darwinian selection among somatic cells (25). Well-established mathematical models quantitatively describe how such evolution requires variation among cells (26, 27), which results from genetic instability.

This well-established evolutionary theory is supported by decades of experimental results showing that effective cancer ‘initiators’ act by inducing genetic variation in somatic cells (5); More recent empirical studies have also confirmed that genetic instability drives oncogenesis ((24, 28).

Mechanism 9: Hyperlipidemia induces Adipocyte Hypertrophy, and reverse

Hyperglycemia and hyperlipidemia lead adipocytes (fat storage cells) to add lipid to their central lipid droplet, increasing in volume up to several thousand times. With increased size, the cell becomes stiff and the membrane signaling disturbed, leading to pathology (14).

Thus, adipocyte size is an important predictor of metabolic pathology (29). Adult weight gain is mostly due to adipocyte expansion (hypertrophy), and weight loss leads to a decreased adipocyte size independent of the method employed for weight loss (14).

In the reverse direction, adipocyte hypertrophy increases hyperlipidemia because hypertrophic adipocytes release lipid back into the circulation. Furthermore, release of free fatty acids through lipolysis is also increased in hypertrophied adipocytes, an effect regulated by insulin (14).

Mechanism 10: Hyperglycemia induces Insulin Resistance, and reverse

Systematic overeating can cause insulin resistance through repeated administration of excess levels of glucose, which stimulate insulin secretion (30).

In the reverse direction, insulin resistance reduces uptake of glucose, exacerbating hyperglycemia (30).

Mechanism 11: Insulin Resistance induces Hyperinsulinemia, and reverse

Hyperinsulinemia is often both a driver and a result of insulin resistance (31).

In the reverse direction, after extended hyperinsulinemia, most cells have their needs for glucose already met, and therefore do not continue to respond to insulin with increased glucose uptake (32). As uptake falls, the glucose level rises, and insulin resistance follows.

Mechanism 12: Hyperinsulinemia induces Cell Hyperproliferation

As described in Mechanism 11 above, extended hyperinsulinemia supports maximal cell uptake of glucose. This induces cell hyperproliferation (2).

Consequently, in experimental animal models, increased circulating levels of insulin via overnutrition have been shown to promote oncogenic cell proliferation (11).

Mechanism 13: Hyperglycemia induces Premature Cell Senescence

Stress-induced premature senescence (SIPS), is triggered in various cells even without shortened telomeres, upon exposure to various stressors (33). These senescent cells arise from normal cells in multiple organs due to signals of inflammation, metabolic or DNA damage, or tissue damage. The resulting non-proliferating SIPS cells remain metabolically active and secrete a range of proinflammatory and proteolytic factors as part of their senescence-associated secretory phenotype (34).

Cells can enter SIPS in response to a variety of stressors. These include metabolic stresses, such as high glucose levels and hyperproliferation (34).

The high glucose levels common in obesity can induce SIPS in a variety of different cell types (13, 35). Evidence indicates that glucose accelerates SIPS through activation of gene *p38* (35). When sustained, hyperglycemia leads to increased ROS production in otherwise normal cells (36) Thus, hyperglycemia and excess glucose exposure may drive excess metabolic activity with ROS over-production, triggering cellular stress and SIPS.

Mechanism 14: Premature Cell Senescence induces Metabolic Inflammation

When cells enter stress induced premature senescence (SIPS) (Mechanism 13 above), they express a senescence-associated secretory phenotype, that is highly pro-inflammatory. The burden of senescent cells increases in obesity and contributes to chronic metabolic inflammation (37).

Adipose tissue can constitute a significant number of senescent cells, particularly in obesity. In diet-induced obese mice, visceral adipose tissue contains the highest burden of senescent cells (37).

Mechanism 15: Hyperlipidemia induces Ectopic Lipid

Excess lipid in non-adipose tissues is called ectopic lipid. When adipose tissue fails to store all excess nutrients as triglyceride, lipid begins to accumulate as large intracellular lipid droplets in various tissues, including liver, pancreas, and heart (4, 38).

As part of metabolic syndrome, ectopic lipid also accumulates in colorectal tissue and in skeletal muscle (39). While most normal cells contain small lipid droplets, ectopic lipid is pathological, and may cause various types of lipotoxicity including insulin resistance in the liver and skeletal muscle, and insufficient insulin secretion in the pancreas (40).

Ectopic lipid deranges cell biology because lipid droplets are normally involved in cell metabolism, signaling, and proliferation (41). Lipid droplets are an integral part of the cellular stress response, and emerging studies suggest that these organelles regulate various aspects of inflammation (42).

Mechanism 16: Premature Cell Senescence induces Hyperlipidemia

Premature senescence of adipose progenitor cells (APCs) blocks adipose hyperplasia, shifting the load of lipid storage onto adipose hypertrophy (43).

This blockage results from over-proliferation of APCs due to over-nutrition, leading to their stress-induced premature senescence (Mechanism 13), which blocks their proliferation and differentiation, preventing the recruitment of new adipocytes (44).

Mechanism 17: Ectopic Cell Lipid induces Insulin Resistance

Cells store excess free fatty acids in the form of triglyceride contained in intracellular lipid droplets. This normally occurs only in adipose tissues, but under extreme positive energy balance, it also occurs in non-adipose tissues, where it is called ectopic lipid (4).

Accumulation of ectopic lipid in non-adipose cells contributes to insulin resistance (45). Lipid-induced reduction of cellular glucose uptake in response to insulin is due to an intracellular fatty acid–derived signal, in the form of diacylglycerol (DAG), which inhibits the intracellular insulin signaling cascade. First discovered in mouse models, these molecular mechanisms have since been confirmed in humans as well (46).

Mechanism 18: Ectopic Cell Lipid induces Metabolic Inflammation

Ectopic lipid accumulation leads to local inflammation in locally affected tissues. Systemically, overnutrition also triggers uncontrolled inflammatory responses in white adipose tissue, leading to chronic low-grade systemic inflammation (47).

In metabolically important tissues such as liver, ectopic lipid accumulation promotes insulin resistance by activation of inflammatory pathways (48).

Certain forms of ectopic lipid may be especially important. Saturated fatty acid (SFA) stimulates pro-inflammatory responses in vascular endothelial cells through mechanisms mediated by toll-like receptor (49).

Mechanism 19: Adipocyte Hypertrophy induces Insulin Resistance

In hypertrophic adipocytes, endoplasmic reticulum stress activates two principal inflammatory pathways that impair the action of insulin. Thus, in hypertrophic obesity, adipose tissue inflammation contributes to systemic insulin resistance (50).

Even without inflammation, hypertrophic adipocytes exhibit impaired insulin-dependent glucose uptake. Thus, adipocyte hypertrophy alone may cause insulin resistance even in mild obesity or normal weight (51), and even without significant inflammation.

Based on direct measurements of cellular response in isolated adipocytes, insulin responsiveness was negatively affected by cell size. This effect was mediated by insulin-induced GLUT4 translocation to the plasma membrane of only small, not hypertrophic, cells (52).

Mechanism 20: Adipocyte Hypertrophy induces Adipocyte Hypertrophy

In a direct feedback loop, the cell dysfunction resulting from adipocyte hypertrophy impairs two distinct functions that would normally limit adipocyte hypertrophy. Those two functions are first, the ability to dispose of excess lipid through mitochondrial oxidation, and second, the ability to recruit new adipocytes (adipogenesis) to share the load of further lipid storage.

In the first blocked response, hypertrophic adipocytes showed reduced mitochondrial respiration in an *in vitro* model of adipocyte hypertrophy, and thus a failure to respond to lipid accumulation with increased mitochondrial oxidation of lipids. Consequently, they accumulated lipid faster than did normal adipocytes (53).

In the second blocked response, hypertrophic adipose loses the ability of healthy adipose that has exceeded its capacity for lipid storage, to trigger increased storage capacity through adipogenesis -- the differentiation of precursor cells into new adipocytes. This ability is impaired in hypertrophic obesity (52). Adipose progenitor cells from individuals with hypertrophic obesity have increased levels of cellular senescence, which blocks their

proliferation and differentiation, impairing adipogenesis, and leaving adipocyte hypertrophy as the only way adipose tissue can store excess lipids.

The net effect of these two dysfunctions is that adipocyte hypertrophy leads to loss of ability to increase lipid storage. Within a single tissue, gene expression patterns can distinguish different adipocyte subpopulations, and demonstrate that diets causing adipocyte hypertrophy lead to disappearance of the lipid-storing adipocyte subpopulation (54).

Mechanism 21: Metabolic inflammation induces Ectopic Lipid

Excess lipid in non-adipose tissue is called ectopic lipid (Mechanism 15). Inflammation decreases the capacity for fat storage by adipose tissue. Inflammatory cytokines decrease lipid storage capacity by inhibiting the differentiation of preadipocytes; and also by increasing lipolysis, which increases free fatty acids in serum, driving ectopic lipid accumulation in non-adipose tissues. Without sufficient differentiation of preadipocytes into new adipocytes, existing adipocytes become hypertrophic, after which excess lipids spill over from the overloaded and dysfunctional adipose tissue, exposing other tissues to an excessive flux of lipids, leading to ectopic lipid deposition (55).

In a parallel mechanism, metabolic inflammation may cause obesity-induced metabolic insulin resistance, inducing hyperinsulinemia, which suppresses lipolysis and facilitates lipogenesis, thereby increasing the lipid storage burden on already overloaded adipocytes (56).

Mechanism 22: Hyperglycemia induces Metabolic Inflammation

Metabolic inflammation (or metaflammation) is chronic, low-grade systemic inflammation (Mechanism 5). Hyperglycemia creates metabolic inflammation through several distinct mechanisms, both direct and indirect.

The direct inflammatory effects are responses to glucose itself. In response to high glucose, adipocytes increase the secretion of pro-inflammatory factors and become important contributors to systemic inflammation (23, 57). Also in response to high glucose, adipocytes, endothelial, and other cells induce inflammation through production of reactive oxygen species, leading to the induction of pro-inflammatory cytokines such as IL-6 (23).

In an indirect mechanism, hyperglycemia induces inflammation through the intermediary of advanced glycation end products (AGE). These are metabolic by-products of high glucose concentration that arise when proteins or lipids become glycated (covalently attached to sugars non-enzymatically). AGEs are detected by widespread cell-surface receptors for AGE, which trigger chronic systematic inflammation in response (58, 59).

Mechanism 23: Premature Cell Senescence induces Premature Cell Senescence

When cells enter stress induced premature senescence (SIPS) (Mechanism 13), part of their senescence-associated secretory phenotype is the secretion of cytokines that can spread senescence in a paracrine or endocrine manner to previously normal cells, locally or distantly. Senescent cells also evade apoptosis through upregulation of antiapoptotic pathways. These pathways let senescent cells resist the proapoptotic factors that they produce.

As a consequence, a pathogenic positive feedback loop can form in which senescent SIPS cells beget ever more SIPS cells (36).

Mechanism 24:Adipocyte Hypertrophy induces Hypertrophic Adipose

Adipocyte cell hypertrophy (see Mechanism 9) is a short-term adaptation to an acute lipid storage problem, but it is not sustainable under chronic overnutrition. As adipocytes fill and then become hypertrophic, they reduce their glucose uptake and increase their release of free fatty acids. This induces hypertrophy of neighboring adipocytes, so that an entire adipose tissue may become hypertrophic and swollen, increasing tissue volume without a corresponding increase in vascular supply, which leads to tissue-level pathology (see Mechanism 27).

Mechanism 25: (This number was intentionally left unused)

Mechanism 26: Adipocyte Hypertrophy induces Metabolic Inflammation

In hypertrophic adipocytes, endoplasmic reticulum stress activates inflammatory pathways (50). Consequently, increased adipocyte size triggers an inflammatory response (14). At the molecular level, increasing adipocyte size leads to expression of the inflammatory genes *NF-kappa-B* and *TNF-gamma*, and expression of TNF receptor.

Beyond the individual cell level, there are also tissue-level and systemic effects. Within hypertrophic adipocytes, endoplasmic reticulum stress activates the JNK AP-1 and TNF-kB pathways, which trigger the release of macrophage chemoattractant proteins, which then, in chronic inflammation, leads to hypertrophic adipocyte death. The infiltrating macrophages release inflammatory proteins that cause further recruitment of macrophages into adipose tissue as well as the further release of inflammatory cytokines (50).

Mechanism 27: Hypertrophic Adipose induces Hypoxic Adipose

Hypertrophic adipose cells undergo hypoxia when they enlarge to sizes approaching the limits of oxygen diffusion, which hypertrophic adipocytes can easily exceed (43, 60, 61).

Animal studies have provided strong evidence supporting the presence of adipose tissue hypoxia in obesity (60).

Unlike other tissues, the hypoxic response of visceral adipose tissue does not induce new vascularization. A distinct subpopulation of adipose stromal cells can express a set of genes associated with neoangiogenesis. However, this cell subpopulation is found mostly in subcutaneous, as opposed to visceral, adipose (62).

Mechanism 28: Hypoxic Adipose induces Metabolic Inflammation

In hypertrophic adipocytes, endoplasmic reticulum stress activates inflammatory pathways (Mechanism 26). But in an escalating second mechanism, when hypertrophic adipose becomes hypoxic without a response of neoangiogenesis, (see Mechanism 27), hypoxic stress augments inflammatory infiltration and increases the pro-inflammatory output of the hypertrophic adipose tissue (43).

Obesity in rodents and patients is known to induce localized hypoxia (63). Moreover, exposure of cultured adipose tissue to hypoxic conditions induces upregulation of numerous genes involved with inflammation, especially hypoxia-inducible factor-1 (HIF1), a transcription factor that is activated in hypoxic conditions (60, 63).

Mechanism 29: Metabolic inflammation induces Adipocyte Hypertrophy

Normal adipocytes are enveloped by a basement membrane, so that only after its extensive remodeling through inflammation can adipocytes increase greatly in size (64).

Mechanism 30: Hypertrophic Adipose induces Overall Obesity

Overall obesity, measured as total fat mass, reflects the cumulative effects of two distinct processes, adipocyte hypertrophy, and hyperplasia, one of which is pathogenic while the other is protective against metabolic disease, and probably cancer risk.

Independent of overall obesity, adipocyte hypertrophy (see Mechanism 9) has long been established as a marker and predictor of metabolic pathology (29). It has been directly implicated in both metabolic disease and cancer risk. Hypertrophic adipocytes can induce a permanent pro-tumor microenvironment as a source of 1) growth factors such as estrogen, IGF-1, and leptin; as well as; 2) constant energy supply via free fatty acids; and 3) pro-inflammatory cytokines including IL-6 and TNF-α. Hypertrophic adipocytes can sustain and promote tumor growth even *in vitro* (29). This effect was stronger for adipocytes cultured in higher glucose concentration (65), which provides greater stimulation and substrate for adipocyte hypertrophy (66).

In contrast to the pathological role of adipose hypertrophy, adipose hyperplasia through adipogenesis (new adipose cells) protects against metabolic pathology by safely storing lipids and preventing lipotoxicity (29). Adipose tissue expansion through adipogenesis offsets the metabolic harms of obesity because the increased ability to sequester lipid prevents ectopic lipid accumulation in other tissues, such as muscle, liver and heart, and correlates with preserved metabolic function at all levels (43). Thus, adipogenesis is likely to be protective against cancer risk as well.

Overall obesity is an imprecise indicator of metabolic disease and cancer risk because it includes protective adipogenic adipose, and especially subcutaneous adipose. In contrast to visceral fat, subcutaneous fat, *per se*, has not been mechanistically connected either to metabolic syndrome or to cancer risk. In obese mice, much less macrophage infiltration was observed in subcutaneous fat, although the adipocytes there exhibited a degree of hypertrophy like that seen in epididymal fat. This may be due to the greater potential for neoangiogenesis in subcutaneous adipose (see Mechanism 27).

While overall obesity (as BMI) is epidemiologically related to cancer risk, it is also strongly associated with all other aspects of MetS, highlighting the need for mechanistic understanding (67). Independent mechanistic effects of BMI have been hypothesized but not demonstrated. A Mendelian randomization study found no significant evidence of a causal effect of either early or later life body mass on prostate cancer risk, while adult BMI had no additional effect on risk of breast cancer after accounting for childhood BMI (68).

Despite high body fat mass, obese people can apparently remain metabolically healthy when they avoid visceral obesity, and especially adipocyte hypertrophy (14).

Mechanism 31 Metabolic Inflammation induces Insulin Resistance

Overnutrition triggers uncontrolled inflammatory responses in white adipose, leading to chronic low-grade inflammation, which fosters insulin resistance (47). In human obesity, the degree of inflammation correlates well with the severity of insulin resistance (63).

Mechanism 32: Hyperinsulinemia induces Hypertension

Without known explanatory mechanisms, associations have been reported between hypertension and increased risk of several specific cancers, including adenocarcinoma of the esophagus and of the gastric cardia (69). Moreover, a study using survey data from NHANES III reported that after adjusting for confounders, systolic blood pressure was significantly associated with an increased risk of death from cancer (total of all types) ($p = 0.002$) (70).

Despite these observations, no mechanistic route from hypertension to cancer has been proposed, and evidence suggests instead, that hypertension and cancer risk are associated only because they share upstream mechanisms in the metabolic syndrome, particularly hyperinsulinemia.

Hyperinsulinemia appears to independently promote both hypertension and cancer risk, through separate mechanistic pathways (Fig. 1). Insulin exhibits a sodium-retaining effect through its direct action on the renal tubules. Enhanced sodium retention because of hyperinsulinemia may lead to a rise in blood pressure. It is suggested that hyperinsulinemia thereby promotes altered vascular function (71). However, it remains uncertain whether hypertension is caused by excessive insulin, by insulin resistance, or by chronically induced vascular effects of those (72).

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