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Molecular links between metabolome and epigenome: AMPK-TET2 signalling pathway and their natural activators

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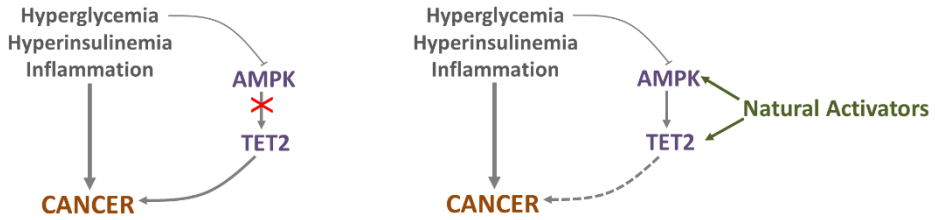
Review

ABSTRACT



Emerging evidence suggests that sustained diabetes-associated factors such as inflammation, hyperinsulinemia, and hyperglycemia are major contributors to aberrant cell proliferation and subsequent neoplastic transformation. Epidemiological studies have also highlighted that diabetes promoting a sedentary lifestyle, with or without the direct involvement of insulin, is frequently linked to cancer. However, our knowledge regarding the molecular mechanisms that correlate hyperglycemia to oncogenic transformations remains limited. In this regard, a recent study has proved that hyperglycemia inactivates AMPK, destabilizing the TET2 and its tumour-suppressive role and ultimately predisposing diabetes mellitus patients to cancer. We must explore a reverse pharmacology-based ethnopharmacological approach to managing hyperglycemia associated with oncogenesis. Botanical-derived natural products have greater structural and functional diversity with fewer or no side effects on humans. The present review discusses the molecular relationship between hyperglycemia and cancer progression and the impact of natural products as therapeutic agents on the hyperglycemia-cancer-associated signaling pathway.

Keywords: Hyperglycemia, Cancer, AMPK, TET2, Natural Activators

INTRODUCTION

Diabetes mellitus (DM) is a multifaceted disorder characterized by hyperglycemia,[1] hyperinsulinemia,[2] high BMI,[3] cardiovascular diseases,[4] and lipid disorders.[5] A myriad of factors can contribute to the development of DM-associated hyperglycemia, such as stress, critical illness (stroke or myocardial infarction),[6] drugs (corticosteroids,[7] octreotide,[8] β-blockers,[9] thiazides,[10] statins,[11] L-asparaginase[12]), as well as hormones.[13] Besides, constitutive secretion of insulin or increased expression of glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) is frequently associated with hyperglycemia.[14] Sustained hyperinsulinemia is a familiar cause of site-specific cancer progression. It promotes the over-expression of insulin receptors A (IR-A) and induces secretion of Insulin-like Growth Factor 1 receptor (IGF-1 Rs).[15] It has been postulated that the development of both DM and cancer within the same individual is more likely.[16] In fact, collaborative meta-analyses of several other investigations have proposed that DM is usually linked with some form of cancer and the risk of occurrences of colorectal,[17] pancreatic,[18] liver,[19] breasts,[20] endometrium,[21] gastric,[22] kidney,[23] bladder,[24] and female reproductive (breast and endometrium) cancers is higher while prostate cancer is considered lower.[25] However, despite these observations, the potential molecular links between DM and cancer are poorly understood, and identifying common molecular targets related to the pathogenesis of cancer and DM remains elusive.

The heritable covalent modifications of DNA, such as methylation, acetylation, phosphorylation, and SUMOylation, are often perturbed in cancer and related cellular defects.[26] Experimental evidence suggests cellular metabolic fates can directly regulate epigenome through nutrient sensors such as the AMP-activated protein kinase (AMPK).[27] Cell metabolism can affect the epigenome because several metabolites can act as substrates, activators, inhibitors, cofactors, or allosteric modulators of the epigenome-regulating enzymes.[28] Conversely, the epigenome can also modify gene expression by altering transcription. AMPK is an extremely conserved protein which senses cellular energetic stress and is also referred to as a fuel

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gauge of the cell. AMPK is stabilized under energy stress, particularly when an increased AMP: ATP ratio is observed.[29] Wu and colleagues proved that hyperglycemia impedes AMPK-mediated phosphorylation of TET 2 at serine 99 residues, resulting in destabilization of TET2 and increasing susceptibility for calpain-mediated proteolysis followed by dysregulation of tumour-suppressive functions and reduced 5hmC level in the CpG Island.[30]

TET proteins are a member of the Fe^{2+}/α-ketoglutarate-dependent dioxygenases (Fe^{2+}/α-KGDDs) family that includes TET1, TET2, and TET3, which are involved in the demethylation of the epigenome. TET2 is a tumour suppressor protein that converts 5-methylcytosine residue (5mC) to 5-hydroxymethylcytosine residue (5hmC) on CpG Island.[31] In-depth investigation and understanding of metabolic glucose (metabolism)-AMPK-TET2-5hmC (epigenome) axis may decode some molecular targets associated with the pathogenesis of cancer and DM The stable form of AMPK phosphorylates numerous downstream substrates, including CREB,[32] glycogen synthase,[33] ACC,[34] FOXO,[35] raptor,[36] and TET2.[30] AMPK phosphorylates TET2, which results in the stabilization of TET2 and prevent its calpain-mediated proteolysis.[30]

Hyperglycemia is recognized when fasting and postprandial blood glucose levels are more than 125 mg/dL and 180 mg/dL, respectively.[37] Untreated hyperglycemia has been associated with several serious physiological complications, including damage to the eye,[38] lungs,[39] heart,[40] kidneys,[41] peripheral vascular,[42] and nervous systems.[43]

The present article meticulously elucidated the intricate molecular relationships linking diabetes and cancer. We focused on unravelling the profound influence of hyperglycemia on the AMPK-TET2 signalling axis, delving into both the structural and functional aspects of AMPK and TET2. Additionally, we explored potential natural activators of the AMPK-TET2 pathway. Moreover, we provided a concise overview of the plausible molecular mechanism. We shed light on how extracellular hyperglycemia can dynamically modulate the intracellular enzymatic machinery that governs metabolism and gene expression in diabetes and cancer.

EPIDEMIOLOGY AND ETIOLOGY OF CANCER AND DIABETES MELLITUS ASSOCIATIONS

DM and cancer are recognized as the defining disorders of the 21st century with remarkable global socio-economic impact. According to the World Health Organization, it is estimated that cancer and DM represent the second (9.6 million, 2018) and seventh (1.6 million, 2016) leading causes of death worldwide, respectively. In addition, both cancer and DM are often co-diagnosed in the same patient, which suggests a significant increase in cancer occurrence within diabetic patients.[17-25] The international diabetes federation estimated that the global prevalence of DM would rise from 425 million in 2017 to 629 million in 2045.[44] Epidemiologic evidence has revealed a definitive association between DM and cancer, and it is also speculated that the occurrence of cancer is linked with DM or risk factors associated with DM

The DM-cancer association has been hypothesized to rely on various hormonal (insulin, IGF1, adipokines), immunological (inflammation), or metabolic (hyperglycemia) characteristics of the disease and even on certain treatments. Transformation of healthy cells into neoplastic phenotypes is probable through numerous genetic alterations due to overexpression on oncogenes and suppression of tumour suppressor genes. The neoplastic progression of cancer cells undergoes different cellular phages, such as growth, invasion, and metastasis.[45] The positively modulated factors that restrain any steps of the neoplastic progression could be associated with cancer treatments and management. In contrast, negatively modulated factors promote the neoplastic progression that could be associated with the development of cancer or fatality.[46] DM could directly or indirectly promote neoplastic progression through several systemic factors, including hyperinsulinemia, elevated IGF1 level, cytokine imbalance, and chronic inflammation (Figure 1).

HYPERINSULINEMIA

In sustained hyperinsulinemia, insulin acts as a growth-promoting factor functionally similar to insulin-like growth Factor-1 (IGF-1), and both factors are responsible for promoting the rate of tumorigenesis.[47] Approximately 98% of serum IGF-1 is coupled with IGF-1 binding proteins (IGF-BP), a functionally inactive form.[48] Hyperinsulinemia-induced overexpression of IGF-1 and suppression of IGF-BP results in elevation of the active form of serum IGF-1.[49] In humans, I.R.s generate two isoforms, IR-A and IR-B, and the majority of cancer cells express IR-A and IGF-1 receptors (IGFs-1Rs) on their surface.[50] The IR-A has a binding affinity with insulin, proinsulin, and IGF-2, and thus, IR-A efficiently induces insulin-mediated mitogenesis.[51] Insulin and IGF-1 are both involved in cell proliferation and inhibit apoptosis.[52] An elevated level of serum IGF-1 has been shown to increase the probability of colorectal cancer development.[53] Further, when insulin and IGF-1 interact with IRs and IGF-1 Rs respectively, both activate PI3K-Akt-mTOR and Ras-Raf-MEK-ERK signalling cascade.[54] Akt inhibits AMPK,[55] and glycogen synthase kinase 3β (GSK3β)[56], which can now not inactivate β-catenin, thus promoting an environment of sustained cell proliferation with implications in tumour development.[57] Akt also suppresses apoptosis and induces cell death by dissociating the anti-apoptotic protein B-Cell Lymphoma 2 from Bad.[58] Thus, it can be emphasized that the sustained active forms of IRs and IGF-1Rs-mediated signalling cascades can augment susceptibility to tumorigenesis (Figure 1).

INFLAMMATION

Elevated insulin levels induce the secretion of many factors that promote fates accumulation in adipose tissues. The adipose cells can produce inflammatory mediators including sialic acid,[59] fibrinogen,[60] IL-6,[61] C-reactive protein (CRP),[62] plasminogen activator inhibitor-1 (PAI-1)[63] and TNF-α,[64] that leads to the inflammation. TNF-α has shown potential physiological impacts on metabolism *via* inducing insulin resistance.[65] The normal secretion of IL-6 steadily activates the IL-6 receptor and consequently acts as a signal transducer and activator of

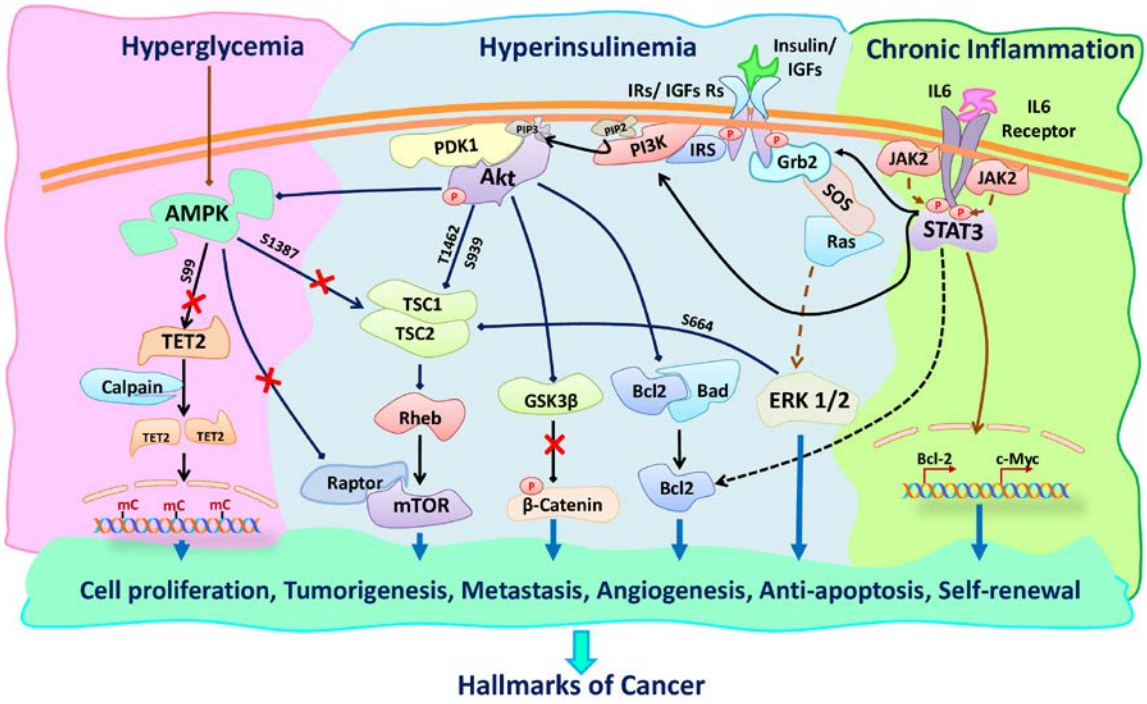


Figure 1: The cellular signalling pathways that link DM to cancer *via* hyperinsulinemia by over-activating insulin receptors and IGF-1 leads to downstream activation of the PI3K-Akt-mTOR pathway and Ras-Raf-MEK-ERK pathway. The Akt activates several targets like mTOR and Bcl2 while inhibiting AMPK and β-catenin. Chronic inflammation has responses by interleukin-6 to trigger STAT3, which promotes Bcl2 and c-Myc overexpression. Hyperglycemia destabilizes AMPK, so it cannot phosphorylate TET2 and TSC1/2 complex. Unstable AMPK could also not inhibit raptor, which regulatory-associated protein of mTOR. All these cellular cascades are cooperatively responsible for cancer progression by promoting angiogenesis, apoptosis, metastasis, and tumorigenesis.

transcription protein-3 (STAT3). Inflammation-mediated over-activation of STAT3 provoked neoplastic progression and seized host anti-tumour immunity.[66] The occurrence of leukocytes enclosed in tumours was first observed by Rudolf Virchow, representing the first sign of a possible association between inflammation and tumorigenesis. T-cells and tumour-associated macrophages (TAMs) are rottenly found leucocytes near the tumour microenvironment. T-cells are exhibited both tumour-promoting and tumour-suppressive,[67] while TAMs frequently induce angiogenesis, tumorigenesis, invasion, and metastasis.[68] The inflammation-associated components such as TNF-α, IL-6, TAMs, and other inflammatory mediators modulate signalling pathways associated with tumorigenesis (Figure 1).

HYPERGLYCEMIA

Hyperglycemia is the well-understood systemic and metabolic factor that links DM to cancer. Cancer cells utilize more glucose than normal cells to fulfil metabolic demands. Otto Warburg, in the 1920s, clarified that cancer cells use glycolysis for glucose metabolism and ATP generation instead of oxidative phosphorylation, even in the hyperoxia environment.[69] Cancer cells require more glucose for ATP generation as a prime energy source; thus, they have a high rate of glucose uptake, unlike their healthy counterpart. Hence hyperglycemia facilitates tumorigenesis and cancer progression and is considered a potential anti-tumorigenesis target. Hyperglycemia links DM to cancer by increasing the secretion of circulating soluble factors, including growth factors (insulin/IGF1)[70] and inflammatory cytokines (TNF-α/IL6/Adipokines).[71] However, the direct effects of hyperglycemia upon cancer cells, a moderately understood, which are direct influences on cancer signalling pathways. Most cancer cells efficiently uptake glucose through the independence of insulin/GLUT4[72] Hyperglycemia stimulates insulin secretion, which results in hyperinsulinemia; this physiological heterogeneity leads to the hyperactivation of IR-A and IGF-1Rs, which induce neoplastic cellular expansion.[51] Metabolically active cells are significantly involved in generating free radicals and other reactive species, which may create mutations in DNA through oxidative damage. Sustained hyperglycemia plays a key role in neoplastic progression by promoting ROS formation, DNA mutation, DNA damage, and dysregulation of oncogenes, tumour suppressors, and DNA repair systems.[73,74] The initiation of cancers can often be traced to mutations in oncogenes and tumour suppressor genes.[75]

Additionally, chronic hyperglycemia increased the non-enzymatic formations of advanced glycation end (AGE) products linked with nucleic acids,[76] proteins,[77] and lipids.[78] The AGEs accumulation in the tissues can lead to DNA damage by coupled with amino groups of DNA bases and promoting inflammation,[79] NFkB secretions,[80] ROS formation,[81] overexpression AGE receptors,[82] which have collectively contributed to carcinogenesis. The cell cycle rate is accelerated by high glucose levels by altering the function of key cell cycle regulatory proteins, resulting in increased cellular proliferation.[83]

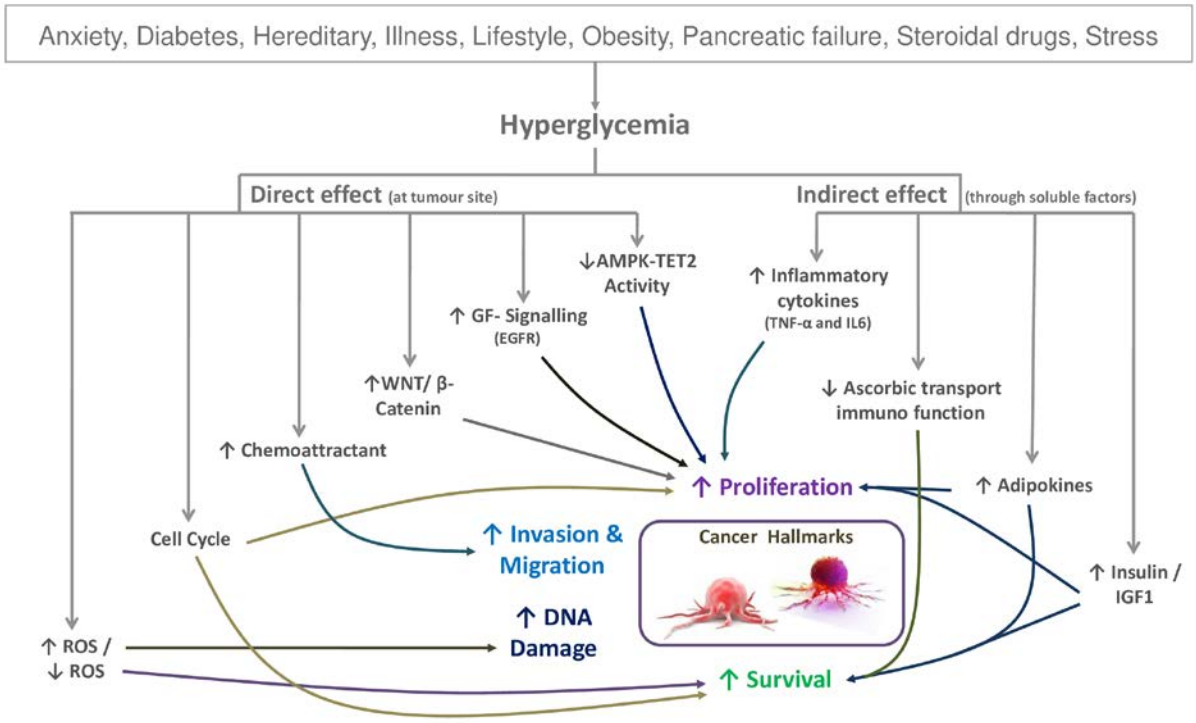


Figure 2: The physiological, genetic, social and lifestyle factors are responsible for the development of hyperglycemia. Hyperglycemia stimulates cancer hallmarks by several direct and indirect cellular mechanisms. Direct effects of hyperglycemia on the tumour site initially increase ROS production and accumulation to increase the mutagenesis rate. After that, it decreases the production of ROS to ensure survival; accelerates the rate cell cycle; elevates the secretion of chemo-attractants such as glial cell line-derived neurotrophic factor (GDNF) for invasion and migration; An over-activates the WNT/β-catenin signalling which promotes proliferation; overexpression of growth factor receptors (EGFR); destabilization of AMPK-TET2 signalling axis, results in dysregulation of 5hmC conversion and tumour-suppressive activity of TET2. The indirect effects of hyperglycemia on cancer cells are mediated through the soluble factors: increased circulatory levels of insulin/IGF1; increased production of inflammatory cytokines TNF-α, IL6, and adipokines; and decreased ascorbic acid transportation in immune cells that minimized immunological surveillance. Both direct and indirect effects of hyperglycemia unite on cancer hallmarks (increased proliferation, invasion, migration, DNA damage, and survival).

Hyperglycemia promotes the growth and survival of DM-coupled cancers by triggering various direct and indirect associated factors that cooperate to promote immunological escape, tumorigenesis, neoplastic progression, and transformation. In addition, hyperglycemia activates the Wnt/β-catenin signalling cascade in neoplastically transformed cells, which induces over-proliferation, promotes survival, and represents one of the direct molecular mechanisms which link hyperglycemia to cancer, *i.e.* gastrointestinal cancers.[84] A recent study has observed that hyperglycemia-mediated inactivation of AMPK results in the destabilization due to proteolysis of TET2 followed by dysregulation 5-hydroxy-methylcytosine (5hmC) conversion and tumour-suppressive function of TET2, which predisposes DM patient to cancer thereby suggesting a link between DM and cancer (Figure 2).[30]

A Novel 'Glucose-AMPK-TET2-5hmC Axis' That Links Hyperglycemia to Cancer

The contrasting impacts of hyperglycemia on the AMPK-TET2 signalling in the functionally distinct tissues and the probability of cancer progression. Wu et al. observed that hyperglycemia-mediated inactivation of AMPK results in proteolysis-induced destabilization of TET2 followed by dysregulation 5hmC conversion and tumour-suppressive function of TET2, which predisposes DM patients to cancer, thereby suggesting a link between DM and cancer.[30] The activated and stabilized form of AMPK has maintained optimum level intracellular ATP by modulating key proteins involved in glucose transport,[85] glycolysis,[86] and tricarboxylic acid cycle,[87] and by inhibiting ATP consuming processes.[88] AMPK has a few upstream regulators but numerous downstream targets, and thus AMPK is a central regulator of metabolism which maintains cellular homeostasis. In energy stress AMP: ATP and ADP: ATP ratio increased, which activated AMPK via promoting phosphorylation at Thr-172 of the α-subunit of AMPK and restore energy balance.[89] The AMPK phosphorylation was carried out by the three kinases such as (Serine-Threonine Kinase 11 or liver kinase B1) LKB1, which are functionally active in association with STRAD and MO25.[90] Calcium/calmodulin-dependent Kinase Kinase 2 (CAMKKβ or CaMKK2),[91] and TGFβ-activated kinase 1 (TAK1).[92] Binding of AMP or ADP to γ subunits that inhibits pThr-172 dephosphorylation mediated by protein phosphatase 2C (PP2C);[93] and protein phosphatase 2A (PP2A).[94] AMPK has played a significant role in epigenetic

regulation via phosphorylation at Ser-99 of TET2, which is involved in the demethylation of CpG Island.[30] AMPK phosphorylates TET2 at Ser-99, which stabilizes it, resulting in the activation of TET2. Due to hyperglycemia, AMPK is in an inactive form, which is inadequate to phosphorylate Ser-99 resulting in destabilization of TET2 that causes reduced transformation of 5mC to 5hmC (Figure 3).[30] The decline of 5hmC residues is considered an epigenetic hallmark of tumorigenesis, which decreases levels of TET2 expression and has an essential function.[95] 5hmC residues are frequently restricted to the promoters and intragenic regions, which leads to reduced gene expression.[30,96] 5hmC residues associated genes, including MCM3, CDC73, EIF-5A, ALDH2, BNIP3, and P2RX5, showed a close relation with cell cycle regulation and cancer-related pathways.[30]

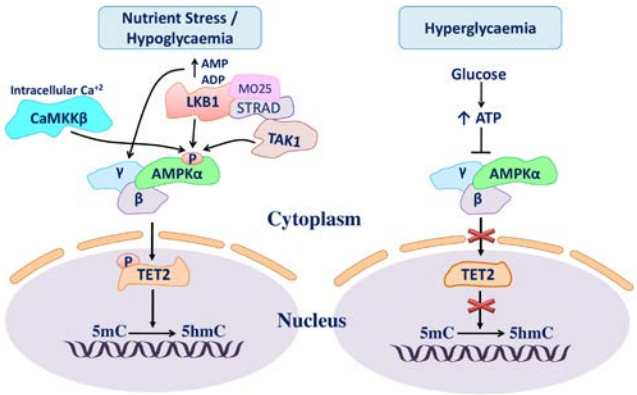


Figure 3: Intracellular glucose level modulates the activity of AMPK, which is a cellular nutrient sensor. The active form of AMPK phosphorylates and stabilized TET converts 5mC to 5hmC for the demethylation of CpG-enriched regions. AMPK is destabilized due to hyperglycemia's high intracellular ATP level; a thereby unstable form of TET2 results in halts the conversion of 5mC to 5hmC and tumour-suppressor activity.

Does hyperglycemia universally impede the AMPK-TET2 axis?

Under hyperglycemic conditions, GLUT4-mediated glucose uptake remains restricted in the skeletal muscles, cardiac muscles, and adipocytes due to the unavailability of insulin or insulin resistance. These insulin-dependent cells (IDCs) have possibly intracellular hypoglycemic milieu resulting in nutrient stress and an increased AMP: ATP ratio, resulting in AMPK activation and, as a result, TET2 stabilization. On the other hand, insulin-independent cells (IICs) uptake blood glucose *via* GLUT 1-3 and by facilitated diffusion. Thus, these cells may exhibit intracellular hyperglycemia resulting in an increased ATP: AMP ratio, which may allosterically inhibit AMPK and obstruct TET2-dependent demethylation of 5mC. Based on this assumption, we argue that the genesis of cancer could be due to the unstable form of the AMPK-TET2 axis under persistent hyperglycemia, and it could be frequently associated with IICs. If this putative mechanism is physiologically operable, it will justify this hypothesis that IICs are more susceptible to cancer progression than IDCs (Figure 4). This hypothesis predicts hyperglycemia may not be the critical factor for AMPK-TET2-mediated neoplastic transformation in the IDCs compared to IICs. Wu and colleagues examined peripheral blood mononuclear cells (PBMCs) from DM patients and various cell lines such as HUVEC, TF-1, A375, A2058, and SK-MEL-5 under normal glucose (1g/L) and high glucose (4.5g/L) concentrations for comparison of 5hmC levels. [30]

The authors observed that PBMCs, HUVEC, and TF-1 have significantly reduced 5hmC expression under high glucose concentrations.[30] These cells belong to IICs and originate from the skin, blood, umbilical cord, and bone marrow tissues. Therefore, IICs under hyperglycemia appear to be predisposed to tumorigenesis.

STRUCTURAL AND FUNCTIONAL INSIGHTS OF AMPK AND TET2

AMPK is a cellular nutrient sensor, highly conserved and ubiquitously expressed in all eukaryotic species, which restores energy homeostasis at the cellular levels.[97] Structurally, AMPK is a heterotrimeric protein complex, which is composed of three subunits, catalytic α-subunit encoded by two isoforms, and regulatory β- and γ-subunit encoded by two and three isoforms, respectively.[98] The tissue-dependent expression pattern of AMPK has varied due to the occurrences of 12 different isoforms in mammals.[99] The *N*-terminus of the α-subunits comprises the Kinase Domain (K.D.), while the C-terminus consists of important regulatory domains, known as the auto-inhibitory domain (AID). This also interacts with β- and γ-subunits.[99] The β-subunits have two conserved domains: a carbohydrate-binding module (CBM) and a C terminus domain interacting with α- and γ-subunits. The γ-subunit is composed of two Bateman domains, each containing two cystathionine β-synthase repeats (CBS), which significantly recognize and bind AMP, ADP, or ATP competitively to regulate AMPK activity (Figure 5A).

Intracellular hypoglycemia activates AMPK and downstream phosphorylation of several proteins, including TET2, which converts 5mC to 5hmC. The structural insights of the TET-family (TET1-3) demonstrated that these are high molecular weight (~180- to 230-kDa) and multidomain proteins (Fig. 5B). The catalytic domain of TET consists of a cysteine-rich segment and double-stranded β helixes (DSBH, also called a jelly-roll motif) with non-conserved low-complexity insert (NCLC) in the C terminus.[100] TET specifically recognizes the 5mC at CpG Island. Fe^{+2} and *N*-oxalylglycine, a 2-oxoglutarate (α-ketoglutarate) analogue, are the preferable substrate of TET2.[100] The cysteine-rich domain wraps around the DSBH core and stabilizes the DNA-DSBH core interaction.[100] Structural investigations decipher that the core catalytic domain selectively interacts with cytosines in a CpG region context but does not bind with adjacent nucleotide bases, showing no hindrance in DNA sequences. DNA methylation and demethylation occur in a cyclic mode with DNA modifying enzymes (Figure 5C). AMPK and TET2 are metabolisms and epigenome regulatory components, respectively. Disrupting the metabolic regulatory system can result in impeding the epigenome regulatory component. Thus, metabolic and epigenetic regulatory proteins link metabolic

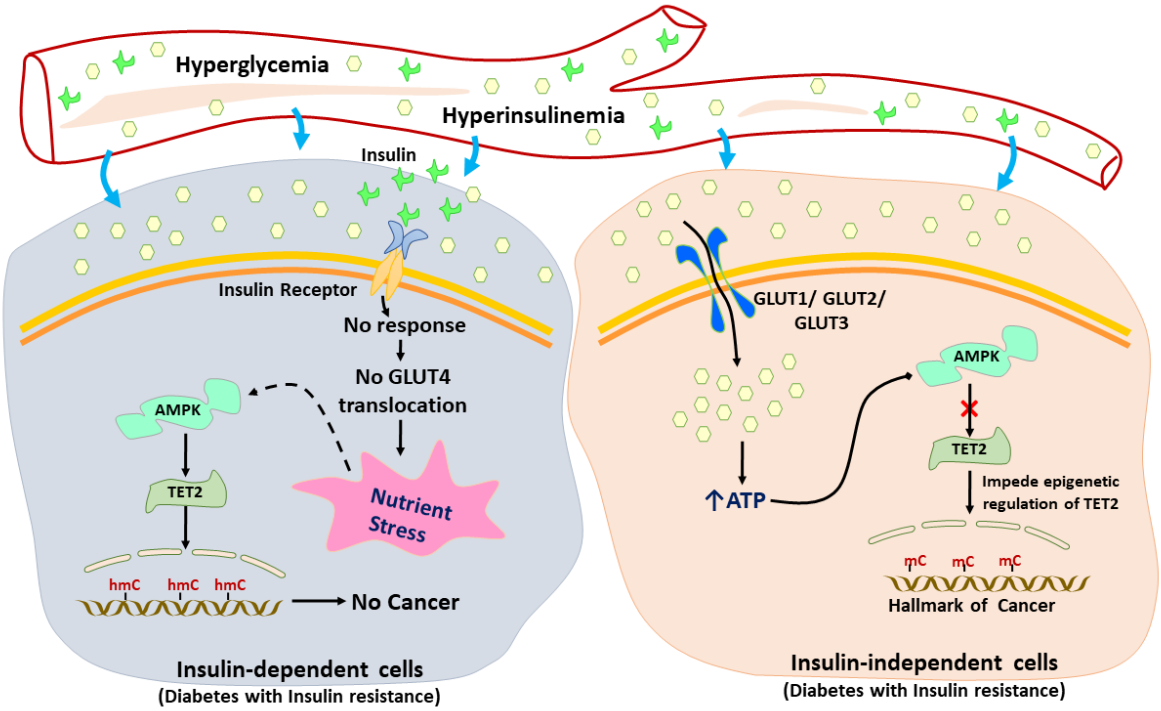


Figure 4: A hypothetical scheme shows the effect of hyperglycemia on the insulin-dependent and insulin-independent cells for the stability of AMPK and TET2 in DM Insulin-dependent cells have suffered from nutrient stress, so they have activated AMPK; subsequently, a stable form of TET2 which converts 5mC into 5hmC. Insulin-independent cells uptake glucose by either GLUT 1-3 or glucose co-transporters. Under hyperglycemia, insulin-independent cells have high intracellular glucose, which alters AMPK stability by the ATP as a negative modulator. An unstable AMPK in insulin-independent cells cannot phosphorylate at Ser-99 of TET2, which results in dysregulation of 5mC and 5hmC levels and the tumour-suppressive role, consequently, the possibility of oncogenesis. (↘ Activation; ↘ Inhibition).

disorders like diabetes to dysregulated genome-born conditions like cancer.

NATURAL ACTIVATORS OF AMPK AND TET2

Hyperglycemia negatively impacts cancer therapy results through drug inactivation, chemo-resistance and influences drug pharmacokinetics.[101] Natural products have evolved by the biological system to serve as a survival function, including growth regulation, metabolic and epigenetic regulation, defence from biotic and abiotic stress, and reproduction. The surrounding ecological conditions of the organism influence the structural and functional diversity of natural products. The structure and function of natural products are the outcomes of a million-year evolution, and it continues. They are biologically more compatible and relevant and have a high hit rate due to structural diversity still synthesized by living organisms for their defence mechanism. Natural products have been usually considered a treasure trove for potent and novel drug designing, and approximately 46% of Food and drug administration (FDA) approved drugs are derived from natural products from 1981 to 2014.[102]

AMPK activators

The AMPK is an evolutionarily conserved energy sensor of cells; it has been activated and stabilized by Metformin, an important drug in treating DM.[103] AMPK has also been activated and stabilized by numerous plants derived natural products, including salicylate and galegine.[104] Several other natural products were traditionally utilized as herbal medicines, which currently have been scientifically explored as AMPK activators, including berberine (*Coptis chinensis*), curcumin (*Curcuma longa*), epigallocatechin gallate (green tea), ginsenoside (*Panax ginseng*), hispidulin (snow lotus), quercetin (many fruits and vegetables), resveratrol (red grapes), and theaflavin (black tea).[105] (Table 1) Many of these natural products are claimed to have anti-diabetic and anti-cancer effects. Berberine inhibits F1 ATP synthase,[106] inhibiting ATP production in mitochondrial. This increases AMP: ATP and ADP: ATP ratios, activating AMPK. Resveratrol is a stilbenoid, a dietary phenolic and phytoalexin biosynthesized by several plants, such as berries and peanuts, in response to plant injury or pathogen attack. Several scientific pieces of research suggest a need for more high-quality evidence proving the substantial impact of resveratrol on lifespan or other diseases.[107] There is no proof of the anti-cancerous effect of resveratrol in humans.[108] Still, in the case of diabetes, *in vivo*, a study supports that resveratrol might improve insulin sensitivity.[109] Some studies documented resveratrol as an activator of AMPK[110] for managing diabetes.[111] Murase *et al.* reported that resveratrol activates AMPK *via* phosphorylation of AMPK α and β subunits in Hepa 1-6 (mouse hepatocyte cell line) and C2C12 (mouse muscle cell line). The experimental results indicated that resveratrol (150 μM) activated 538 % of

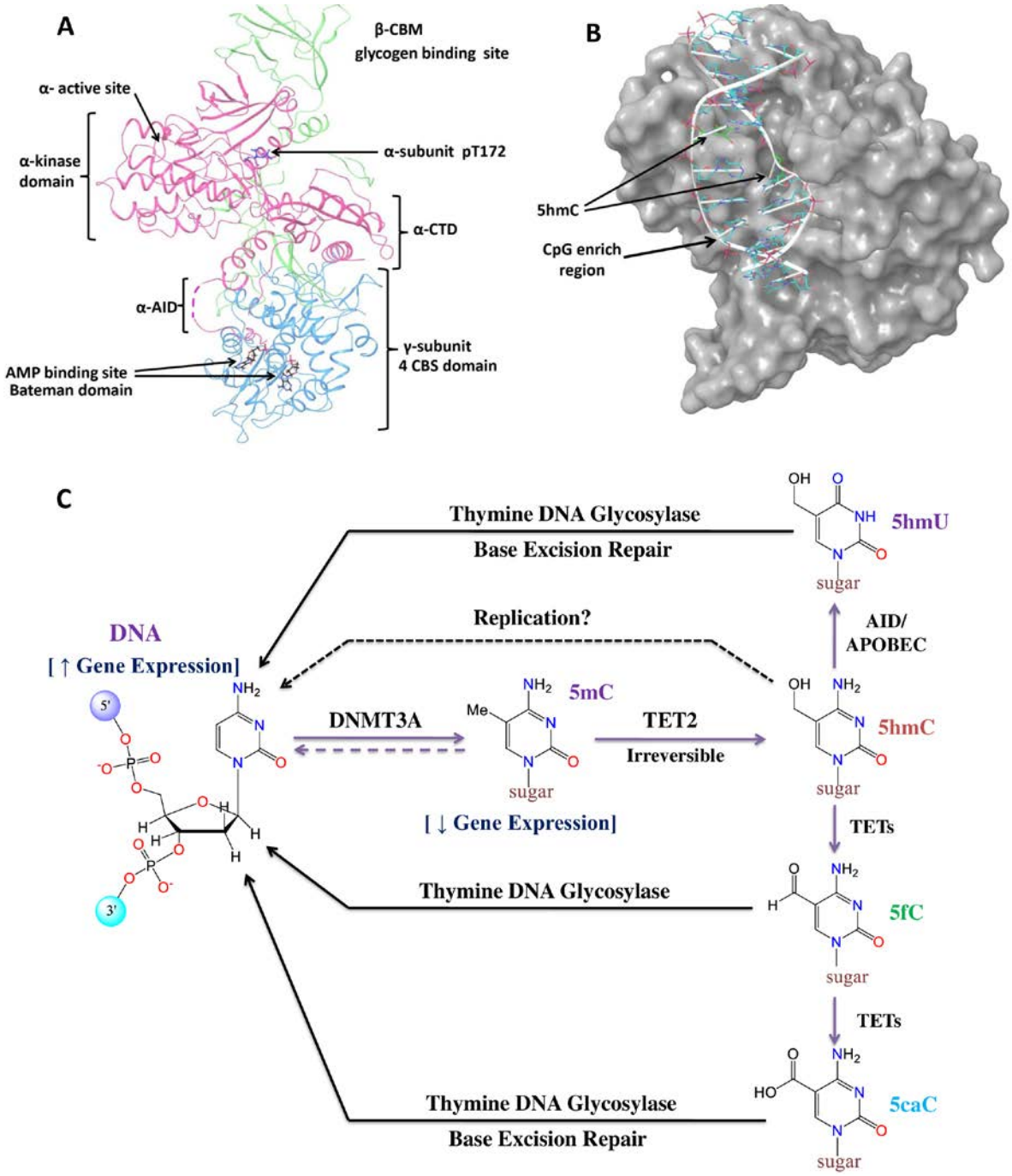


Figure 5: A) The ribbon structural representation of AMPK (PDB entry: 6C9F), with two AMP molecules bound at γ-subunit. AMPK consist of the α subunit shown in pink, which phosphorylated on Thr172, a catalytically active kinase domain, a carboxy-terminal domain (CTD), and an autoinhibitory domain (AID); the β-subunit has carbohydrate-binding site (CBS) domains, shown in green, and the γ-subunit shown in blue, it has two Bateman domain, and each one has two cystathionine β-synthase repeats (CBS), that stand for allosteric modulators binding site, such as AMP, ADP, ATP. **B**) The virtual representation of the solid surface structure of the human TET2 catalytic domain associated with GpC enrich DNA duplex shown in the white strand with blue nucleotide residues (PDB entry: 5DEU). 5hmC residue in the DNA demonstrated in green colour. AMPK and TET2 structure had drawn and edited using the Schrödinger suite. **C**) The diagrammatic representation of DNA methylation/demethylation cycle by a DNA methyltransferase (DNMTs)/TETs/thymine-DNA-glycosylase (TDG)/base excision repair (BER). Cytosine residues in the CpG Island can be methylated by the DNMT1 or DNMT3A/DNMT3B to transform into 5mC, and SAM can donate the methyl group. The TETs enzymes can demethylation of 5mC residue through the 5hmC, 5fC, and 5caC residue. Then both 5fC and 5caC are recognized by TDG results of excised oxidized cytosine residue. The excision of modifying cytosine that produces an abasic site restored by the BER mechanism results in the generation of the unmodified cytosine residue. Besides that, 5hmC can be converted into 5hmU by the action of activation-induced cytidine deaminase (AID)/apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) that further transformed into unmodified cytosine residue by the TGD/BER pathway.

AMPK-α and 168 % of AMPK-β in Hepa 1-6 compared to control. In contrast, 848 % of AMPK-α and 425 % of AMPK-β subunits are activated in C2C12 cells.[112] Obovatol is a biphenolic compound isolated from the bark of *Magnolia obovata* and is therapeutically known for anti-inflammatory, nootropic, and anti-anxiety.[113] The *in vitro* study by Huh et al. proved that obovatol activates AMPK in the L6 cell line dose-dependent manner. In addition, the animal study of obovatol to db/db mice (oral administration for four weeks) reduced the blood glucose level.[114] Nootkatone is responsible for grapefruit's distinctive flavour and taste (*Citrus paradisi*). Although Murase et al. investigated nootkatone as an activator of AMPK, especially in muscle cells, to promote carbohydrate and lipid metabolism.[115] *In vitro* screening indicated that nootkatone at (150 µM) concentration activates AMPKα (1077%) and AMPKβ (358%) more than the control of C2C12 muscle cells. Nectandrin B is a type of 2,5-bis-aryl-3,4-dimethyltetrahydrofuran lignan isolated from *Myristica fragrans*, which acts as a potent activator of AMPK and ACC.[116] Glabridin is a dietetic isoflavone and an important active component in *Glycyrrhiza glabra*. Lee *et al.* revealed its therapeutic role in obesity-related metabolic disorders *via* activating AMPK.[117] Glabridin activates AMPK by 2-fold at 30 µM concentration in the C2C12 myoblast cell line and is claimed as a potential therapeutical agent for diabetes and related metabolic syndromes.[118] Damulin A and B are dammarane-type open-chain glycosides isolated from *Gynostemma pentaphyllum*, a powerful activator of AMPK evaluated using i*n vitro* studies. Both elevate the activity of AMPK in a concentration-dependent manner in L6 myotube cells.[114] Besides that, several natural compounds are evaluated as AMPK activators, some of which are listed in Table 1.

TET2 activators

Therapeutic exploration of TET2 remains limited, with only a few ligands currently being investigated as potential activators. These ligands are structural analogues of Vitamin C and α-ketoglutaric acid, as discussed by Peng et al.[119] To expand the repertoire of TET2 activators, it is worth considering natural analogues of vitamin C (Fig. 6) and α-ketoglutaric acid (α-KG) (Fig. 7). These natural compounds serve as co-substrates for TET2 during oxygenation processes.[120] Since the loss of TET2 function is linked to developing myeloid malignancies and other cancers, identifying small molecules that can act as agonists for TET proteins may provide valuable tools for suppressing cancer progression.

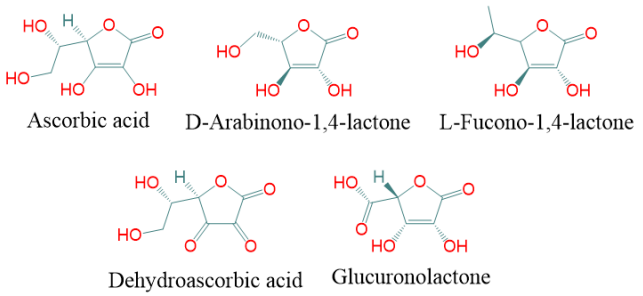
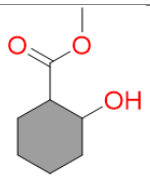
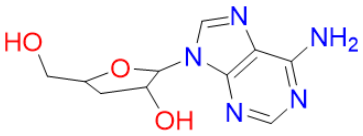
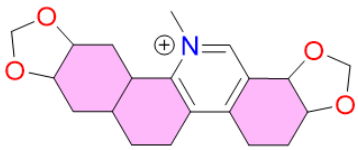
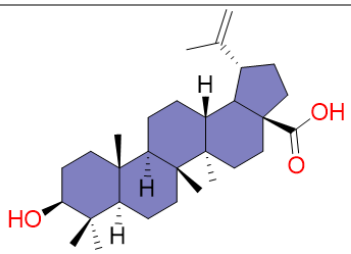
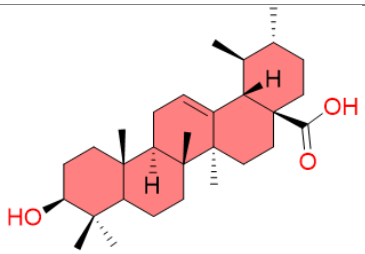
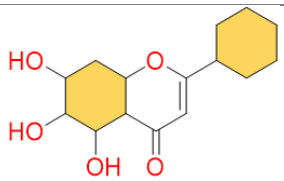
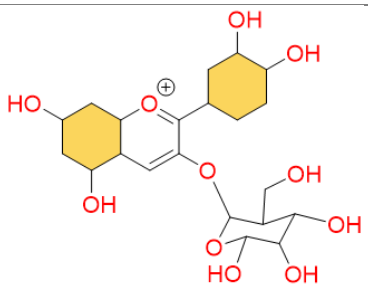
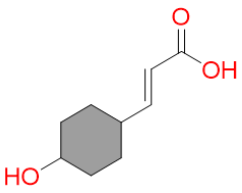
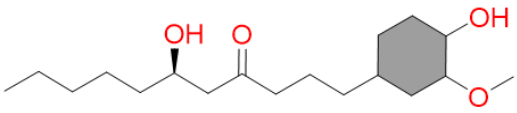
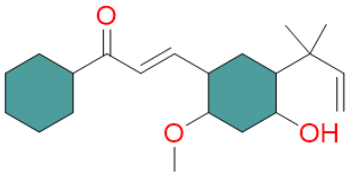
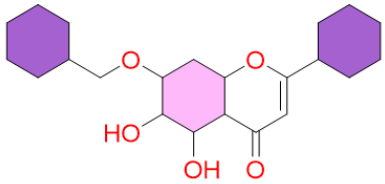
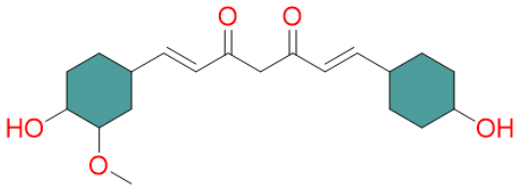
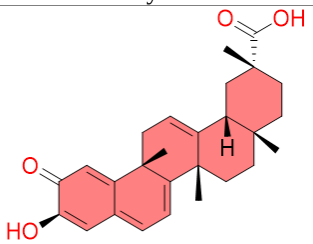
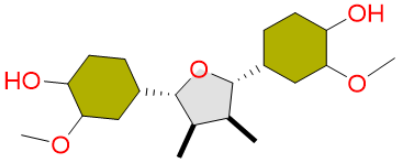
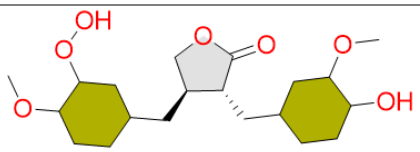
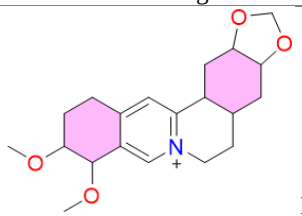
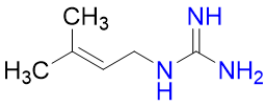
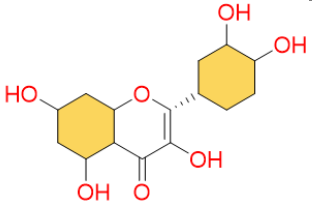


Figure 6: Natural analogues of ascorbic acid

Table 1: Natural products evaluated as direct or indirect AMPK activators.

Compound	Bioactivity	Reference
	Direct activators	
 Salicylate	Interact with β1 subunit and allosterically inhibit Thr172 dephosphorylation. Elevates fatty acid oxidation in HEK-293 Primary mice hepatocytes at 3 µM. Increases fat utilization in mice at 250 mg/kg.	121
 Cordycepin	Interact with γ1 subunit to activate AMPK at 100 Mm in human cells.	122
Sanguinarine	Interact with α1β1γ1 α1β2γ1 subunits and allosterically activates AMPK.	123
 Sanguinarine	Upregulate the activity of AMPK and induce autophagy in breast cancer cells.	124

Indirect activators		
 Betulinic acid	Sow down lipid accumulation and lipogenesis in HepG2 at 40 µM. Restrain intracellular lipid accumulation in high fat-fed ICR mice at 5 mg/kg.	125
 Ursolic acid	Inhibits adipocyte differentiation at 3T3l-1 cells at 20 µM.	126
 Baicalein	Decreases the serum lipid in high-fat diet mice at 400 mg/kg.	127
 Cyanidin-3-*O*-*β*- glucoside	Promotes fatty acid β-oxidation in HepG2 cells at 1-5 µM.	128
 *ρ*-Coumaric acid	Promotes oxidation and glucose uptake in the L6 cell line at 12.5 µM.	129
 Gingerol	Promotes glucose uptake in the L6 cell line at 150 µM.	130
 Licochalcone A	Inhibits triglyceride accumulation in HepG2 cells at 5-10 µM. Inhibits triglyceride accumulation in the liver of High fat-fed ICR mice at 10 mg/kg.	130

 (-)-5,7-Dihydroxy-3-(4-hydroxybenzyl)-4-chromanone	Phosphorylation of AMPK in IAR-20 at 10 µM.	132
 Demethoxycurcumin	Inhibits human triple-negative breast cancer cell proliferation at 5 µM.	133
 Celastrol	Induce apoptosis in MCF-7 cells at 3 µM.	134
 Nectandrin B	Inhibit vascular smooth muscles cells proliferation at 1-3 µM.	135
 Arctigenin	Inhibits Complex I of ETC.	136
 Berberine	Inhibits Complex I of ETC.	106
 Galegine	Inhibits Complex I of ETC.	136
 Quercetin	Inhibits Complex I of ETC.	138

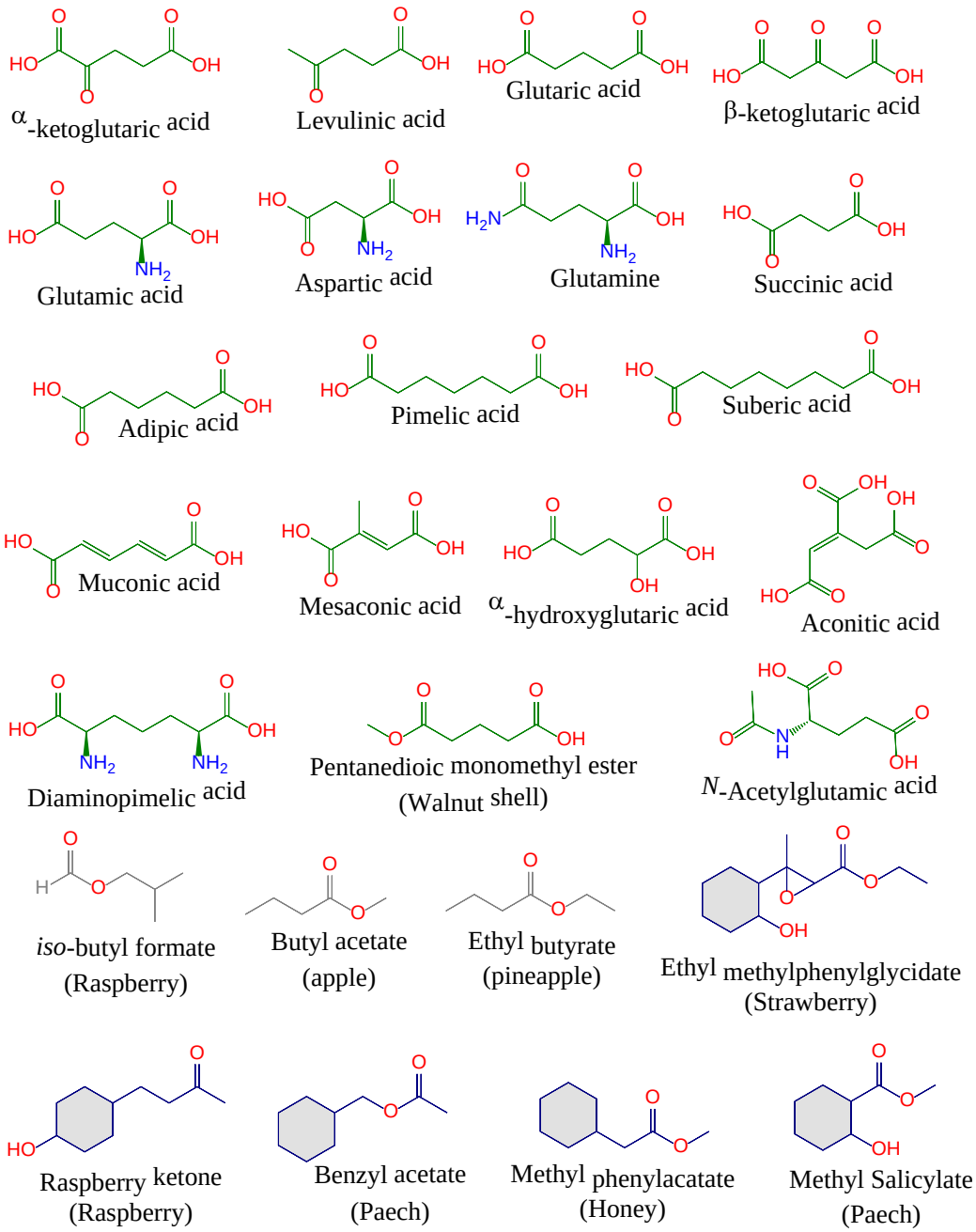


Figure 7: Natural analogues of α-ketoglutarate.

CONCLUSION AND FUTURE PERSPECTIVE

Hyperglycemia links diabetes to cancer *via* the glucose-AMPK-TET2-5hmC axis to regulate the expression of genes involved in cell cycle regulation and cancer-related pathways. Prolonged hyperglycemia associated with hyperinsulinemia may strongly support tumorigenesis through the overactivation of Akt and ERK1/2, resulting in AMPK destabilization and subsequently suppressing the activity of TET2. Hyperglycemia and hyperinsulinemia may contribute to destabilizing the AMPK-TET 2 axis. Along with glucose (hyperglycemia), some other molecules, including α-KG, oxygen, and vitamin C, have directly or indirectly modulated TET2 stability. TET2 utilized oxygen and α-KG as co-substrates for the oxygenation reactions along with vitamin C. Higher intracellular glucose results in a high level of ATP and α-KG, ATP is a negative allosteric modulator of AMPK, while α-KG has co-substrates for TET2.

If we alter the biosynthesis of AMPK and TET2 allosteric modulators through the inhibition of the TCA cycle, ETC, or other cellular pathways, it may be facilitated to stabilize AMPK and TET2. AMPK is primarily considered a therapeutic target for treating metabolic diseases, while TET2 is for oncogenic diseases. Under hyperglycemia, the alteration in the AMPK-TET2 signalling axis is associated with tumorigenesis, which may engage individually or couple with another cellular pathway.

In many cancers, the kinase activity of LKB1 is lost, resulting in unstable AMPK. In this condition, it is possible to activate AMPK by treating it with some natural (berberine, salicylate, resveratrol) agents that activate AMPK. Likewise, for AMPK activators, one of the future's key challenges is finding some molecules that activate TET2 in either AMPK-dependent or independent manner. To stabilize TET2 tumour-suppressive activity by the small molecule, activators are essential for epigenome regulation. This connecting link between metabolism and epigenome may decode some unrevealed facts, which can contribute to identifying novel molecular markers or targets for treating DM and cancers.

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