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Energy sensing pathways: bridging type 2 diabetes and colorectal cancer?

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Abstract

The recently rapid increase of obesity and type 2 diabetes mellitus has caused great burden to our society. A positive association between type 2 diabetes and risk of colorectal cancer has been reported by increasing epidemiological studies. The molecular mechanism of this connection remains elusive. However, type 2 diabetes may result in abnormal carbohydrate and lipid metabolism, high levels of circulating insulin, insulin growth factor-1, and adipocytokines, as well as chronic inflammation. All these factors could lead to the alteration of energy sensing pathways such as the AMP activated kinase (PRKA), mechanistic (mammalian) target of rapamycin (mTOR), SIRT1, and autophagy signaling pathways. The resulted impaired SIRT1 and autophagy signaling pathway could increase the risk of gene mutation and cancer genesis by decreasing genetic stability and DNA mismatch repair. The dysregulated mTOR and PRKA pathway could remodel cell metabolism during the growth and metastasis of cancer in order for the cancer cell to survive the unfavorable microenvironment such as hypoxia and low blood supply. Moreover, these pathways may coupling metabolic and epigenetic alterations that is central to oncogenic transformation. Further researches including molecular pathologic epidemiologic studies are warranted to better address the precise links between these two important diseases.

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Use of Standardized Official Symbols:

We use HUGO (Human Genome Organisation)-approved official symbols for genes and gene products, including PRKA; mTOR; PIK3CA; all of which are described at www.genenames.org.

Keywords

PRKA; Biomarker; Carcinoma; Colon; Energy balance; Molecular pathologic epidemiology

1. Preface

Type 2 diabetes mellitus (hereafter, referred to as “type 2 diabetes”) and colorectal cancer are both common diseases that cause great burden to our society. Moreover, convincing evidence indicates that type 2 diabetes is associated with an elevated risk for colorectal cancer [1, 2]. Epidemiological studies have also proved that in colorectal cancer patients, diabetic patients have a worse prognosis and higher mortality than those without diabetes. Type 2 diabetes and colorectal cancer also share many risk factors such as aging, obesity, sedentary life style, diet, and smoking. Therefore, studying the underlying mechanisms would provide insights into the prevention and treatment strategy of cancer in diabetic patients.

2. Epidemiological association between type 2 diabetes and colorectal cancer

The International Diabetes Federation (IDF) reports that the number of diabetic patients will increase from 415 million in 2015 to 642 million by 2040 [3]; while the World Health Organization (WHO) -projected global incidence of cancer will increase from 14 million in 2012 to 22 million in 2032 [4]. In parallel, a strong association between colorectal cancer and diabetes has been supported by increasing epidemiological studies.

2.1 Type 2 diabetes increases the risk of colorectal cancer

Compared to the general population, type 2 diabetes increases the risk of colorectal cancer by up to three times [5, 6]. In the meta-analysis by Sun and Yu [7], which included 11 case–control and 28 cohort studies, diabetes is associated with a 29% increase of colorectal cancer [95% confidence index (CI): 1.23–1.35]. This effects persist even after adjustment for body mass index (BMI) and physical activity in the Nurses’ Health Study and Cancer Prevention Study [relative risk (RR) = 1.49 and 1.24, respectively] [8]. Even in young patients at 40–49 years, a dramatic increase of colorectal adenomas in diabetic patients has been reported [odds ratio (OR) = 3.1; 95% CI: 1.5–6.4]: these patients have similar incidence of adenomas as those who are 50–59 years old without diabetes [9] . Recently, the link between DM and colorectal cancer has been recognized in American Diabetes Association (ADA) guideline which suggests that patients with diabetes should receive age- and sex-appropriate cancer screenings and should also reduce their cancer risk factors which are modifiable such as smoking, obesity, and physical inactivity [10].

2.2 Type 2 diabetes aggravates the prognosis of colorectal cancer

Type 2 diabetes also increases the cancer specific mortality and overall mortality of colorectal cancer [11, 12]. In a meta-analysis including 26 observational studies in patients with colorectal cancer [13] it is found that diabetic patients have a 17% increased risk of all-

cause mortality and a 12% increased risk of cancer-specific mortality, compared to those without diabetes. The disease-free survival and overall survival of the CRC patients were also associated with blood glucose levels in a multivariate analysis [14]. Results from one pathologic analysis has found that patients with diabetes have deeper tumor invasion, greater lymphovascular invasion, and higher TNM staging compared to those without diabetes [15]. Finally, one genetic research has found that some genes, which are associated with metabolic syndrome such as *APOA2, APOC1, APOD* and *ABCA1*, predict disease-free survival in stage II colorectal cancer patients [16]. Therefore, genetic factors as well as environmental factors contribute to the poorer prognosis of colorectal cancer in diabetic patients compared to the general population.

3. Energy sensing pathways and colorectal cancer

The molecular mechanism by which type 2 diabetes increases the incidence or aggravates the prognosis of colorectal cancer is not clear. However, nutrient-sensing pathways which coupling energy metabolism to signals of cell growth and survival are often dysregulated in diabetes, and are important contributors to cancers for diabetic patients.

3.1 PRKA (AMPK) signaling pathway

PRKA is the primary energy sensor in the cell, and actively participates in the control of cell metabolism and several cellular processes including proliferation and apoptosis [17, 18]. In mammals, PRKA is activated by increased AMP : ATP or ADP : ATP ratios. Any cellular process that either decreases ATP levels or increases AMP concentrations (such as fasting or exercise) can activate PRKA, whereas high nutrition (such as in obesity or diabetes) can inactivate PRKA (Figure 1).

PRKA activation promotes a metabolic and proliferative phenotype unfavorable to cancer cell growth, and as such is thought to negatively impact tumorigenesis [19]. There is a close association between PRKA and colorectal cancer. Germ-line mutations in STK11 (PRKA activator) are linked to Peutz-Jegher syndrome characterized by predisposition to gastrointestinal polyps and malignant tumors [20, 21], where colorectal cancer is the most common cancer [11]. In another study, it is found that low phosphorylated PRKA levels are associated with worse overall survival in a cohort of metastatic colorectal cancer patients treated with chemotherapy plus bevacizumab [22].

3.2 mTOR signaling pathway

mTOR is another important energy sensor in cell which may function dependently and also independently on PRKA. mTOR has two distinct multimolecular complexes differ in composition, substrate specificity, and mechanism of growth regulation. mTORC1 is a nutrient and energy sensor responding to changes in growth factor, amino acid and nutrient levels. Growth factors (such as insulin and IGF-1) are strong activators of mTORC1 acting through AKT signaling. AKT phosphorylates TSC2 and dissociates it from TSC1, which then activate mTORC1 [23, 24]. High nutrition will lead to mTORC1 activation because of the loss of PRKA inhibition [25]. Withdrawal of glucose, amino acids, or oxygen leads to rapid suppression of mTORC1 activity through PRKA dependent mechanism. Amino acids,

particularly leucine and arginine, also activate mTORC1 through unknown mechanism [26]. Figure 2.

Strong evidences supporting the tumorigenesis role of mTOR come from the positive associations between familial cancer syndromes and mutations of mTOR regulators such as TSC1-TSC2, STK11 and PTEN [27]. Moreover, sporadic mutation or deregulation of mTOR upstream regulators (such as PI3K, AKT and PTEN) and downstream effectors (such as EIF4EBP1) are frequently reported to be associated with human cancer [28, 29]. High mTORC level, rictor expression and mTORC downstream effectors are also associated with poor prognosis of colorectal cancer patients [30, 31].

3.3 SIRT1 signaling pathway

SIRT1 is another important energy sensing protein which couples the cellular metabolic status to chromatin structure and regulation of gene expression by deacetylating histones, transcription factors, and transcription co-factors, and is associated with numerous cellular signaling pathways that include senescence [32, 33], apoptosis [34], DNA damage repair [35], and autophagy [36]. Upon glucose starvation or other metabolic changes associated with caloric restriction, elevation of $NAD^+/NADP^+$ ratio activates SIRT1, which then acts on its downstream targets including: (1) TP53. TP53 is one of the best-defined target proteins of the SIRT1 deacetylase. SIRT1 deacetylates and inactivates TP53, thereby exerting an antiapoptotic effect [37]. (2) ATM and histone deacetylase 1 (HDAC1). SIRT1 collaborates with ATM and HDAC1 to maintain genomic stability [38]. (3) Liver X receptor proteins (LXRP). SIRT1 can also deacetylate and activate LXRP, thereby facilitating cholesterol efflux from the cell [39]. (4) Peroxisome proliferator-activated receptor γ coactivator 1α (PPARGC1A, also PGC-1α). PPARGC1A is another important modulator of metabolic pathways. SIRT1-dependent deacetylation of PPARGC1A enhances its ability to cooperate with transcription factors such as PPARG (peroxisome proliferator-activated receptor γ) which in turn induces expression of genes involved in fatty acid oxidation and gluconeogenesis [40, 41]. (5) HIF1A. SIRT1 deacetylates and inactivates HIF1A, thus inhibits the expression of genes targeted by HIF1A in certain tumors [42]. (6) NFKB1. SIRT1 inactivation leads to G1-phase arrest via NFKB1/CCND1 (cyclin D1) signaling [43].

It is proved that heterozygous deletion of SIRT1 accelerates tumor formation in TP53 $^{+/-}$knock-out mice [44], and overexpression of the protein reduces intestinal tumor formation in *adenomatous polyposis coli (*Apc) $^{min/+}$ mice [45]. In colorectal cancer patients, SIRT1 shows lower nuclear expression in tumor samples than in normal tissue samples; Patients with high nuclear expression of SIRT1 showed better survival and a lower chance of tumor recurrence [46]. In patients with colorectal adenocarcinoma, SIRT1 overexpression is observed in approximately 25% of stage I/II/III tumors but rarely in advanced stage IV tumors and approximately 30% of carcinomas shows lower SIRT1 expression than normal tissues [47]. Moreover, SIRT1 protein expression is gradually decreased during the normal-adenoma-adenocarcinoma-metastasis sequence in colorectal cancers [48]. Figure 3.

However, an increase in SIRT1 expression has also been reported in many types of cancer including colorectal cancer [49], and high level of SIRT1 serves as an independent marker of poor prognosis for cancer patients [50]. Recently, it is found that intestine-specific SIRT1

heterozygous mice have enhanced intestinal tumor formation, whereas intestine-specific SIRT1 homozygous knockout mice have reduced development of colon cancer; Furthermore, SIRT1 reduction, but not deletion, is associated with human colorectal tumors, and colorectal cancer patients with low protein expression of SIRT1 have a poor prognosis [51]. Therefore, SIRT1 may function as a double-edged sword in colorectal cancer, but the consensus is that SIRT1 is a DNA stability guardian and possesses anticancer effects during the initiation of cancer.

3.4 Autophagy-related pathway

Autophagy is a cell process whereby proteins and organelles are recycled via lysosomal degradation to maintain cellular homoeostasis; however, autophagy can also be induced in response to various stresses including nutrient and oxygen deprivation [52]. Therefore, autophagy functions as another type of energy sensor. A major regulator of autophagy is mTOR pathway. The down regulation of mTOR under cellular stress triggers autophagy [53], and mTOR inhibitors, including rapamycin, have also been shown to induce autophagy [54]. The activation of PRKA will also repress mTOR and initiate autophagy [55]. A recent study found that PRKA can directly phosphorylate ULK1, which is required for mitochondrial homeostasis and cell survival during starvation [56]. It is also suggested that amino acid inhibit autophagy by inactivating RAF1/MEK/ERK1/2 pathway [57].

Autophagy has been found to inhibit inflammation [58], mitochondrial dysfunction [59] and genome instability [60] which are known promoters of cancer initiation (Figure 4). Autophagy is important in the switch from normal to malignant colorectal cells. UVRAG is a key autophagy effector and a guardian of chromosomal stability; one recent study discovered that a frame shift mutation leading to shortened form of UVRAG protein, which counteracts most of the tumor-suppressor functions of wild-type UVRAG and promotes tumorigenesis, epithelial-to-mesenchymal transition, and metastasis of colorectal cancer [61, 62]. Other mutations of autophagy related genes (ATG5, ATG2B) were also reported to be associated with colorectal cancer [63, 64]. Besides, BECN1 (Beclin 1) protein expression is found negatively related to liver and distant metastasis of colorectal cancer, and also positively associated with good prognosis in patients with colorectal cancer [65, 66]. Figure 4.

However, autophagy has paradoxical and complex functions in cancer development. Increased autophagy was also found correlated with poor prognosis in colorectal cancer. The consensus is that autophagy possesses an anticancer effect at least in the initiation of tumors. At this stage, autophagy promotion may help preventing cancer.

4. Roles of energy sensing pathways in colorectal cancer in type 2 diabetes

As were discussed above, energy sensing pathways play important roles in coupling energy metabolism and DNA stability, and dysfunction of these pathways are closely associated with colorectal cancer. In type 2 diabetes, high level of glucose, FFA, insulin and IGF-1 will inactivate PRKA pathway which then lead to the activation of mTOR pathway and the inhibition of autophagy pathway both in colorectal epithelial tissues and in pancreatic tissues [67–75]. However, abnormal intestinal bacteria in type 2 diabetes may also inhibit PRKA

activity through the modulation of metabolic products such as butyrate [76]. Additionally, high level of pro-inflammatory cytokines such as tumor necrosis factor-α and leptin increase mTORC1, whereas low level of adiponectin decreases mTOR level; Adiponectin also decreases the proliferation of intestinal epithelial cells in rats fed with high fat diet [77, 78]. Moreover, in type 2 diabetes, activated IκB kinase β (IKBKB) caused by hyperglycemia increases the activation of mTOR by phosphorylating TSC1 or interacting with racor [79, 80]. Besides, increased level of NAD+ because of high glucose or lipids will inhibit SIRT1 pathway which also contributes to the activation of mTORC pathway and the inhibition of autophagy pathway [81].

All of these dysregulated pathways may then increase the risk of carcinogenesis by decreasing genetic stability and DNA mismatch repair, or remodeling cell metabolism which is hepful for cancer cell to survive the unfavorable microenvironment such as hypoxia and low blood supply, or promoting protein synthesis, nucleotide synthesis and lipids synthesis which will favor the rapid proliferation of cancer cell (Figure 5).

4.1 Effects on reprogramming metabolic pathways to boost nutrient needs for cancer progress

PRKA inhibits cancer cell progression by down-regulating the metabolic pathways that support uncontrolled proliferation of cancer cells. The Warburg effect is a key hallmark of cancer, whereas PRKA opposes Warburg effects by suppressing anabolic signals and promoting signals of oxidative phosphorylation [82, 83]. PRKA inhibition promotes a metabolic shift toward the Warburg effect in both non-transformed and malignant cells, indicating that this enzyme is a negative regulator of glycolysis and suppressor of tumor development through regulation of metabolic pathways that support uncontrolled proliferation. Moreover, mTORC1 promotes angiogenesis by activating hypoxia-inducible factor 1α (HIF1A, also HIF1α) to promote angiogenesis and glycolysis to sustain tumor growth and infiltration [84].

4.2 Effects on macromolecules synthesis to support rapid cancer cell proliferation

It is found that PRKA decreases the *de novo* synthesis of fatty acids and cholesterol through directly phosphorylating and inhibiting acetyl CoA carboxylase (ACACA, also ACC) and sterol regulatory element binding transcription factor 1 (SREBF-1, also SREBP-1) [85], which promotes cancer growth [86]. The decreased level of PRKA in type 2 diabetes may therefore lose its inhibition on protein synthesis, fatty acid and cholesterol synthesis and then promote cancer cell growth [87].

Inhibited PRKA could also promote the growth of cancer cells by activating autophagy through unc-51 like autophagy activating kinase 1 (ULK1) [88]. Recently, researchers have found that TRB3, which is closely associated with diabetes related cancer, interacts with autophagic receptor SQSTM1 (p62) and hinders SQSTM1 to bind to LC3 and ubiquitinated substrates, and therefore produces potent antitumour efficacies against tumor growth and metastasis [89].

Activated mTORC1 will directly phosphorylates the translational regulators eukaryotic translation initiation factor 4E (EIF4E) binding protein 1 (EIF4EBP1) and RPS6 kinase 1

(RPS6KB1, also S6K1), which, in turn, promote protein synthesis [90]. mTORC1 also promotes lipid biogenesis to sustain the rapid proliferation of cancer cells through SREBF1, SREBF2 and fatty acid synthase (FASN) [91]. In diet induced obesity/prediabetic mice, mTOR inhibitor rapamycin significantly reduced pancreatic tumor growth through inhibiting mTOR-regulated growth and survival signaling [92].

4.3 Effects on DNA stability and cancer initiation

Increasing evidences have also proved that PRKA may function as a house-keeper of DNA stability and play roles in DNA damage response pathway. It is found that in cancer cells, PRKA is rapidly phosphorylated and activated in response to radiation in order to survive the cancer [93, 94]; PRKA also functions as downstream of ATM which is a key mediator of the DNA damage response [95]. It is found that AMPKα1 deletion down-regulates cyclin-dependent kinase inhibitor p21 which play important roles in decreasing DNA double-strand breaks (DSB) [96]. Recently, it is found that in renal proximal tubular mouse cells exposed to high glucose as well as in kidney of db/db mice, activation PRKA by AICAR increases 8-oxoG-DNA glycosylase (OGG1) proteins and reduces oxidative DNA damage [97].

Several studies in mouse support the contention that SIRT1 improves genetic stability and suppresses tumor growth [98, 99]. Cockayne syndrome (CS) is an accelerated aging disorder characterized by progressive neurodegeneration caused by mutations in genes encoding the DNA repair proteins CS group A or B (CSA or CSB). Recent study has found that NAD(+) supplementation can rescue CS-associated phenotypes by activating SIRT1 [100]. In another study, it is proved that cancer cell survival following DNA damage-mediated premature senescence is regulated by mammalian target of rapamycin (mTOR)-dependent Inhibition of sirtuin 1; restored SIRT1 deacetylase activity can sensitize prematurely senescent cancer cells for apoptosis [101].

5 The anti-cancer effects of hypoglycemic agents depend on energy sensing pathways

Metformin has apparent role in decreasing colorectal cancer risk in type 2 diabetes [102, 103]. Moreover, in a meta-analysis it is found that metformin therapy reduce the risk of all cause of death by 44% and the risk of cancer specific death by 34% in colorectal cancer patients compared to those in non-users [104]. In another study, it is showed that the administration of low-dose metformin for 1 year to patients without diabetes was safe. Low-dose metformin reduced the prevalence and number of metachronous adenomas or polyps after polypectomy [105]. It is proved recently that metformin lowers blood glucose levels by inhibiting hepatic glucose production through intestinal PRKA but not hepatic PRKA dependent pathway [106]. In another study it is found that administration of metformin to P. obesus with insulin resistance and type 2 diabetes led to an up-regulation of intestinal PRKA signaling pathway and a reduction in ACC activity as well as improved blood lipids [70]. These data suggest that PRKA fulfills key functions in metabolic processes in the small intestine. It is also found that metformin suppresses colonic epithelial proliferation via the activation of PRKA [107]. Yang et al. have found that reduced cancer risk associated with metformin use is most evident in patients with T2DM who have low levels of HDL

cholesterol [108]. Since HDL can also activate PRKA [109], therefore their results strongly supports the hypothesis that dysregulation of the PRKA pathway is a key feature linking T2DM and cancer.

Resveratrol, a phytoalexin present in few plant species, has demonstrated beneficial antidiabetic effects in animals and humans [110–112]. The beneficial effects of resveratrol occurred via mechanisms such as anti-inflammation, antioxidation, antihyperglycaemia, etc. The molecular targets of resveratrol include SIRT1, AMPK and autophagy [113–115]. It is found that resveratrol suppressed proliferation and invasion of two different human colorectal cancer cells in a dose-dependent manner, and interestingly, this was accompanied with a significant decrease in Ki-67 expression in SIRT1 dependent manner [116].

Thiazolidinediones (TZDs) is another important hypoglycemic agents which possess anti-cancer effects. One study has found that compared with other hypoglycemic agents, TZDs decreased cancer risk (including colorectal cancer) to 40%–50% in type 2 diabetic patients and this effect was dose-dependent [117]. In a meta-analysis, it is also found that TZDs is associated with decreased risk of colorectal cancer [118]. The anti-cancer effects of TZDs appear mainly to be independent of their PPARγ agonist activity but the molecular mechanisms involved in the anticancer action are not yet well understood. However, Wei et al. have declared that the anti-cancer effects of TZDs may be explained by its energy restriction effects including the transient induction of SIRT1 and the activation of AMPK [119]. Because of this, TZDs is considered as a new energy restriction-mimetic agent similar to resveratrol and 2-Deoxy-D-glucose which are also used as anti-cancer agents.

6. Prospects

In the future, it will be increasingly important to facilitate a seamless synergism between basic science, and clinical and population-based research. Ample evidence suggests that colorectal cancer represents a heterogenous group of neoplasms with differing sets of tumor molecular alterations [120–124]. Towards achievement of that goal, further studies based on molecular pathological epidemiology (MPE) are needed for us to uncover the underlying mechanism of the link between type 2 diabetes and colorectal cancer in large populations, and to strategize preventive measures of colorectal cancer incidence and mortality [125, 126]. The concept of MPE has gained considerable recognitions in the recent literature [127–134]. The MPE paradigm has been topics in international meetings [135–142]. In 2008, we have found that the adverse prognostic effect of obesity is present in patients with FASN-positive colon cancers, but not in patients with FASN-negative colon cancers [143]. Our subsequent investigations have found that a number of other tumor molecular changes interact with prediagnosis BMI to modify tumor aggressiveness [144–146]. Therefore, we have opened a new direction of MPE research to investigate interactive effects of dietary or lifestyle exposures and tumoral molecular features on tumor behavior (prognosis or clinical outcome), so that one can attribute the effects of dietary or lifestyle variables to a specific molecular subtype of cancer [126]. In future MPE projects, type 2 diabetes can be examined in relation to specific subtypes of colorectal cancer in analyses of colorectal cancer incidence and mortality. As another example, metformin, as a commonly used hypoglycemic agent for type 2 diabetes, has been proved possess strong anti-cancer effects in many studies

[102, 147, 148]; however, in other studies, it is proved that metformin has no effect or even increase the risk of cancer in type 2 diabetes[149, 150]. Therefore, further MPE studies are needed for us to find the connection between type 2 diabetes, metformin use, and cancer, which may be helpful in the diagnosis, prevention and treatment of type 2 diabetes and cancer.

In conclusion, energy sensing pathway may bridge type 2 diabetes and colorectal cancer. Further studies including MPE studies are needed to address the links between these two diseases, which may bring great promise in the coming era of “precise medicine”.

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Abbreviations

ACACA	ACC, acetyl-CoA carboxylase
AICAR	5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide
AKT	Proteinase kinase B
BECN1	Beclin 1
BMI	Body mass index
CAMKK2	Calmodulin-dependent protein kinase beta
EEF2	Eukaryotic translation elongation factor 2
FASN	Fatty acid synthase
FFA	Free fatty acid
GLUT1	Glucose transporter 1
GLUT4	Glucose transporter 4
HDAC1	Histone deacetylase 1
HIF1A	HIF-1alpha, hypoxia-inducible factor-1 alpha
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A
IGF1	Insulin growth factor-1
IKBKB	IKKbeta, I kappa B kinase
LDH	Lactate dehydrogenase
LXR	Liver X receptor

mTOR	Mammalian target of rapamycin
NAD	Nicotinamide adenine dinucleotide
NFKB1	NF-kappaB, nuclear factor-KappaB
PDK1	Phosphoinositide-dependent kinase-1
PFK2	Phosphofructokinase-2
PI3K	Phosphatidylinositol 3-kinase
PPARGC1A	PCG-1alpha, peroxisome proliferator-activated-bold gamma coactivator-1 α
PRKA	AMPK, AMP-activated protein kinase
PTEN	Phosphatase and tensin homolog
ROS	Reactive oxygen species
SIRT1	NAD-dependent deacetylase sirtuin-1
SREBF1	SREBP-1, sterol regulatory element-binding proteins-1
STK11	LKB1, liver kinase B1
TSC	Tuberous sclerosis complex
ULK	Unc-51-like kinases
VEGFA	Vascular endothelial growth factor

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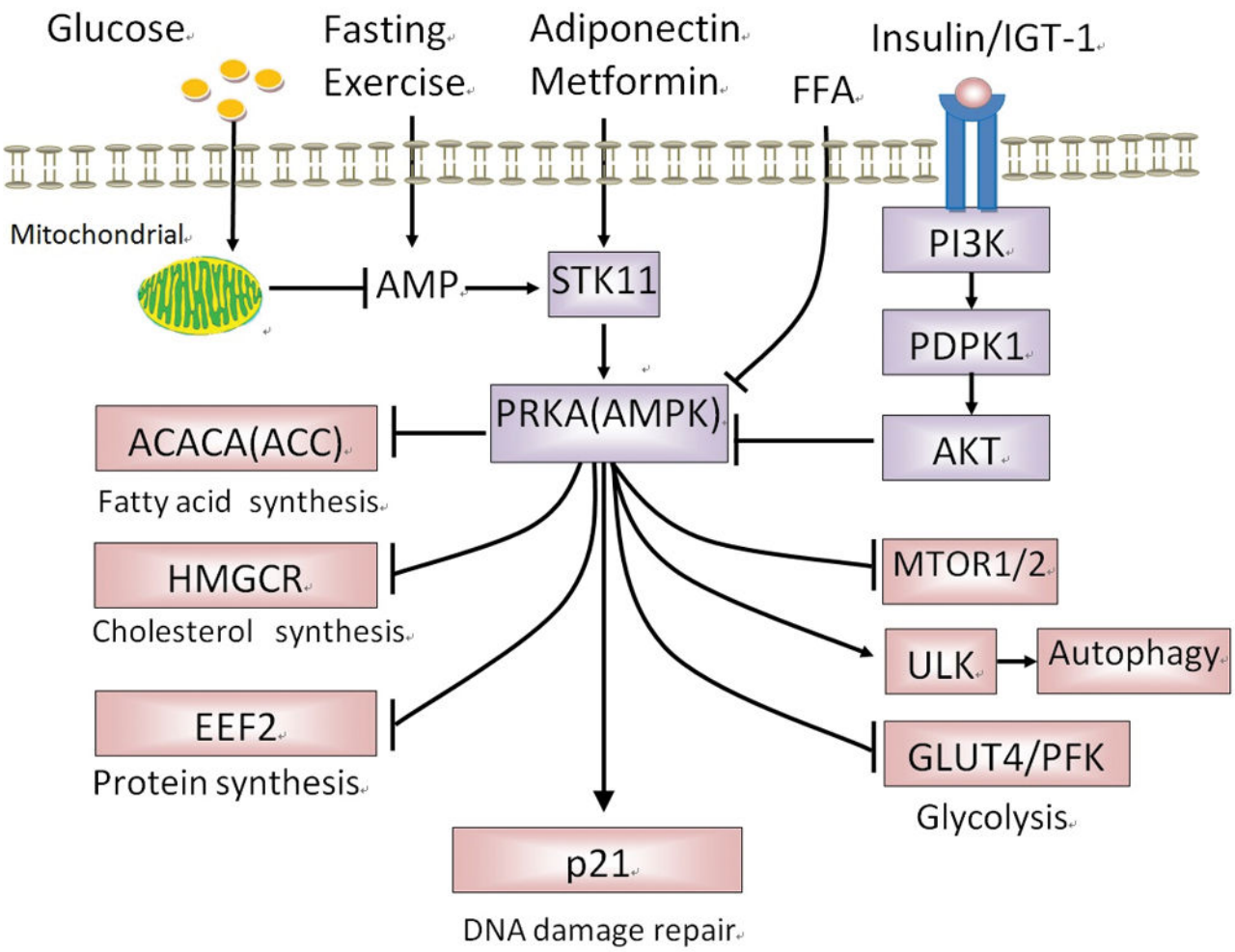

Figure 1.

Roles of AMPK in cancer in type 2 diabetes. Under nutrition deficiency state, such as fasting, exercise, glucose deprivation, increased AMP activates AMPK which then switches off the synthesis of protein, fatty acid and cholesterol, but switches on the glycolysis and autophagy in order for the cell to survive in energy insufficient. However, in type 2 diabetes, AMPK is inhibited by high levels of plasma glucose, insulin and IGF1, which may promote anabolism to meet the increasing demanding of cancer cell growth. CaMMKK:calmodulin-dependent protein kinase 1 alpha; AICAR: 5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide; GLUT4: Glucose transporter 4; PFK-2: phosphofructokinase-2; eEF-2: eukaryotic translation elongation factor 2; STK11 (LKB1: Liver kinase B1); AMPK: AMP-activated protein kinase; ACC: acetyl-CoA carboxylase; IGF1: insulin growth factor-1; PI3K: phosphatidylinositol 3-kinase; PDPK1: phosphoinositide-dependent kinase-1; AKT: proteinase kinase B; mTOR: mechanistic (mammalian) target of rapamycin; ULK: Unc-51-Like Kinases; HMG-CoA:3-hydroxy-3-methylglutaryl-coenzyme A

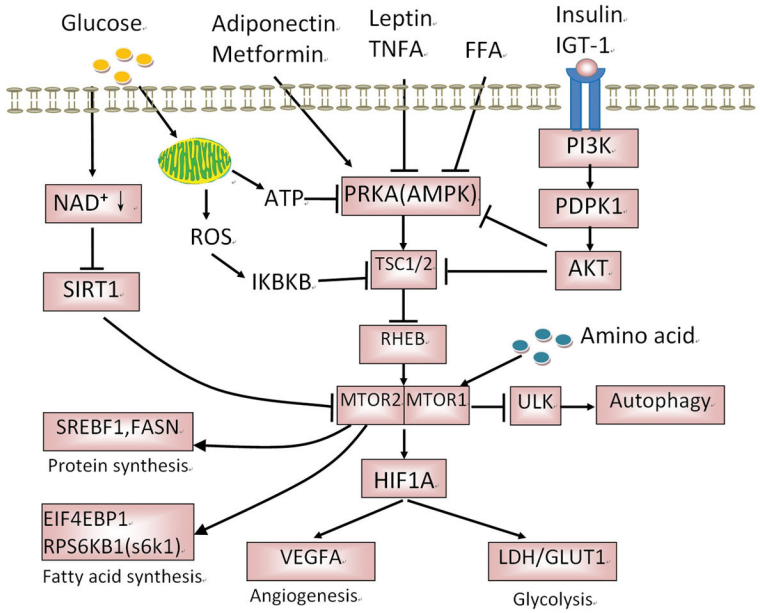

Figure 2.

Roles of mTOR signaling pathway in cancer in type 2 diabetes. mTOR signaling pathway is a key energy sensing pathway. In type 2 diabetes, the high level of nutrition (glucose, FFA and amino acid) as well as increased level of ROS, adipokines, insulin and IGF1, all contribute to the activation of mTOR. The activated mTOR will then inhibit autophagy, promote the synthesis of protein and fatty acid, up-regulate glycolysis, and stimulate angiogenesis, which is helpful for the cancer cell growth and metastasis. GLUT1: Glucose transporter 1; PRKA: AMPK, AMP-activated protein kinase; IGF1: insulin growth factor-1; PI3K: Phosphatidylinositol 3-kinase; PDPK1: phosphoinositide-dependent kinase-1; AKT: proteinase kinase B; mTOR: mammalian target of rapamycin; ULK: Unc-51-Like kinases; IKBKB: IKKkappa, I kappa B kinase; ROS: Reactive oxygen species; HIF1A: HIF-1alpha, Hypoxia-inducible factor-1 alpha; VEGFA: VEGF, Vascular endothelial growth factor; LDH: Lactate dehydrogenase; SREBF: SREBP, sterol regulatory element-binding proteins; FASN: Fatty acid synthase.

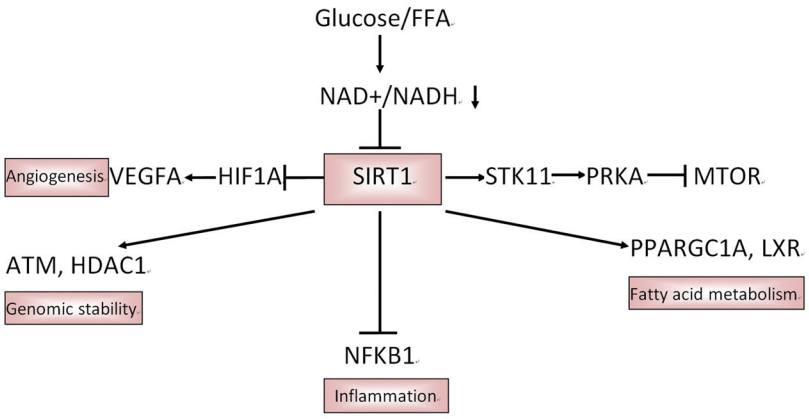

Figure 3.

Roles of SIRT1 signaling pathway in cancer in type 2 diabetes. SIRT1 signaling pathway is an important energy sensing pathway bridging energy metabolism to DNA stability. In type 2 diabetes, the high level of glucose and FFA will reduce the level of NAD+/NADH, which then decrease SIRT1 activity. The decreased SIRT1 activity loses its stimulation of fatty acid metabolism and its ability to maintain genomic stability, as well as its inhibition of inflammation and angiogenesis. All of those alterations may initiate the formation and growth of cancer cell. FFA: free fatty acid; PRKA: AMPK, AMP-activated protein kinase; mTOR: mammalian target of rapamycin; HIF1A: Hypoxia-inducible factor; VEGFA: VEGF, Vascular endothelial growth factor; NAD: Nicotinamide adenine dinucleotide; SIRT1: NAD-dependent deacetylase sirtuin-1; STK11: LKB1, liver kinase B1; PPARGC1A: PCG-1alpha, peroxisome proliferator-activated receptor gamma coactivator-1 α; LXR: liver X receptor; NFKB1: NF-kappaB, Nuclear factor-KappaB; HDAC1: histone deacetylase 1

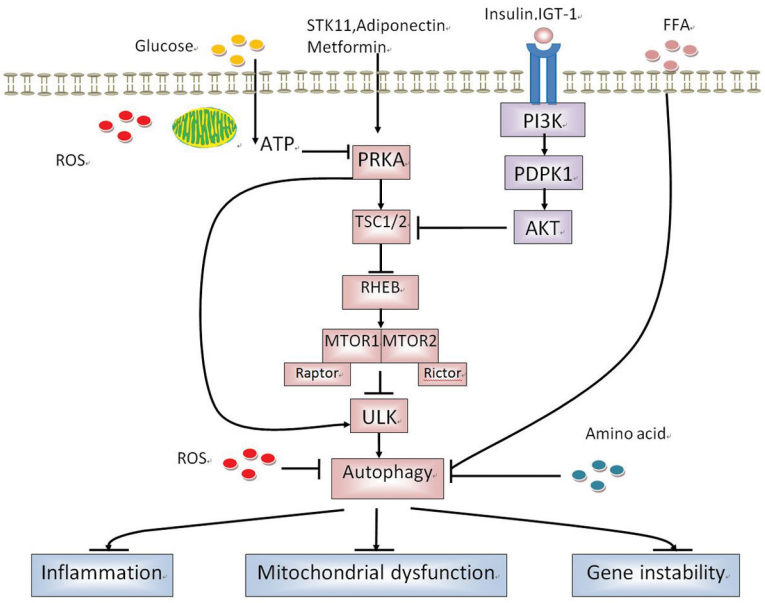

Figure 4.

Roles of Autophagy signaling pathway in cancer in type 2 diabetes. Autophagy has been found to limit inflammation, mitochondrial dysfunction and genome instability which are known promoters of cancer initiation. In type 2 diabetes, the high level of nutrition (glucose, FFA and amino acid) as well as increased level of ROS, insulin and IGF1, all contribute to the inhibition of autophagy, which may play key role in the initiation of cancer of type 2 diabetes. PRKA: AMP-activated protein kinase; IGF1: insulin growth factor-1; PI3K: Phosphatidylinositol 3-kinase; PDPK1: phosphoinositide-dependent kinase-1; AKT: proteinase kinase B; mTOR: mammalian target of rapamycin; ULK: Unc-51-Like kinases; IKBKB: I kappa B kinase; ROS: Reactive oxygen species; HIF1A: Hypoxia-inducible factor; VEGFA: VEGF, Vascular endothelial growth factor; LDH: Lactate dehydrogenase; SREBF: Sterol regulatory element-binding proteins; FASN: Fatty acid synthase; TSC: Tuberous sclerosis complex; BECN1: Beclin 1

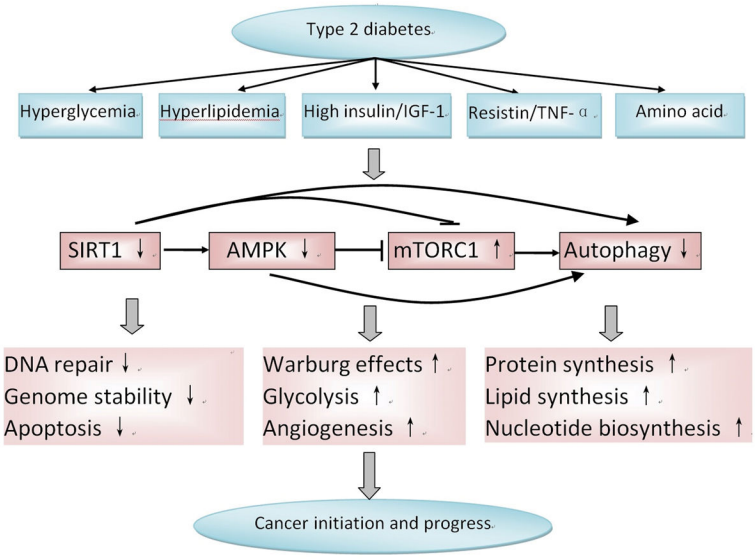

Figure 5.

Alteration and interaction of energy sensing pathways in type 2 diabetes and their association with colorectal cancer. The energy sensing pathways are dysregulated in type 2 diabetes because of high glucose, insulin and IGF-1 level. In the mean time, these dysregulated pathways may then increase the risk of carcinogenesis by decreasing genetic stability and DNA mismatch repair to promote cancer genesis, or remodeling cell metabolism to promote protein synthesis, nucleotide synthesis and lipids synthesis which will favor the rapid proliferation of cancer cell. AMPK: AMP-activated protein kinase; IGF-1: insulin growth factor-1; mTORC1: mammalian target of rapamycin complex 1.