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Review

Enzyme targeting strategies for prevention and treatment of cancer: Implications for cancer therapy

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ARTICLE INFO

Abbreviations:
uPA
Urokinase plasminogen activator
CAXII
Carbonic anhydrase XII
LDHA
Lactate dehydrogenase A
SOD
Superoxide dismutase
MMPs
Matrix metalloproteinases
ALDH1
Aldehyde dehydrogenase 1
ALPs
Alkaline phosphatases
CAT
Catalase
HKII
Hexokinase II
PK
Pyruvate kinase
NSE
Neurone-specific enolase
G6PD
Glucose-6-phosphate dehydrogenase

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ABSTRACT

Extensive growth of cancer in humans is a major cause of death. Numerous studies are being conducted to improve the early diagnosis, prevention, and treatment of cancer. Recent technological advancements in medical science and research indicate molecular target therapy holds much promise in cancer treatment. In the past, therapeutic and diagnostic targeting of non-glycolytic and glycolytic enzymes in cancer have been successful, and discoveries of biomarker enzymes in cancer hold promise for therapeutic treatments. In this review, we discuss the roles of several cancer-associated enzymes that could potentially act as therapeutic targets, and place special focus on non-glycolytic and glycolytic enzymes. This review indicates that the targeting of metabolic signaling offers a promising means of developing novel anti-cancer therapies.

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1. Introduction

Cancer poses a huge challenge to all nations because it remains a major cause of mortality and morbidity. Reportedly, cancer is responsible for more than 7 million deaths annually, that is, 13% of the global mortality burden [1]. Approximately 600,000 deaths occurred and 1.7 million newly diagnosed cancer cases were reported in the United States alone in 2017 [2]. Furthermore, problems associated with cancer are increasing in developing countries in line with population aging and the adoption of cancer-associated lifestyles.

A thorough understanding of the roles of cancer biomarkers is essential for diagnostic purposes and to aid treatment decision making, because early diagnosis and the choice of appropriate treatment has substantial patient benefits. The amount of information available about cancer biomarkers has expanded remarkably during recent years, and this will undoubtedly result in earlier diagnoses and better treatments and management strategies. Furthermore, this scientific progression has encouraged studies of numerous potential biomarkers and revived interest in the development of novel biomarkers [3].

Biomarkers can be produced by tumors or by the body in response to the presence of malignancy, and proteomic, enzymatic, and imaging biomarkers can be used to determine the presence of malignancy and for the study of disease transmission. Several enzymes are currently used as cancer biomarkers. The use of protease urokinase plasminogen (uPA), as a prognostic marker in human malignancies was first reported in 1996 [4], and its prognostic role has been studied in colorectal, bladder, lung, gastric, cervical, and ovarian cancers. Similarly, cathepsin D (another protease) has proven to be a prognostic element in breast cancer [4]. Hexokinase activity has been shown to be associated with the development of most cancers, and an array of reports point to the importance of metabolic pathways in cancer development [5]. Many enzymes have been reported to be under- or over-expressed in various cancers (Tables 1 and 2)

Table 2
List of reported enzymes under expressed in cancer.

Enzyme	Associated malignant disease	Reference
Aspartoacylase (ASPA)	Glioma tumors	[151]
Aminopeptidase N (AP-N)	Lung cancer	[152]
Catalase (CAT)	Lung cancer cells, Bladder cancer	[153,154]
Cysteine dioxygenase 1 (CDO1)	Advanced Lung cancer, Colorectal cancer, Colon cancer	[155]
Glycine amidinotransferase (GATM)	Renal cell carcinoma	[156]
Glutathione S-transferase mu1 (GSTM1)	Lung, Colon, Breast and Bladder cancer	[157]
Hydroxysteroid (11-beta) dehydrogenase 2 (11betaHSD2)	Colon adenocarcinoma	[158]
Inositol Polyphosphate-5-Phosphatase F (INPP5F)	Glioblastoma	[159]
Monoamine oxidase A (MAOA)	Hepatocellular carcinoma (HCC)	[160]
Superoxide dismutase (SOD)	Bladder cancer	[154]

Energy metabolism alterations are hallmarks of cancers, and targeting glycolytic pathway enzymes offers a means of treating the disease. Much effort has been made and continues to be expended on the identification and validation of enzymes that participate in this metabolic pathway as potential therapeutic targets. In this review, we mainly address cancer biomarker enzymes, which can be broadly classified as enzymes involved or not involved in the glycolytic pathway (Fig. 1). In addition, we discuss the roles played by these enzymes in cancer progression, suppression, and treatment, offering insights regarding the use of plant callus extracts that target various proliferative enzymes.

Table 1
List of reported enzymes overexpressed in cancer.

Enzyme	Associated malignant disease	References
Aldehyde dehydrogenase (ALDH)	Rhabdomyosarcoma, Non-small-cell lung cancer (NSCLC)	[117] [118]
Alakaline Phosphatases (ALP) (isozymes: placental, liver and bone)	Osteosarcoma; Bone metastases, Advanced Colorectal cancer, Liver metastasis, Seminomas and Ovarian cancers	[32]
Aminopeptidase N (AP-N)	Breast, Ovarian, and Prostate cancer	[119]
ATP citrate lyase	Glioblastoma, Colorectal cancer, Breast cancer, Non-small cell lung cancer, Hepatocellular carcinoma	[120]
Carbonic anhydrase	Brain, Breast, Cervical, Rectal or Lung cancer	[121] [122]
Catalase	Mammary cancer cells	[123]
Creatine Kinase (CK-BB)	Adrenocarcinoma of the Prostrate, Lung and Stomach	[124]
Farnesyl diphosphate synthase	Human CRC, Human hepatocellular carcinoma (HCC), Prostate tumor cell lines	[125] [126]
Farnesyltransferase	Human skin basal carcinoma, Ovarian carcinoma	[127] [128]
Fatty Acid Synthase (FAS)	Cancer of the breast, Prostate, Colon, Ovary, Thyroid and Endometrium	[129] [130]
Fucosyltransferase	Multiple malignant tumors	[131]
Galactosyltransferase II	Ovarian, Liver and Esophageal cancers	[132]
Glutathione Peroxidase (GPx)	Breast cancer	[133]
Glutathione reductase (GR)	Prostate cancer	[134]
Lipoprotein lipase (LPL)	Non-small cell lung cancer tissue, Colorectal cancer	[135,136]
Lysozyme	Colon cancer, Monocytic & Myelomonocytic leukemia	[137,138]
Urokinase plasminogen activator	Breast cancer, Ovarian cancer	[139,140]
Prostatic acid phosphatase	Prostate carcinoma, Late stage	[141]
Thymidine kinase	Hodgkin's lymphoma; Certain Leukemia; Small cell carcinoma of lung	[142]
5′-nucleotide phosphodiesterase	Lung cancer; Liver metastases	[143]
MMP-1, −9, −11, −12, −13, −15, −24 and −25	Breast cancer	[144,145]
HKII	Breast, lung, and Liver cancers	[146,147]
GLUT1	Breast cancer and Endometrial cancer	[148]
LDHA	Breast cancer	[149]
Glucose-6-phosphate dehydrogenase (G6PD)	Cervical cancers, Hepatocellular carcinoma	[91,150],

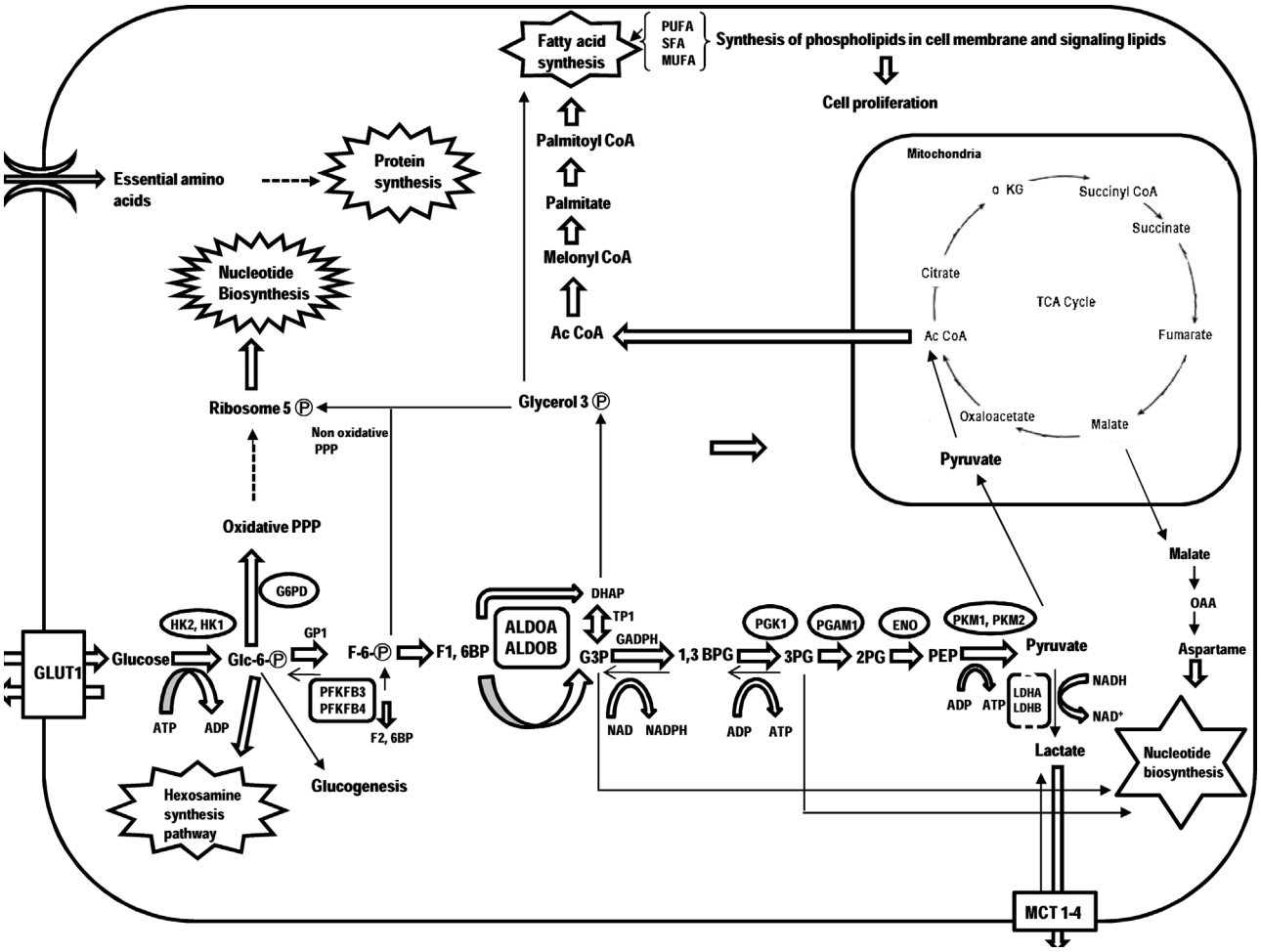

Fig. 1. Altered enzymatic activity in cancer cells. Glucose metabolism and glycolysis occur more rapidly in cancer cells than in normal cells due to the enhanced expressions of enzyme isoforms and transporters that favor glucose flux to meet the anabolic demands of cancer cells. Enzymes that are up-regulated in cancer cells are shown in bold. Relative fluxes are represented by arrow thicknesses. 1,3-bisphosphoglycerate (1,3BPG); 2-phosphoglycerate (2 PG); 3-phosphoglycerate (3 PG); 6-phosphofructo 2-kinase/fructose-2,6-bisphosphatase (PFKFB); acetyl CoA carboxylase (ACCA); acetyl CoA synthetase (ACS); acetyl-CoA (AcCoA); aldolase(ALDO); α-ketoglutarate (α-KG); dihydroxyacetone-phosphate (DHAP); enolase (ENO); fatty acid synthase (FASN), fructose-1,6-bisphosphate (F1,6BP); fructose-2,6-bisphosphate (F2,6BP); fructose-6-phosphate (F6P); glucose transporter (GLUT); glucose-6-phosphate (G6P); glucose-6-phosphate isomerase (GPI); glyceraldehyde-3-phosphate (G3P); glyceraldehyde-3-phosphate dehydrogenase (GAPDH); glycerol-3-phosphate (glycerol-3P); hexokinase (HK); lactate dehydrogenase (LDH); mono unsaturated fatty acid (MUFA); monocarboxylate transporter (MCT); oxaloacetate (OAA); pentose phosphate pathway (PPP); phosphoenolpyruvate (PEP); phosphofructokinase 1 (PFK1); phosphoglycerate kinase 1 (PGK1); phosphoglycerate mutase 1 (PGAM1); poly unsaturated fatty acid (PUFA); pyruvate kinase (PK); saturated fatty acid (SFA); tricarboxylic acid (TCA); triosephosphate isomerase (TPI).

2. Non-glycolytic enzyme biomarkers in cancer

Traditionally, enzymes have been used as biochemical markers for cancer identification and validation, and thus, are often considered potential targets for therapeutic agents. The rationale behind this concept is that meaningful alterations in the gene expressions of enzymes during malignant transformation can be detected in resulting tumors. Although no such cancer-specific enzyme has been identified, this imbalance in enzyme activity has been used for clinical evaluations. Although levels of a single enzyme alone cannot clinically detect all types of tumors, such determinations are clinically useful for cancer screening, prognosis, monitoring treatment response, early stage detection, and others. We discuss below in detail the roles of important non-glycolytic enzymes in cancer.

2.1. Urokinase plasminogen activator (uPA)

The abilities of cancer cells to invade adjacent tissues and other distant body sites are indicators of disease aggressiveness and are often associated with extensive tissue damage during progression. Various natural barriers, such as, basement membranes and interstitial connective tissues must be degraded before cancer cells can invade tissues and metastasize, and primary tumors are believed to release a number of proteolytic enzymes that facilitate the breakdowns of these barriers. The detailed roles of these proteases in metastasis and invasion have been reported elsewhere [7–9]. uPA, a serine protease, is a multi-role enzyme that is involved in cellular migration, tissue remodeling, and cancer proliferation [6]. Plasmin is capable of degrading vitronectin, laminin, fibronectin, fibrin, and proteoglycans and can activate latent collagenases. The activation of plasminogen is catalyzed by uPA or tissue-type plasminogen activators (tPA). uPA is considered to be an important trigger of plasmin generation during cell migration and invasion, while tPA is believed to crucially control the degradation of intravascular fibrin.

Significant increases in the gene expression of uPA and its receptor uPAR have been reported in breast, bile duct, colon, gastric, esophageal, ovarian, liver, lung, and prostate cancer [7–10]. uPA overexpression is often associated with malignant invasion and metastasis, and thus, is considered a major predictor of prognosis. Furthermore, reductions in the gene expression of uPA or of its receptors can inhibit tumor cell growth, invasion, and survival [11]. The uPA/uPAR system is involved in regulation of tumor cell proliferation, migration,

adhesion, angiogenesis and invasion [12]. PAI-1 (plasminogen activator inhibitor-1) has been reported to modulate the activity of uPA, and combined assessments of uPA and PAI-1 levels in tumor tissues were found to be of prognostic value [13,14], which demonstrates the impact of overall proteolytic balance on tumor progression.

2.2. Carbonic anhydrase XII (CAXII)

CAXII is a membrane-associated isoform of carbonic anhydrase (CA), and was initially identified as a marker in several cancers [15]. Although CAXII has been detected in several normal tissues, its expression is several fold higher in cancer tissues. It has been reported that CAXII level in cancer tissues may be correlated with disease outcome. In renal cancer, its expression been observed mainly in clear cell carcinomas and oncocytomas. In clear cell carcinoma, CAXII levels correlate with histological grade. However, in colorectal tumors, the extent of positive staining of CAXII increases with grade of dysplasia, which is unlike that observed in other tumor tissues. CAXII overexpression has also been detected in meningiomas, hemangioblastomas, gliomas, brain tumors [16], and many other cancers such as, breast [17], non-small cell lung [18], and cervical cancer [18] also express this enzyme. In breast cancer, expression level of CAXII predicts potential onset of the disease [19].

2.3. Aldehyde dehydrogenase 1 (ALDH1)

ALDH1 is responsible for oxidizing intracellular aldehydes, and converts retinol to retinoic acid in cytosol during stem cell differentiation [20]. Reports suggest, ALDH1A1-positive tumor cells demonstrate chemo-resistance in ovarian cancer [21,22]. Interestingly, knocking down ALDH1A1 has been reported to dramatically reduce the colony formation ability of ovarian cancer cells [23]. In another study, $ALDH^+$ cells demonstrated greater invasiveness than $ALDH^-$ cells, and that ALDH1 overexpression was positively related to tumor grade and stage [24].

Elevated ALDH1 activity has been observed in breast cancer, brain cancer, acute myeloid leukemia, and multiple myeloma [25–28], which suggests ALDH1 might be used as a marker of normal and malignant cell populations [36]. Studies on some lung cancer cells have also reported ALDH1 up-regulation. Thus detection of ALDH1 protein expression could be usable as a prognostic biomarker for cancer.

2.4. Matrix metalloproteinases (MMPs)

The MMPs are members of the zinc-containing proteolytic enzyme family and can break down extracellular matrix proteins, and the degradation of basement membrane is prerequisite for cancer invasion [29]. MMP activity is tightly regulated by cytokines, growth factors and proto-oncogenes, and its activity can be assessed by determining MMP expression in tissues by zymography. Many studies have reported the involvements of different MMP family members during different stages of cancer progression (Table 3). In particular, MMPs may promote or inhibit cancer development depending on other factors, such as, tumor site, tumor stage, substrate profile, and enzyme localization [30]. The expression of MMP-8 in squamous cell cancer is positively associated with survival, whereas MMP-9 may act as a tumor promoter or inhibitor (under specific situations) during later disease stages. This dual role played by MMP-9 was encountered in a MMP-9 knockout mouse models study, in which, MMP-9 expression was associated with reduced carcinogenesis frequency, and MMP-9 deficiency with aggressive disease [31].

Table 3
Matrix metalloproteinases involved in different stages of cancer progression.

Cancer stage	MMPs involved
Cancer cell invasion	MT1-MMP, MMP (2,9 and several others)
Cancer cell proliferation	MMP (1,2,3,7,9.11 and 19)
Cancer cell apoptosis	MMP-7 and several others
Tumor angiogenesis and vasculogenesis	MMP (2, 3, 8, 9, 10, 11and 13)

2.5. Alkaline phosphatases (ALPs)

ALPs catalyze the hydrolysis of phosphate monoesters under alkaline conditions. These membrane-bound glycoproteins are divided into four isozymes, that is, germ cell (GCALP), tissue nonspecific, intestinal, and placental ALPs (PALP). The roles played by ALPs in a number of cellular processes have been elucidated and include cell growth, regulation of phosphorylation, and cellular migration during embryonic development and apoptosis. Anomalies in the expressions of ALPs have been associated with various human cancers. Altered ALP expression patterns have been reported in malignant tissues GCALP and PALP [32]. ALPs have been reported to be highly expressed in choriocarcinoma and breast cancer-derived cells. PALP is a marker for lung, gastrointestinal tract, ovarian, and testicular cancer. Plasma tissue nonspecific ALP or Tissue-nonspecific alkaline phosphatase (TNALP) levels can indicate the presence of osteoblastic bone metastasis, osteosarcoma, and Paget's disease [33]. Higher ALP activities have also been reported in breast cancer patients [34], and Usoro et al. reported elevated Intestinal alkaline phosphatase (IALP) levels in hepatocellular carcinoma [35]. Furthermore, the abnormal expressions of ALP genes in cancer [36,37] indicates associations between ALP isozymes and tumorigenesis in mammalian tissues [38].

2.6. Antioxidant enzymes

- Oxidative damage to cellular macromolecules is considered to be one of the environmental factors of cancer and several other diseases [39,40]. This damage plays a major part in cancer development by stimulating DNA damage, and thus, disrupting intracellular signal transduction pathways [41]. The roles played by of reactive oxygen species (ROS) in the developments and sustainabilities of oncogenic phenotypes have been elucidated in a number of studies [40–42]. In order to protect itself, the body maintains complex systems of antioxidants (C and E), glutathione, and enzymes, such as, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-S-transferase (GST) [40,42], and the expression levels of these enzymes and the presence of genetic polymorphisms have been associated with susceptibility to DNA damage and cancer risk.

Superoxide dismutase (SOD) is involved in the conversion of superoxide radicals to oxygen and peroxides, and thus, protects cells against the toxic products formed during aerobic respiration, and it has been shown SOD defects are associated with numerous cancers, including hepatocellular carcinoma [43]. However, reports on SOD expression levels and their association with cancer are contradictory. Aggarwal et al. reported observing reduced SOD activity in all brain tumor patients as compared with controls, but associations between high levels of SOD and H_2O_2 with other cancers [44] such as, breast cancer and laryngeal carcinoma [45], which were suggested to arise from increased H_2O_2 levels and a consequent intracellular environment favoring DNA damage and cancer [46].

Catalase (CAT) is present in all living organisms and catalyzes the decomposition of H_2O_2 to water and oxygen. In 1993, Craemer et al. reported decreased hepatic CAT activity in patients with malijavascript:void(0)gnant diseases [47]. In another study by Ahn et al., the CC genotype of the CAT gene was found to be associated with a 17% reduction in breast cancer risk as compared with the presence of one variant allele [48]. Furthermore, it has been shown effective therapy

against breast cancer is associated with increased CAT activity [49]. A number of studies have linked elevated cancer risk of cancer with altered GPx and GR activity. Hu and Diamond in 2003 investigated the role of an allelic variation (proline/leucine) within the GPx1 gene in breast cancer, and found that the leucine-containing allele, but not the proline-containing allele, was associated with breast cancer recurrence [50]. Park et al. observed a significant association between a specific Glutathione S-transferase (GST) genotype and breast cancer risk [51], and Mao et al. suggested a Ile105Val polymorphism of GST had a positive impact on the risk of prostate cancer [52]. Significant elevation of GST activity in colorectal cancer suggests it use as marker for this type of cancer [53], and Prabhu and Bhat suggested alterations in total serum GST levels may play a role in cancer progression [54].

3. Glyolytic enzymes in cancer therapy

The glycolytic pathway consists of a priming phase and an energy-yielding phase, and both phases require the involvements of a number of enzymes. Two molecules of ATP are consumed in the first phase during the conversion of glucose to fructose-1,6-bisphosphate, which is catalyzed by various enzymes such as, hexokinase, phospho-glucose isomerase, and phosphofructokinase. In the energy-yielding phase, fructose-1,6-bisphosphate is converted to pyruvate in a stepwise manner and this results in the production of four ATP and two NADH molecules.

In mammals, lactate is the end product of glycolysis, or CO_2 in case of the complete oxidation of glucose via respiration in mitochondria. To generate energy from ATP, cancer cells exhibit higher rates of glycolysis, and rates of glucose uptake are remarkably increased in tumor and in other highly proliferating cells. Most cancer cells exhibit increased aerobic glycolysis, which constitutes a major metabolic alteration.

The most important change in metabolic activities during tumor transformation is referred to as the Warburg effect [55]. Alterations in the metabolic network are widely and commonly observed in cancer cells, and therefore, targeting the glycolytic pathway is considered a preferred therapeutic strategy [56–59]. In fact, a large number of recently devised therapeutic strategies target cellular energetic metabolism, and the selection of suitable target enzymes has received considerable research attention. To be considered an attractive therapeutic candidate, these selected enzymes must exhibit substantial activity differences in cancer cells and normal cells. We provide a schematic representation of the cancer glycolytic pathway in Fig. 2, in which roles of several such enzymes that are cancer biomarkers and overexpressed in different cancers are highlighted.

3.1. Hexokinase

This enzyme utilizes ATP to catalyze the phosphorylation of glucose to glucose-6-phosphate (G6P), which is one of the initial rate-limiting reactions during glycolysis [60,61]. This phosphorylation step leads to the conversion of nonionic glucose to anionic G-6P, which serves as the point of entry into the glycolic pathway or the pentose phosphate pathway for glycogen synthesis. To date, four different mammalian isoforms of hexokinase have been identified. Several studies have reported the overexpression of Hexokinase II (HKII) in various cancer types such as, breast, lung, and liver cancers [62]. Apart from its role in phosphorylation, HKII also has the ability to interact with voltage dependent anion channel (VDAC) that is present on the outer membrane of mitochondria [63]. The interaction between HKII and VDAC aids the production of glycolytic fuel through ATP, which is generated by mitochondria. Furthermore, HKII stabilizes the mitochondrial membrane and the discharge of several pro-apoptotic factors (like cytochrome C) [64]. Thus, it appears hindering the HKII-VDAC interaction could obstruct cell proliferation and initiate apoptosis by lowering the supply of ATP and destabilizing mitochondrial membranes. These important roles played by HK makes it an important target for designing drugs against cancer. 2-Deoxyglucose and 3-bromopyruvate are two well-known inhibitors of HKII [65]. Both disrupt the binding of hexokinase to mitochondria, which leads to ATP depletion and cell death. Small-molecule drugs like lonidamine have also been reported to inhibit HK activity. Additionally, various azoles and their derivatives, such as, bifonazole and clotrimazole, interrupt binding between HK and VDAC [66]. Thus, apoptotic events can be mediated either by direct inhibition of HK or by disrupting HK-VDAC binding. Methyl jasmonate, a plant lipid derivative has been found to bind to hexokinase, and disrupt its interaction with VDAC [67]. Therefore, HKII in cancer cells presents a potential target for the development of therapeutic agents.

3.2. Lactate dehydrogenase a (LDHA)

Lactate dehydrogenase A (LDHA) catalyzes formation of lactate and NADP from pyruvate and NADPH, respectively. Because it is an important part of the final step of the glycolytic pathway, LDHA is considered to play a critical role in tumor maintenance. Reports suggest knockdown of LDHA in tumor cells increases mitochondrial respiration, decreases the proliferation of cells in hypoxic environments, and suppresses tumorigenicity [68]. A large number of studies have reported inhibiting LDHA in cancer cells lead to cell death [69], and it has been observed in several studies that inhibition of LDHA causes no significant toxic effect on normal tissue, which makes LDHA a promising therapeutic target in cancer. Furthermore, inhibiting LDHA with FX11 or siRNA caused reductions in ATP levels and resulted in substantial oxidative stress culminating in cell death [70].

3.3. Pyruvate kinase (PK)

PKR and PKL, which are both encoded by the *PKLR* gene, are expressed in red blood cells and liver, respectively. Pyruvate kinase is the last rate-limiting enzyme in the glycolytic pathway, and is involved in the conversion of phosphoenolpyruvate (PEP) to pyruvate and ADP to ATP [71]. This reaction is important as it leads to the glycolysis or oxidative phosphorylation of pyruvate (Figs. 1 and 2). Different cell types in mammals contain different isoforms of PK, that is, PKM1, PKM2, PKL, and PKR [72]. PKM1 is expressed in an active tetrameric form in many normal cells, whereas PKM2 is predominantly expressed either as a high or a low-activity dimeric form in most cancer cells [73]. Furthermore, PKM2 is responsible for tumor growth and cancer metabolism and is highly expressed in tumor cells and promotes aerobic glycolysis.

The binding ability of PKM2 to phospho-tyrosine proteins promotes aerobic glycolysis [74], PKM2 is present in human cancer biopsy tissues at higher levels than in normal tissues [75]. The expression of PKM2 is directly related to enhanced glucose uptake, increased lactate production, and reduced O_2 consumption, and these characteristics mean it promotes the Warburg effect. As compared with PMK1 expressing cells, cancer cells expressing higher levels of PKM2 show increased growth in tissue culture and in xenografts in mice [75]. In cancer cells, PKM2 exists in dimeric or tetrameric forms [76]. There are two different strategies for targeting PKM2. The first involves its inhibition and the second its activation.

High throughput screening has identified several selective PKM2 inhibitors [77]. The fructose-1,6-bisphosphate (FBP) binding site of PKM2 is the target site of these molecular inhibitors. However, several toxicity issues have been reported as these inhibitors act to suppress PK activity in liver and red blood cells. Shikonin and alkannin (both natural products) are inducers of necrosis and inhibit PKM2 activity without affecting the activities of PKM1 and PKL [78]. The inhibition of PKM2 by these natural inhibitors was partially reversed when FBP was added to protein lysates. Targeting of PKM2 with RNA interference (RNAis) attenuated tumor cell growth. Furthermore, in several cancer cells, these RNAis induced caspase-dependent apoptosis [79]. Though

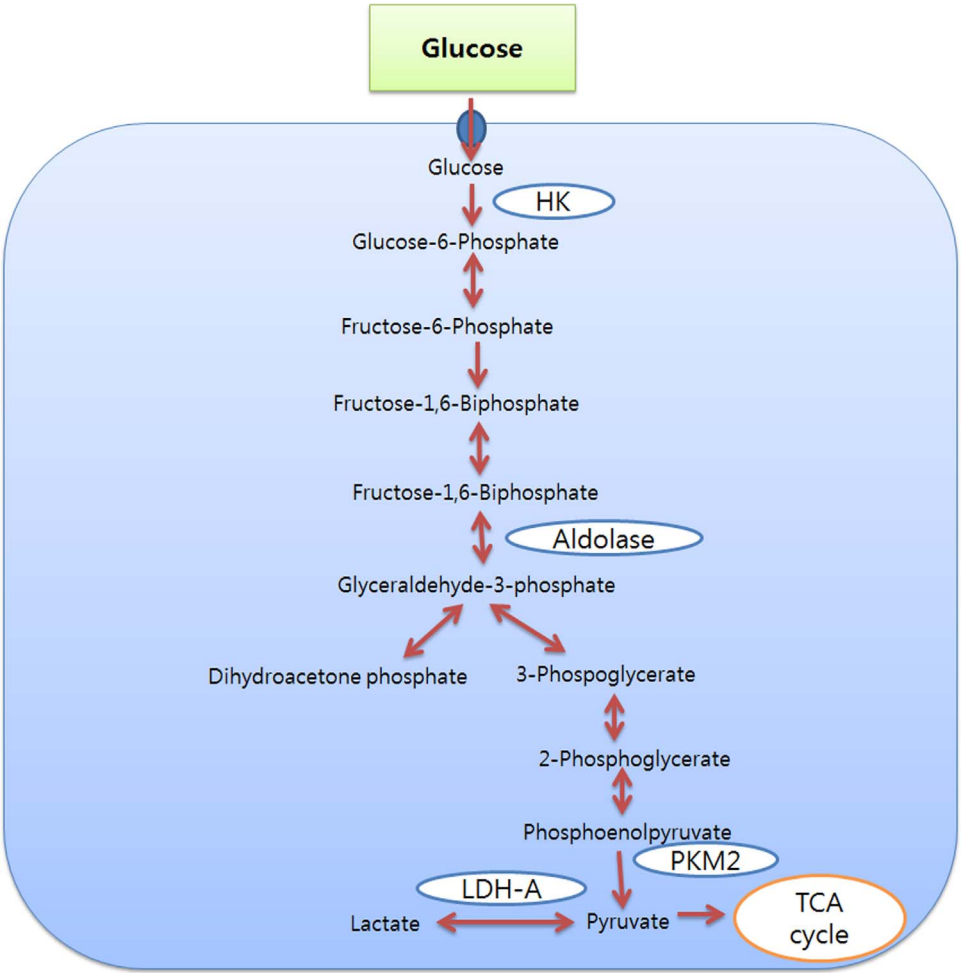

Fig. 2. Overview of the cancer glycolytic pathway. Schematic flow illustrates the relationships between some glycolytic pathways in cancer cells. Major enzyme biomarkers implicated in cancer are depicted in boxes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

PKM2 inhibition appears to be a successful approach to combat cancer cell proliferation, most cancer cells later demonstrate high levels glutaminolysis, presumably to meet their energy requirements [80]. Therefore, inhibiting PKM2 is not considered to be sufficient for reducing tumor cell proliferation. PKM2 also functions as a protein kinase and regulates tumorigenesis or acts as a transcriptional co-activator [81]. Most cancer cells express PKM2 [82], which may finely regulate the on and off switching of ATP production and cell proliferation, respectively. [83]. Quinolone sulfonamide pyridopyrimidine analogs have been reported to potently activate PKM2, and several more PKM2 inhibitors have also been identified using an *in silico* screening approach [84]. Alterations in cancer cell metabolism cannot be acquired solely through PKM2 activation, and many activators and inhibitors of PKM2, are at preclinical or preliminary investigational stages of development. Furthermore, previous studies have suggested PKM2 activators offer considerable promise as cancer therapeutics.

3.4. Neurone-specific enolase (NSE)

In most diseases associated with neuronal damage, NSE levels are elevated in cerebrospinal and serum fluid, which is attributed to the localization of NSE in axons. Therefore, NSE levels are useful for determining the extents of various neuronal injuries, such as, intracerebral hemorrhages, seizures, and traumatic brain injuries. For this reason, serum NSE level was initially employed to predict the prognosis of patients with neuronal injury [85,86], and investigated as a possible tumor marker for neuroblastoma and small cell lung cancer (SCLC) [87]. NSE is now a well-known tumor marker in renal cell carcinoma, seminoma, melanoma, carcinoid tumor, Merkel cell carcinoma, dysgerminoma, immature teratoma, medullary thymic cancer, and other cancers [86], and an established biomarker of various tumor of neuroendocrine origin. Although elevated serum NSE levels have been detected in some patients with non-small cell lung cancer (NSCLC), its prognostic value is more obviously specified in patient subgroups, such as, those harboring epidermal growth factor receptor (EGFR) mutation +ve tumors on EGFR-TKI therapy.

3.5. Glucose-6-phosphate dehydrogenase (G6PD)

Almost all cells express glucose-6-phosphate dehydrogenase (G6PD), which is the rate-limiting enzyme in the pentose phosphate pathway. G6PD catalyzes the formation of glucono-D-lactone-6-phosphate via the oxidation of glucose-6-phosphate and the reduction of NADP to NADPH [88]. Studies have shown the involvement of G6PD in cell growth regulation and tumorigenesis, and it has been reported G6PD overexpression in NIH 3T3 cells results in morphology changes and contact inhibition characteristics. In nude mice, G6PD overexpression led to rapid fibrosarcoma growth, which with other results suggest G6PD acts as a tumor driver gene [88]. Recent studies have revealed that G6PD expression andactivity are evident in a number of human cancers, including breast [89], bladder [90], cervical [91], ovarian [92], and prostate cancer [93]. Furthermore, in a by Wang et al., G6PD was suggested to be independent predictor of prognosis in gastric and breast cancer [94,89], and in another study, it was suggested silencing G6PD expression might decrease melanoma cell proliferation and promote apoptosis [95].

4. New strategies and cancer prevention

New strategies must be developed for the discovery, identification, and determination of signaling pathways in cancers because the knowledge obtained will undoubtedly play a pivotal role in the developments of novel therapeutics for many different cancers. Some types of cancer are easily diagnosed during early disease stages and are treatable. Whereas others are difficult to diagnose early and are generally diagnosed when are at later advanced stages. The reason for this is that different cancers have different regulatory pathways and employ varied signaling and metabolic cues. From the developmental perspective this means different cancer types respond in quite different ways to therapeutic agents. Nonetheless, many successful anticancer drugs have been discovered. For example, vinca alkaloids from Madagascar periwinkle inhibit tubulin polymerization [96], etoposide (a semi-synthetic derivative) from Podophyllum species inhibits topoisomerase II [97], and paclitaxel (Taxol®) from Pacific yew stabilizes mitotic tubules and causes mitotic arrest [98].

Instead of identifying and targeting each and every pathway, we could target cancers as a single entity and focus our attentions on the development of a single 'magic bullet' containing a holistic combination of anticancer chemicals that targets all cancers and is free of adverse side effects. To accomplish this huge double-edged task, the exploration of single anti-cancer molecules is a futile endeavor. Instead, combinations of molecules derived from natural extracts [99–101] appear to be near ideal candidates for the development of an universal anti-cancer strategy. With this goal in mind, we discuss potential universal anticancer therapeutics.

4.1. Callus and cancer prevention

A callus is a mass of undifferentiated totipotent somatic plant cells, which can be viewed as "plant stem cells" because they possess the ability to transform into whole plants [102]. As compared with the extracts of parts of plants, such as, leaves, roots or bark, plant callus secondary metabolite extracts exhibit more oxidative and anti-cancer properties. For example, whole leaf extract of *Aegele marmelos* were less effective at lowering blood sugar levels than its callus extract [103]. Similarly, rice extracts and methanolic protein extracts of rice were found to have weaker anti-cancer properties than whole callus extracts [99,104].

4.2. Plant extracts and cancer prevention

Deshpande et al. and Rahman et al. convincingly reported that whole callus rice secondary metabolite extracts (rice callus suspension culture – RCSC) exhibited stronger anti-proliferative effects than Paclitaxel and Etoposide, which are effective clinically proven anticancer drugs [99,100]. They showed RCSC at a dilution of 1:20 totally suppressed cancer activity in renal cancer (RXF 393) and colon cancer (SW 620) cells, after an incubation period of 96 h. Further, RCSC at a 1:40 dilution specifically targets colon cells and at dilutions of 1:80 or 1:160 targets only renal cancer cells. These findings suggest the presence of a wide range of bioactive compounds which at different concentrations affect specific cancer cells [105]. These findings demonstrate the presence of clinically active entities in RCSC. A considerable loss in the anti-proliferative activities of HPLC derived RCSC fractions was also reported, indicating that the holistic extract approach produced the best results [100]. This is ascribed to synergism between different bioactive molecules present in RCSC, and presents a topic for further study. Furthermore, in another paper published by Rahman et al. scanning electron microscopy (SEM) of rice-callus treated colon cancer cells (SW 620 cells) showed changes in morphology and increased adhesiveness, which are both indicators of apoptosis (Fig. 3). Moreover, gene expression analysis of RCSF treated colon cancer cells revealed considerable up-regulations of cell cycle arrest factors like cJUN, NF-kB2, and ITGA2B.

4.3. Nutrients and cancer prevention

Fermented whole wheat germ extract (FWGE) exhibits anti-proliferative properties like cytotoxicity and cytostatic effects in various cancer cells [106]. Dimethoxy benzoquinone (DMBQ) is the major anti-proliferative compound in FWGE. Comparative analysis of the anti-proliferative activities of FWGE and DMBQ revealed both exhibited cytotoxic activity and that FWGE also exhibited cytostatic activity in different cancer cells. Furthermore, whereas DMBQ exhibited cytotoxic effects on normal cells, as is the case with many of quinones with anti-proliferative properties, FWGE showed no visible cytotoxic effects on normal cells and in fact increased their growths.

4.4. Target enzymes and cancer prevention

The enzymes that play a major role in the proliferation of cancer cells are glycolytic enzymes like lactate dehydrogenase (LDH), caspases, cyclin-dependent kinases, and redox-detox enzymes regulated by p53. Cancer cells often utilize non-glycolytic enzymes to generate energy rapidly, which inevitably results in the excessive production of lactate by LDH [107,108]. Thus the generation of glycolytic fluxes via the productions of NADH and NAD simultaneously provides anabolic substrates that promote cancer progression [109], which seems to be the primary checkpoint targeted by both FWGE and RCSC to induce an anti-proliferative effect. FWGE seems to inhibit glucose uptake by cancer cells, whereas RCSC seems to inhibit LDH, thereby activating oxidative phosphorylation resulting in the production of ROS and subsequent apoptosis. In addition, caspases (members of the cysteine-aspartic acid protease family) are also activated by these extracts, and when activated they initiate and execute apoptosis [110]. CDKN1A and c-Jun play essential roles in the regulation of cyclin-dependent kinases, and thus, in the maintenance and progression of the cell cycle [111–113]. CDKN1A and c-Jun control the expression of p53, a negative regulator of cell growth, that exerts its influence by regulating the redox and detox enzymes (Fig. 4). RCSC and FWGE both seem directly or indirectly influencing all of the above-mentioned events and the expressions of enzymes responsible for their anti-proliferative properties. However, it remains to be determined how these extracts perform these putative functions. The active anti-proliferative compound in FWGE is DMBQ, which is converted by intracellular flavoenzymes to active quinones that are responsible for its anti-proliferative activity. On the other hand, the active compound in RCSC has not been identified. Even trying with each HPLC fraction failed to identify the most active compound, suggesting two or more compounds in RCSC are responsible for its anti-proliferative effects, though it is also possible, compounds in RCSC react intracellularly to produce the responsible bioactive molecule.

Usually compounds like flavonoids, anthocyanins, and phenolic acids [114,115] are considered to contribute to the anti-proliferative properties of plant extracts. However, the concentrations and efficacies of such compounds depends on, the plant parts used to make these extracts, the solvent types employed for extract preparation, and the type of extraction process used. Simple filter sterilization processes result in pure extracts and do not influence the activities of compounds, and these extracts usually have longer shelf lives other types of plant extracts.

5. Conclusions

Metabolic alterations are a major hallmark of cancer, which is characterized by the upregulations of glycolysis, lipid metabolism, and other processes. The metabolisms of cancer cells can be influenced by means of reducing the access to essential substances for proper metabolic function. Differences between the metabolisms of cancer and

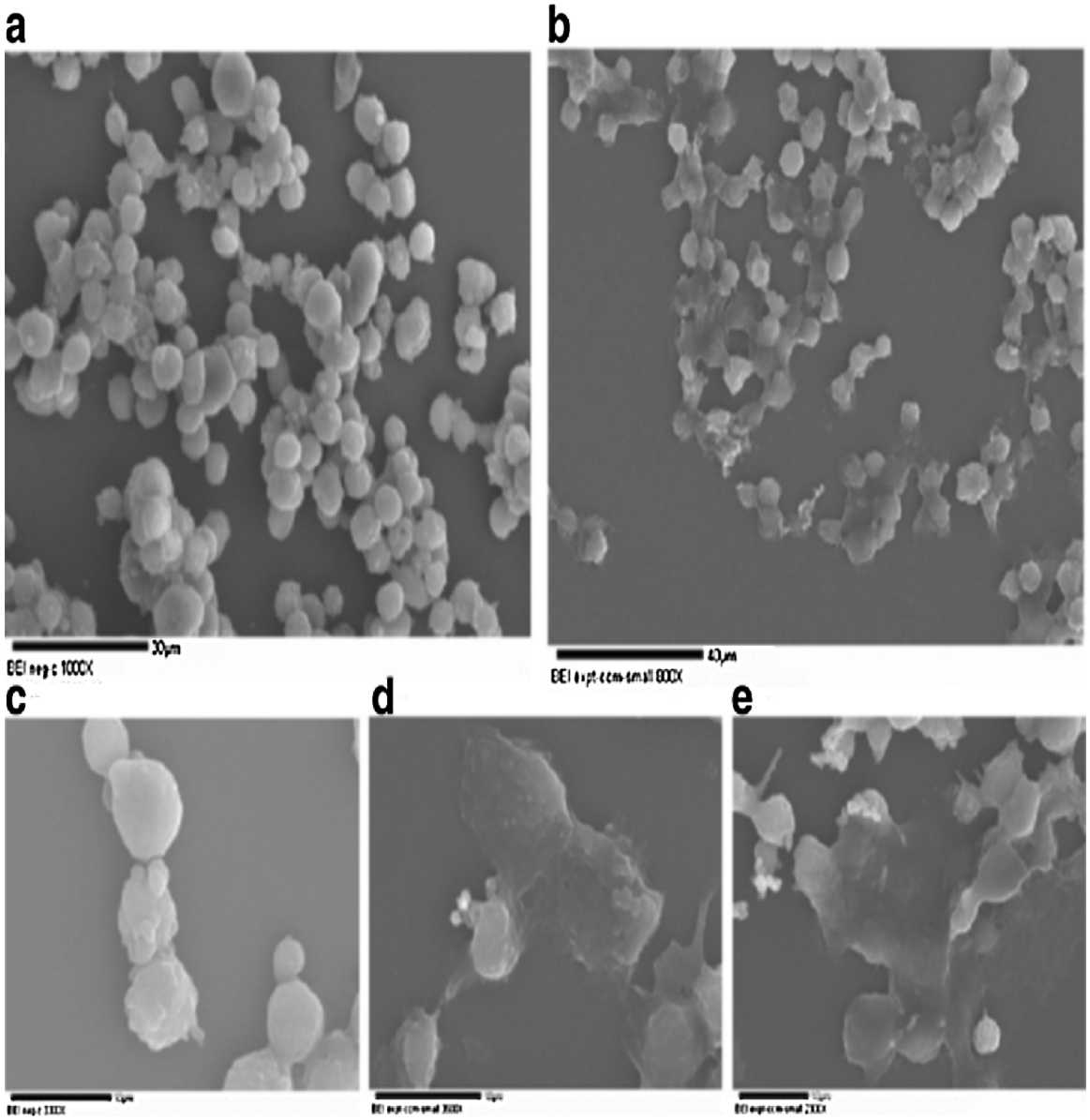

Fig. 3. Scanning electron microscopic results for the colon cancer cell line (SW620) grown for 96 h (a) without (negative control) or (b) with a 1:5 dilution of rice callus culture. Higher magnifications of the colon cancer cell line (c) not treated and (d and e) treated with rice callus culture [116].

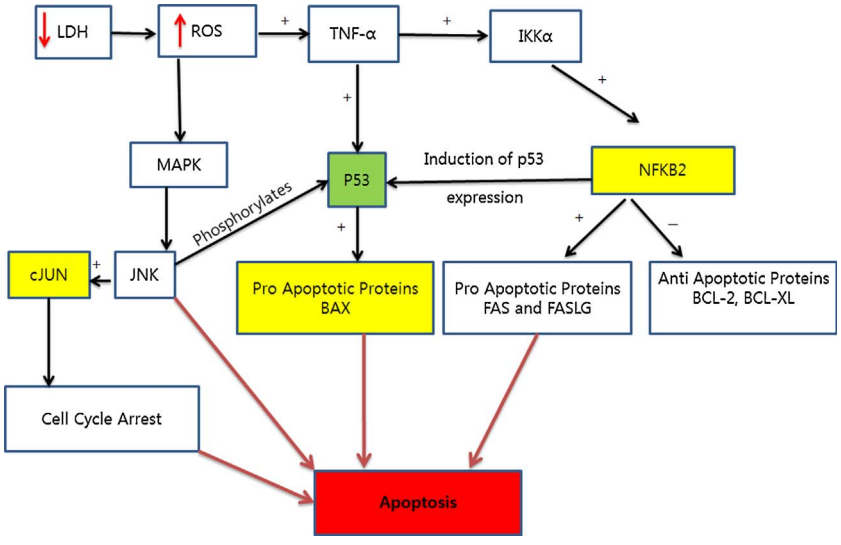

Fig. 4. Putative pathways involved in RCSC induced apoptosis. Proteins regulating apoptosis and encoded by genes up-regulated by RCSC are indicated by yellow boxes [116]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

normal cells provide a biochemical basis toward the development of new therapeutic strategies to preferentially kill cancer cells by targeting metabolism associated enzymes. Targeting cellular metabolism alterations that are associated with cancer progression offers much promise and remains a largely unexplored topic. Currently, enzyme biomarkers are viewed as offering a means of diagnosing or treating cancer and by interfering with cancer growth pathways may be useful for overcoming drug resistance. A comprehensive understanding of the metabolic differences between cancer and normal cells would undoubtedly open new developmental vistas for combating cancer.

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