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Reviews

Inhibition of tumor energy pathways for targeted esophagus cancer therapy

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ABSTRACT

Interest in targeting cancer metabolism has been renewed in recent years with the discovery that many cancer related pathways have a profound effect on metabolism and that many tumors become dependent on specific metabolic processes. Accelerated glucose uptake during anaerobic glycolysis and loss of regulation between glycolytic metabolism and respiration, are the major metabolic changes found in malignant cells. The non-metabolizable glucose analog, 2-deoxy-D-glucose inhibits glucose synthesis and adenosine triphosphate production. The adenosine monophosphate-activated protein kinase (AMPK) is a key sensor of cellular energy and AMPK is a potential target for cancer prevention and/or treatment. Metformin is an activator of AMPK which inhibits protein synthesis and gluconeogenesis during cellular stress. This article reviews the status of clinical and laboratory researches exploring targeted therapies via metabolic pathways for treatment of esophageal cancer.

1. Introduction

Esophageal cancer (EC) ranks ninth among the most common cancers and sixth among the most lethal cancers in the world [1–3], and also affects more than 450,000 people worldwide with rapidly increasing [4].

Surgery (as the first choice for patients with early-stage), radiotherapy, chemotherapy and combination therapy (typically including chemotherapy in combination with surgery and radiotherapy) are common treatment modality of esophageal cancer. Typical agents that are utilized in management of EC include: cisplatin, 5-fluorouracil, taxanes, irinotecan, and mitomycin C [5,6]. Recent technical advances in surgery (such as the use of neoadjuvant chemoradiotherapy and also new cytotoxic drugs) have improved the rate of EC therapy and survival benefit and consequently has provided an impetus for the current attention that has been directed to therapeutics selectively targeting molecular pathways in cancer cells [7,8].

Considering the recent understanding of cancer metabolism and the increasing information about the enzymes and the pathways involved, current interests in targeting cancer metabolism have been improved with the detection that many cancer related pathways (e.g. oncogenic and tumor suppressor) have a profound effect on metabolism and that many tumors become dependent on specific metabolic processes [9].

Abbreviations: 2-DG, 2-deoxy-D-glucose; AMPK, adenosine monophosphate activated protein kinase; ATP, adenosine triphosphate; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma.

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There is a fundamental difference in the bioenergetic metabolism of aggressive cancer cells compared to normal cells [10]. Cancer cells, in order to sustain their high proliferation rates, rely on glycolysis, which is known as the "Warburg effect" [10–12].

In summary, it is well accepted that some new targeted drug therapies need to be developed for advanced esophageal cancers due to the poor prognosis of these types of cancer. Moreover, chemotherapy instantly helps radiotherapy via more localization and also more sensitization of tumor with ionizing radiation [2,12,13]. This review tries to describe the current preclinical and clinical trial molecule targeted agents and metabolic pathways as targets in combination with ionizing radiation for cancer therapy in the esophageal cancer.

1.1. *Glycolysis and cancer treatment*

An alternative strategy to achieve both therapeutic selectivity and efficiency is to take advantage of the fundamental difference between cancer cells and normal cells in their biochemical metabolism. One of the most prominent metabolic alterations in cancer cells is increased aerobic glycolysis and dependency on the glycolytic pathway for ATP generation, known as the Warburg effect and that is to say the malignant cells become additive to glycolysis and dependent on this pathway to generate ATP [13–15]. Because ATP generation via glycolysis is far less efficient (two ATP per glucose) than through oxidative phosphorylation (36 ATP per glucose), cancer cells consume far more glucose than normal cells to maintain sufficient ATP supply for their active metabolism and proliferation and in brief, maintaining a high level of glycolytic activity is essential for cancer cells to survive and to growth. This metabolic feature has led to the hypothesis that inhibition of glycolysis may severely abolish ATP generation in cancer cells and thus may preferentially kill the malignant cells [16–18].

2-deoxy-D-glucose (2-DG), as the most effective in inhibition of cell metabolism and adenosine triphosphate (ATP) production, is a structural analog of glucose differing at the second carbon atom and appears to selectively accumulate in cancer cells by metabolic trapping and also has been best characterized in animal model studies and human clinical trials [13,17,19].

Through the glucose transporter, 2-DG enters the cell and phosphorylated by hexokinase to 2-deoxy-D-glucose-6-phosphate (2-DG-6-P) that is not a substrate for glucose-6-phosphate dehydrogenase or phosphohexoisomerase (2-DG-6-P is not further metabolized in the pentose cycle as well as incapable of metabolism to pyruvate) and therefore, the output from glycolysis and the pentose phosphate pathway gets diminished (Fig. 1) [13].

The previous study in mice model has shown that administration of 2-DG could be an effective way to inhibit glucose metabolism (lethal dose 50 ≥ 2 g/kg body weight and could be tolerable in humans when administered up to 200 mg/kg). Hence, using 2-DG in vivo may provide a very effectual addition to multi modality cancer therapies considered to improve radio- and chemosensitivity in human cancers [12,13].

In vivo study demonstrated that 2-DG significantly enhanced the anticancer activity and also toxicity of adriamycin and paclitaxel in mice bearing human osteosarcoma or non-small-cell lung cancer xenografts [20].

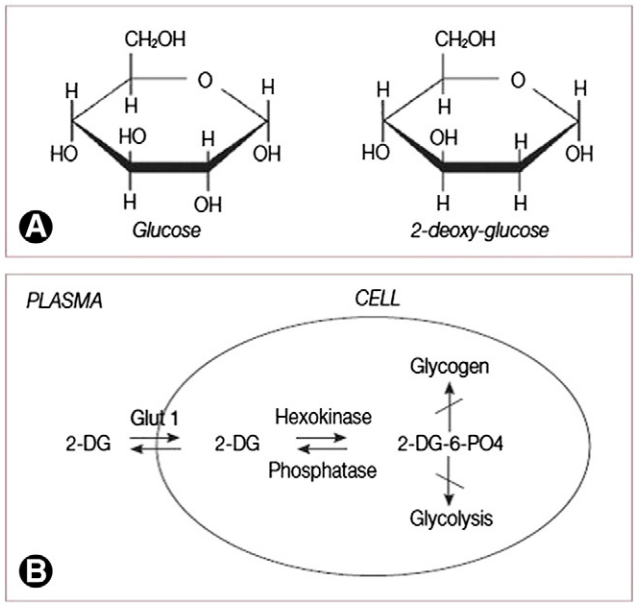

Fig. 1 – (A) Structural comparison of glucose and 2-deoxy-D-glucose (2-DG). 2-DG is a structural analog of glucose differing at the second carbon atom. (B) Schematic diagram of 2-DG action [13].

Another studies performed in glioblastoma multiform patients, phase I/II trials of oral 2DG in combination with radiation, demonstrated that oral administration of 2-DG combined with radiation enhanced tumor necrosis significantly and is safe. Furthermore, they have proved that this combination could be tolerated in glioblastoma patients without any acute toxicity and late radiation damage to the normal tissue brain and also the patients showed the modest survival benefits and improved quality of life [21,22]. However, progress beyond this has yet to be reported and although other trials are planned or underway results from these have not yet been forthcoming [23].

A recent in vitro study on esophagus cancer cell lines have shown that combination of 2DG and metformin (an inhibitor of cellular energy pathway), significantly reduces cell viability in a time-dependent manner [24]. Further, the combination effect of 2DG and metformin resulted in a meaningful increase in cell death compared to either agent alone, and also this combination significantly suppressed tumor growth in two xenograft models in vivo. These results suggested that the tumor cell bioenergetics can be targeted, and the combination of 2DG and metformin warrants further clinical evaluation [25].

In summary, comprehending the clinical benefit of blockade of the Warburg effect may require concomitant inhibition of multiple components of cellular energy pathways. A preemptive blockade of the Warburg effect and compensatory mechanisms may prove to be dominant over the survival and growth promoting effects of growth factors or activated oncogenes. 2-DG, as an inducer of metabolic stress, alone and in combination with other cytotoxic agents such as ionizing radiation and or metformin will be very useful in designing effective protocols in esophagus cancer