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Metabolic Changes in Colorectal Carcinomas: Prospects for Early Detection of Neoplastic Changes

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Abstract

The use of modern analytical techniques and nanotechnology in metabolomics have produced potential metabolomic biomarkers, giving insight into pathophysiological basis and changes, tumorigenesis and molecular mechanisms that underpin better therapeutic, monitoring and prognostic evaluations of malignant tumors of the colon. Thus, enabling early detections and characterization of malignant colon tumors that could reduce mortality and morbidity and mortality rates in colorectal carcinomas. Some metabolic profiling and changes are influenced by environmental factors and biological alterations including diet, lifestyle, medications and chronic diseases. Thus, modifiable risk factors could become targets for enhanced risk reduction. It is shown in this review that metabolic changes in colorectal carcinomas can be used in diagnosis, monitoring, therapy and prognosis of colorectal carcinomas.

Keywords: Metabolomics; Colorectal carcinomas; Metabolites; Early detection; Lifestyle modification

Introduction

The renewed attention given to metabolic processes related to malignant cells has steered a drive towards an understanding of metabolomic phenotyping in the histochemical pathology of cancer tissues. Neoplastic cells go through a series of metabolic transformation in order to maintain the rapid cell division, multiplication, and propagation [1]. The aftermath of this metamorphosis is that several and varied metabolic phenotypes emanate in the cancer cells which are quite dissimilar when compared with non-neoplastic cells. A comprehensive understanding of the natural science of tumour growth would be a mirage without identifying the gamut of metabolites and their diverse nature [2]. This information is vital and more so that it could also enable scientists advance techniques for cancer care while using these metabolites as diagnostic and prognostic markers. Colorectal carcinomas are malignant tumors of the colon [3]. Their growth involves production or increased production of some metabolites and/or dysregulation/ decreased production of some other metabolites. These metabolites cause metabolic changes through effects in general or specific metabolic processes occurring in the body [4]. The change in metabolic processes often produces deleterious effects. Estimation of the metabolites levels could serve as prognostic markers in colorectal carcinomas. Colorectal cancer remains frequently occurring cancer in the general population worldwide, among which sporadic colorectal cancer represents an estimated 70% of all newly diagnosed cases [5]. As it were, colorectal carcinoma emerges gradually *via* a persistent build-up of numerous abnormal alterations in tumor suppressor genes, oncogenes, and downstream metabolic pathway. Colon cells are designated with a definite outline in metabolic processes that confer on them characteristics which distinguish malignant from non-malignant tissues and delineate cancer types with respect to clinico-pathologic physiognomies and response to colorectal cancer-related interventions [6]. Colonoscopy in combination with histopathological examination is the current gold standard for diagnosis and staging of Colorectal Carcinomas (CRC). However, potential risks of complications and relatively poor sensitivity and specificity are the drawbacks of these techniques. Thus, the need for newer non-invasive methods focused on early detection of colorectal cancer [7]. This paper reviews the current status of colorectal cancer metabolic phenotypes and discusses the metabolomics changes involved in the transformation process in CRC with the view to redirecting focus on their use in the early detection of CRC. Scientists came to the realization that the solution to the problem associated with recognizing and categorizing metabolic phenotypes of CRC is 'metabolomics. Information for a narrative review obtained through search engines that included Pubmed, Google scholar and Research Gate [8].

Literature Review

Metabolic chemicals in colorectal cancer

It has been reported that a continuum of metabolic eccentricities associated with an initial remediable Colorectal Cancer (CRC) stage is pertinent for a successful and timely application of molecular diagnostic and therapeutic methodologies whose ultimate goal is to enhance quick recovery and advance the chances of survival. Some of these metabolites include [9]. Hypotaurine β-alanine, glutamate, kynurenine, cysteine, 2-aminobutyrate, palmitoleate, 5-oxoproline, aspartate hypoxanthine, lactate, myristate, glycerol, uracil, putrescine, my oinositol, spermidine, homocysteine, 4-aminobutyrate, asparagine, glycerate, nicotinamide, Adenosine Monophosphate (AMP) ascorbic acid, glucose, xylose, glycine, glyceraldehyde, ornithine, phosphate, laurate, galactose 3-methyl-3-hydroxybutyrate, methiotinamide and 2-aminoadipate [10].

Pathogenesis

Metabolic changes in colorectal carcinomas produce deleterious effects through increased generation of metabolites outlined above which cause inflammation, oxidative stress, angiogenesis and act as acute positive reactants. These features promote tumor growth and proliferation [11]. Metabolites that are reduced in concentrations are usually negative acute phase reactants and are anti-inflammatory and anti-oxidative. These get reduced through fighting inflammatory processes and clearing debris effects like necrosis. From aerobic respiratory processes to anaerobic processes in energy production, the metabolic changes that occur early in colorectal carcinomas tend to produce the Warburg effect [12]. Warburg effect is a survival mechanism in hypoxic situations where energy generation in highly proliferative cells shifts. From normal colon tissues to malignant ones. Glycolysis is enhanced but with shunting of pyruvic acid to lactic acid production instead of glyceraldehyde-3-phosphate and dihydroxy acetone phosphate, to enter the citric acid cycle and the electron transport chain which yields higher energy in form of Adenosine Triphosphate (ATP). This will cause metabolic acidosis from lactic acid [13]. Metabolic acidosis milieu stimulates more cancerous cells proliferation, producing a vicious cycle causing inflammation, necrosis and cell death. Overall, a lot of increased metabolites and decreased metabolites cause deleterious effects. There is increased shunting of glycolytic intermediates from entering the tricarboxylic acid cycle, to the pentose phosphate pathway with increased production of ribose-5-phosphate and reduced Nicotinamide Adenine Dinucleotide Phosphate (NADPH) which are used in Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA) and lipids (especially fatty acids) synthesis to meet needs of increased cellular proloferations [14]. Glucose is a reduced metabolite, and with shunting of glycolytic products to Cori cycle because of Warburg effect, there is increased fatty acids use to generate energy. Cancer cells exhibit metabolic phenotypes that are essential for sustaining high proliferative rates, and resist cell death signals associated with altered flux along key metabolic pathways, such as glycolysis and the citric acid cycle. Equally demonstrated in the Warburg effect, when aerobic glycolysis is augmented or amplified a number of events unfold [15].

Other changes that follow the Warburg Effect include distinguishing manifestations, transmutation, and post-translational modification of enzymes involved in a number of key metabolic pathways these events are due to the adaptation to oxidative stress associated with tumor hypoxia and mitochondrial mutations [16]. Therefore, metabolic regulation is connected to cancer advancement since multiplying is compactly delimited by the ease of use of nutrients. Moreover, proliferation-promoting oncogenes are affected, and conversely, are altered by metabolic changes. There are significantly higher levels of lactate in colorectal cancer samples compared with their non-tumor counterparts [17]. The gene encoding 4-Amino butyrate Amino Transferase (ABAT), which catalyzes the conversion of β-alanine to malonic semi-aldehyde, has higher expression in colorectal cancer tissues, suggesting that β-alanine is metabolized to malonic semi-aldehyde for subsequent fatty acid synthesis through malonyl-Co-enzyme-A (CoA). Taken together, the increased need for acetyl-CoA and malonyl-CoA in fatty acid synthesis may contribute to the increased production of β-alanine in colorectal cancer tissues [18].

The kynurenine pathway is a major metabolic pathway in tryptophan metabolism, which is first catalyzed by indoleamine 2, 3-Dioxygenase (IDO). Elevated expression of IDO is implicated as a mediator of tumor-related immune tolerance, which could shield tumor cells from immune attack. A substantial amplification in expression of the IDO gene is seen in colorectal cancer tissues, but absent in controls [19]. This exaggerated IDO expression results in the release of higher levels of kynurenine. The kynurenine pathway ultimately generates Nicotinamide Adenosine Dinucleotide (NAD) from tryptophan. An activated kynurenine pathway also generates additional NAD for the electron transport chain to cope with the profligate growth of tumor cells. These distinct metabolic signature metabolite markers, are applicable in predicting response to interventions in colorectal carcinoma patients [20]. There are metabolic aberrations identified at gene expression level that indicate a full-bodied metabolic variation due to a sustained and excessive cell multiplication in colorectal carcinoma. These metabolic adaptations seen in abnormal tissues show that beyond the Warburg effect, which addresses the enlarged ATP demand using a desirable glycolytic process; other metabolic changes responsible for maintenance of upgraded energy needs, macromolecular precursors, as well as the maintenance of redox balance under intense oxidative stress are present [21]. It has also been reported that colonic adenocarcinomas are richer in taurine, glutamate, aspartate, and lactate whereas healthy tissues contain a higher amount of myo-inositol and β-glucose. Reactive Oxygen Species (ROS), as by-products of cellular metabolism, are associated with the increased metabolic activities in tumor cells. Greater levels of ROS have been reported to be produced by several types of human tumor cells. Malignant tissue cells get transformed metabolically, and this makes them well-adapted to accelerated anabolic metabolism as well as elevated ROS levels during tumorigenesis. Glutamate, glycine, and cysteine are precursors of Glutathione (GSH) which

are also increased. There is a gamma glutamyl cycle that controls the production and breakdown of GSH, and an intermediate, 5-oxoproline, an important factor in the pathway, which is also significantly lower in non-malignant colon tissues in comparison to cancerous colon tissues. Ophthalmate is a biomarker for oxidative stress and reflects GSH depletion through gamma-glutamyl cysteine synthase activation [22]. Gamm-glutamyl cysteine synthase along with glutathione synthetase catalyze ophthalmate production, glutamate, glycine and 2-minobutyric acid. Glutathione synthetase and 2-aminobutyric acid are markedly raised in malignant colon tissues, which suggests increased ophthalmate synthase activities in colorectal cancer tissues. Also increased is 2-aminobutyric acid in epithelial ovarian carcinoma tissues compared with normal tissues of the ovary. Other enzymes elevated in malignant colon tumors include Glutathione S Transferase pi 1 (GSTP1), GSH Peroxidase 1 (GPX1), GSH reductase (GSR), and Gamma-Glutamylcyclotransferse (GGCT) compared with non-tumor controls [23].

Aminopeptidase N (ANPEP) is an enzyme that is reduced in glutathione metabolism. ANPEP facilitates the breakdown of cysteinylglycine to cysteine and glycine, and thus, cysteinylglycine levels are lower in colorectal cancer tissues when compared with those of the control tissues. The GSH redox cycle is also coupled with the NADP/NADPH transformation, which is needed in enhanced synthesis of fatty acids. An increased NADPH synthesis through the pentose phosphate pathway, increased levels of 5-oxoproline and 2-aminobutyric acid are also seen in malignant tumors of the colon. Increased oxidative stress is usually associated with increased production of fatty acids but also, there is elevation of metabolites involved in antioxidation processes [24]. Increased fatty acids production usually leads to accumulation of 3-hydroxybutyrate supporting the hypothesis of enhanced metabolic changes in tumor cells. Distinct metabolic markers are increasingly being evaluated for colorectal carcinomas and used in diagnosis, chemotherapy, monitoring and prognosis in the management of colorectal carcinomas. There are metabolic aberrations at the points where genes are expressed that indicate alterations in the metabolism of colorectal cancer cells showing features beyond Warburg effect that addresses only the amplified energy demand *via* an ideal glycolytic process, in providing support to the increased needs of energy, macromolecular precursors, and in redox balance homeostasis in the presence of intense oxidative stress. It has also been investigated that metabolic alterations that occur during tumorigenesis in colorectal cells show elevation in the amount and types of amino acids and lipids found in the polyps and tumors, indicating that there is a higher energy requirement during increased cellular proliferation. In contrast, significant glucose and inositol diminution in polyps demonstrates pivotal role played by glycolysis in the initial phase of neoplastic changes [25].

Discussion

In addition, the accumulation of hypoxanthine and xanthine, and the decrease of uric acid concentration, suggests that the purine biosynthesis pathway could have been substituted by the salvage pathway in CRC. They also found that lipid biomolecules, phosphates and several amino acids levels are elevated. On the contrary, glucose, uric acid and inositol levels are markedly reduced. Glutamate and proline are among the elevated amino acids that favour the hypothesis that increased proliferative growth of malignant tumor cells is facilitated by increased protein synthesis. There is increased transport of glutamine into cells for glutamate production through glutaminase. This occurs at a faster rate when compared to non-cancerous colorectal cells showing that increased rate of protein synthesis is vital to survival of malignant colorectal cells in these rapidly growing tumor cells. In addition, over expression of glutaminase favors the formation of glutamate in the tumor cells. The enzyme involved in purine catabolism which transforms hypoxanthine to xanthine, and then to uric acid is referred to as oxido-reductase, and it is well expressed in gastrointestinal epithelial cells. Nonetheless, this is decreased in gastrointestinal epithelial cells of malignant colorectal tumors. This is strongly correlated in the degree of expression in the size of tumor, level of tumor involvement, advanced stage and risk of metastasis. This observation is not unconnected with the fact that salvage pathway of purine nucleotides synthesis uses less ATP (i.e. less energy use) compared to the de novo purine nucleotides biosynthesis-metabolic change in which colorectal neoplastic cells effectively shunt purine bases to the salvage pathway and thereby getting growth advantage over non-malignant colorectal epithelial cells. Choline and phosphocholine levels are increased in malignant colorectal tumors. The increase is associated with new cell membrane synthesis to meet the need for membrane lipids due to accelerated cellular proliferation. Increased choline and phosphocholine synthesis is also correlated with increased inflammatory processes.

Fatty acids synthesis and fatty acid synthase as a target for tumour control

Fatty acids synthesis through generating metabolic processes produce building blocks used in cellular membranes synthesis required to meet fast growth turnover of malignant colorectal tumor cells which are also mainly used in membrane lipid composition, like choline and phosphocholine. The enzyme, Fatty Acid Synthase (FAS), involved in lipid synthesis, is highly expressed in malignant colon tumors and it has been observed that inhibition of FAS is associated with decreased angiogenesis in malignant colon tumors and metastatic processes to other organs like the lungs and liver indicating that inhibiting FAS may be a therapy target in management of cancers of the colon. The field of metabolomics is showing differences between non-malignant and malignant tissues through pathophysiological knowledge of tumor growth.

Conclusion

Metabolic changes in colorectal carcinomas result in production of metabolites that can be used in diagnosis, monitoring of therapy and prognosis in colorectal carcinomas patients. In this review, there are several metabolites that have

been evaluated and there are more still being evaluated for use in colorectal carcinomas diagnosis, therapy monitoring and prognosis evaluations. This involves metabolomics profiling and changes seen in healthy control persons correlated with diseased cases/patients. Some metabolic profiling and changes are influenced by environmental factors and biological alterations including diet, lifestyle, medications and chronic diseases. The use of modern analytical techniques and nanotechnology in metabolomics have produced potential metabolomics biomarkers, giving insight into pathophysiological basis and changes, tumorigenesis and molecular mechanisms that underpin better therapeutic, monitoring and prognostic evaluations of malignant tumors of the colon. Thus, enabling early detections and characterization of malignant colon tumors in order to reduce mortality and morbidity rates. Leucine, isoleucine and glutathione are elevated in all stages of colorectal carcinoma tumors. As metabolomics profile is affected not only by biological changes, but also by environmental exposure, more studies are needed in this field.

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