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CANCER CELL AND ITS ONCOMETABOLITES

R. Deepti*, S. Akila and L. Ramesh Bharathi

Departments of Biochemistry, Sri Muthukumaran Medical College, Thanikachellam Nagar, A Block, IInd Main Road, Ponniamman medu post, Chennai – 110, Tamil Nnadu, India.

ABSTRACT

Cancer is an deadly disease and for the past few decades research is going on to find out a effective treatment. Framing treatment for cancer was impossible because each type of cancer cell behaves and initiate the cancer in a different way compare to another type of cancer cell. In the globe, cancer is the second cause of death after cardiovascular disease. Cancer cells converts the metabolites into oncometabolites which plays an vital role in rapid proliferation of cells and also progression of the cancer. Tumor cells generates microenvironment around them. Microenvironment favours the cancer cells to invade the adjacent normal cells and also protects the cancer cells from the host cell immune response. Understanding the cancer biology helps the researchers to know about the activities of the cancer cells.

Key words: Oncometabolites, Microenviroment and Tumor.

INTRODUCTION

Cancer is one of the biggest and most researched cause of death around the globe. Cancer is a disease related to the uncontrolled rapid proliferation of cells and results in the abnormal functioning of the cells. Greek word "karkinos" is translated to Latin word "Cancer" and cancer is the most commonly used terminology [1-3].

When a normal cell does not function accordingly to these criteria's, it becomes a tumor cell.1, External growth factors are required for the cell division. Gene level influences of increased growth factors or decreased growth factors stimulates or inhibits the cell divisions in the normal cells respectively. 2, Normal cells shows contact inhibition. Cell division take places to fill up the adjacent gap and the cell division stops when the adjacent gap is filled up. 3, Normal cells age and senesce. Senescent cells are degraded by the process known as apoptosis. New cells are replaced in the place of senescent cells. 4, When there is a DNA damage or abnormal cell division, immediately normal cells will stop replicating and enter apoptosis process [4,5].

Tumor refers to the mass of abnormal cell growth(neoplasm). Tumor can be benign or malignant. Benign tumor proliferates at the site of origin and cannot migrate to the other parts of the body. Usually benign tumors are non cancerous tumor, so it is known as primary tumor. Malignant tumor proliferates at the site of origin and can migrate to the other parts of the body through metastasis. Malignant tumors are cancerous tumor, so it is referred as secondary cancer or metastatic cancer [6]. Metastasis mechanism involves the independent detach of cells from malignant tumor and migrates through lymphatic flow or blood circulation.

Tumors are classified depending on the cancer cell site of origin. Carcinomas – cancer origin site is epithelial cells, sarcomas – cancer originated at connective tissues and bones, leukaemia – malignant WBCs, lymphoma - cancer origin site is lymphatic cells and myelomas – cancer originated at bone marrow cells [7, 8]. In children, cancer progression is faster and more aggressive compared to cancer in adults [9]. There are more than 100 types of cancer. All types of cancer does not have similar salient characteristics. But all types of cancer have a common unique characteristic that causes loss of cell cycle control and rapid cell division. Cancer cells uses some specialised modes for survival and proliferating even during unfavourable conditions like nutrient scarcity, hypoxia, cancer treatments, host cell immune response, etc [10].

Cancer biology

In cancer cells, metabolisms are altered and specially some altered metabolisms are considered as

Corresponding Author :- **R. Deepti** Email:- deeptibob@gmail.com

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hallmark of the cancer. Altered metabolisms in cancer cells, provide a selective advantage during tumorigenesis. New metabolites or abnormally altered levels of metabolites in tumor cells is represented as oncometabolites [11].

Oncometabolites Of Cancer Cells

Generally cancer cells requires ATPs which provides energy for rapid cell growth and $NADPH^+$ to maintain the cancer cell redox capacity. Principle nutrients like glucose, non essential amino acid glutamine, citrate are utilized by the cancer cells to produce ATPs and $NADPH^+$. Cancer cells contain mutation at the gene level which causes the altered regulation of major carbohydrate metabolism, lipid metabolism, nucleotide metabolism and protein metabolism [12]. Mitochondria is a sub cellular organelle performs salient functions like energy productions, generates reactive oxygen species(ROS), regulation of cell signalling, cell death, biosynthetic metabolism, etc. Cancer cells take mitochondria under its control and due to this feature cancer cells are flexible to even survive in unfavourable conditions [13].

Cancer cells in nutrients abundant stage

when the cancer cells have abundant nutrients, cell synthesizes macromolecules like protein, non essential amino acids fatty acids, nucleotides. These are required to promote tumorigenesis [14].

Carbohydrate Metabolism

In many types of cancer, cells continues to uptake glucose and glucose is converted to lactate in the presence of abundant oxygen availability. This is called as Warburg effect. In proliferating cancer cells, increased glucose is converted to lactate to provide precursor molecules and reducing equivalents. From the precursor molecules, ribose 5 phosphates, NADPH, hexosamine, phospholipids, serine, tetrahydrofotate (THF), glycine are synthesized (Figure 1). Less glucose enters TCA cycle and generates less NADH and ATPs because increased NADH and ATP concentration is the inhibitor of glucose catabolism. Mitochondrial pyruvate carriers gene is suppressed by the cancer cells to limit the pyruvate uptake by the mitochondria [11-13].

Protein Metabolism

Proliferating cancer cells must synthesize non essential amino acids like glutamine, arginine, proline, etc by transamination reactions. Catabolism of glutamine leads to the generation of α ketoglutarate and non essential amino acids. α ketoglutarate enters TCA cycle for the production of ATPs. During synthesis of non essential amino acids, NADPH is also produced. NADPH is required for redox homeostasis in cancer cells [13].

Arginine – Its serves as a precursor for synthesis of polyamines, creatine, proline, etc. Increased arginine leads to increased polyamines production. Polyamines inhibits apoptosis and promotes tumor growth. Some studies shows increased polyamines levels in proliferating cancer cells. Elevated levels of polyamines are responsible for tumor invasion. Proline – In cancer cells, proline synthesised is up regulated. Proline contributes to collagen formation and this results in new extracellular deposition. Increased proline levels facilitates the tumor invasion [15].

Nucleotides Metabolism

Purine and pyrimidine biosynthesis are stimulated in the cancer cells. Glucose 6 phosphate acts as precursor for nucleotides synthesis. Glucose 6 phosphate enters HMP shunt pathway to produce ribose 5 phosphate. Ribose 5 phosphate is channelled to phosphoribosyl pyrophosphate(PRPP) formation and this is the committed step in the nucleotide biosynthesis. TCA cycle intermediates are transaminated to amino acids like aspartate and glutamate. These amino acids are the substrate for purine and pyrimidine rings formation [16]. In cancer cells, Myc gene is mutated and this genes up regulates the PRPP synthase and carbamoyl phosphate synthase II. These enzymes are responsible for the increased synthesis of purine and pyrimidine respectively [12].

Lipid Metabolism

Most of the cancers, up regulate the lipogenesis to produce cell membranes during rapid proliferations. Citrate is channelled to acetyl CoA formation and acetyl CoA is the precursor for fatty acid synthesis. One carbon and redox metabolism also speeds up in cancer cells because these metabolism also plays vital role in lipogenesis.[16,13] In some cancer cells, tumorigenesis is associated with dramatically increase in cholesterol production. Malonyl CoA is utilized for cholesterol synthesis [17].

Cancer cells in nutrients deprivation stage

Cancer cells often encounters crisis like nutrients scarcity and hypoxia due to increased rate of consumption. Cancer cells in nutrient deprivation state will make sure TCA cycle functions and adequate amount of ATPs are produced. ATPs are required for the survival of cancer cells [11, 12].

Carbohydrate Metabolism

In this stage, many studies had reported that majority of tumor cells dependent on energy produced by complete oxidation of glucose through TCA cycle. Glucose is converted to pyruvate and pyruvate is channelled to TCA cycle as acetyl CoA. TCA cycle provides the energy resource ATPs.

Protein Metabolism

Cancer cells causes protein degradation to resupply the intermediates of TCA cycle. Glutamine is major amino acid which is responsible for the generation of TCA cycle intermediates by glutaminolysis. In

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glutamine deprivation state, aspartate plays an crucial role in maintaining the integrity of TCA cycle intermediates. Branched chain amino acids are degradated to succinyl CoA and succinyl CoA enters TCA cycle to produce ATPs [18]. In extreme nutrient scarcity, cancer cells stimulates the following processes,

- Lysosomal degradation of extracellular proteins by macropinocytosis and results in amino acids generation.
- Digestion of entire living cells through entosis process
- Phagocytosis of apoptotic body. All these process provides free amino acids. Amino acids are converted into the intermediates of TCA cycle and enters TCA cycle to provide ATPs. This situation is sufficient for the cancer cells to survive and proliferate [12].

Lipid Metabolism

Fatty acid oxidation is up regulated by the cancer cells to provide acetyl CoA. Acetyl CoA is channelled into TCA cycle to generate ATPs. In hypoxia condition, lysophospholipids are required for maximal growth of cancer cells [11]. This condition leads to the suppression of biosynthetic reactions which requires oxygen for its activity. Extracellular liberation of free fatty acids from compex lipids are increased due to the over expression of gene responsible for the lipoprotein lipase. Cancer cells induce the neighbour normal cells to release the stored lipids. Cancer cells can even proliferate in a nutrient deprivation state for longer period through autophagy. Autophagy results in liberation of free amino acids and free fatty acids and these are utilized by the cancer cells [19].

Nucleotide Metabolism

Even in the nutrient scarcity condition, cancer cells will continue synthesizing purine and pyrimdine nucleotides for the rapid cell proliferation process.[12]

Cancer Cells And Its Microenvironment

Cancer cells and its microenvironment combines together to create a complex cellular system and this system contributes to the tumor progression exclusively in metastasis. Stephen paget proposed a seed and soil hypothesis. This hypothesis denotes seed as cancer cells and soil as tumor microenvironment. Cancer cells has advantage over its microenvironment in the progression of cancer to the next stage. Microenvironment of cancer cells are related to acidosis condition, high interstitial fluid pressure, angiogenesis, hypoxia, extracellular matrix stiffness, etc [20].

Acidosis

In cancer cells, glucose is converted to lactate and accumulation of lactate inside the cells leads to the influx of lactate into the extracellular space(ECS). Increased levels of lactate stimulate hyaluronic acid production by fibroblasts. This contributes to tumor invasion. Increased accumulation of lactate, hydrogen ions($H^{+)}$ and carbon dioxide in the ECS results in acidification of the cellular microenvironment. Acidification in ECS stimulates the metalloproteinase and cathepsins. These enzymes promotes the degradation of the extracellular components and enhances tumor invasion [21-23].

Immune permissive microenvironment

Some tumors employs a immune permissive microenvironment around them. Solid tumors over expresses the tryptophan degradation enzymes and converts essential amino acid tryptophan to kynurenine. As a consequence, tryptophan depletion triggers amino acid deprivation which leads to the apoptosis of effector T cells. This situation contributes to the suppression of host cells antitumor immune response. Increased accumulation of kynurenine acts as a ligand for aryl hydrocarbon receptor(AhR) and promoting degradation of the extracellular components and invasion [24-25].

Angiogenesis

Due to uncontrolled cell division, tumor enlarges the blood vessels can not reach to the cells present in the central part of the tumor and therefore nutrients, oxygen can not be supplied to these tumor cells tumor overcome this crisis by angiogenesis. Tumor cells synthesizes the angiogenic factors which contributes for the formation of new capillary blood vessels. These vessels supplies the oxygen and nutrients to the cells in the center of the tumor. Angiogenic cells in tumor give rise to malignant tumor. Several studies have reported that angiogenic cells population increases as the size of the tumor increases. Angiogensis is the main criteria for the progression of dormant tumors to malignant tumors. Oncogenes increases the expression of genes that code for the angiogenic factors in the cancer cells [26,27].

Reactive oxygen species

Reactive oxygen species(ROS) are intracellular chemical species containing oxygen, superoxide anion, hydrogen peroxide and hydroxyl radicals. Moderate levels of ROS have beneficial functions in normal cells like cellular signalling, positive regulation of cell proliferation and cellular adaptation to metabolic stress. In cancer cells, ROS moderate levels can support cancer cells proliferation. Increased levels of ROS can cause cancer progression (Figure 2). Solid tumors maintains ROS levels within the limits, so that ROS levels stimulates the cell proliferation without causing cell damage [28, 29]. In cancer cells, oncogene induced cellular senescence can also occur due to the electron transport chain overload and results in increased ROS production. Increased ROS levels stimulates transcription factors which contributes to the tumorigenesis progression.

Hypoxia

Hypoxia is commonly related with the tumor cells. Hypoxia in cancer cells causes over expression of

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hypoxia inducible factor 1(HIF1) which inturn switch on the upregulation of genes responsible for angiogenic factors. Hypoxia is a salient factor in the metastasis process [27].

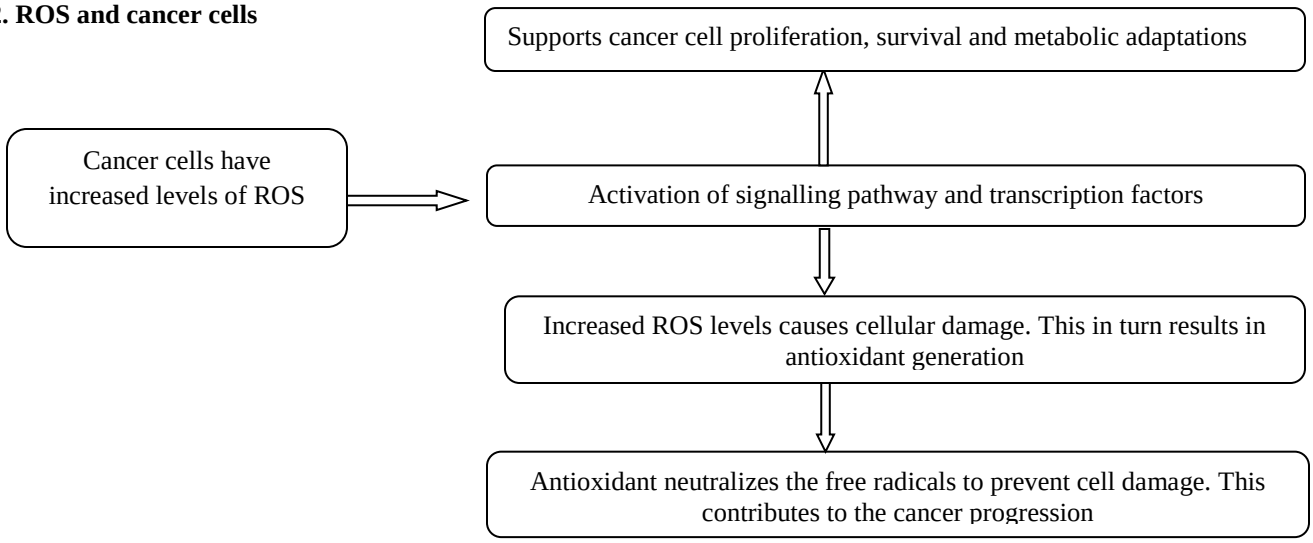
Extracellular matrix stiffness

Two key factors lysyl oxidase and integrins influences the extracellular matrix stiffness. Integrins present in the extracellular space increases the deposition of collagen and fibronectin. This situation is favourable for the cancer cells to invade the nearby cells and progression of cancer [30]. Lysyl oxidase is the major component of the supportive tissues. Cancer cells causes high levels of this enzyme and contributes to increased fibrous collagen formation which results in stiffness. Extracellular matrix stiffness activates oncogenic intracellular signalling, over expression of growth promoting genes and inhibits tumor suppressor genes. Marta cavo et al study has shown that in breast cancer cells lysyl oxidase promotes metastasis [31]. Hence these key factors leads to increased stiffness and inturn contributing to the cell invasion and cancer progression from begnin tumor to malignant tumor [32].

Fig 1. Precursor molecules and its derivatives

Glucose catabolism & precursors	Derivatives	Significances
Glucose → Glucose 6 phosphate	Ribose 5 Phosphate + NADPH	Cancer cells over expresses transketolase & transaldolase. This leads to up regulation of HMP shunt pathway. R5P is involved in nucleotide synthesis. NADPH maintain the redox capacity.
Fructose 6 phosphate	Hexosamine Biosynthesis	This pathway provides heparin sulphate and hyaluronic acid. These contributes to tumor invasion.
Dihydroxy acetone Phosphate	Glycerol 3 phosphate	In cancer cells G3P is utilized in phospholipids synthesis. Phospholipids are structural component of cell membrane. In proliferating cancer cells, rapid production of cell membrane occurs.
3 Phosphoglycerate → Pyruvate → Lactate	Serine / glycine / One carbon Molecules synthesis	Glycine and serine generates methyl donors and NADPH. Methyl donors are involved in transmethylation reactions. NADPH maintains the redox capacity in cancer cells. THF is used in thymidine synthesis and also participates in transmethylation reactions.

Fig 2. ROS and cancer cells



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CONCLUSION

Highlights of oncometabolites in the cancer cells serves as a bridge between cancer biology and therapeutic treatment in the field of oncology.

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CONFLICT OF INTEREST

No interest

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