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Role of fatty acid in metabolism of oral cancer – A biochemical perspective

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Abstract

Cancer cells are often exposed to a metabolically challenging environment with scarce availability of oxygen and nutrients. This metabolic stress leads to changes in the balance between the endogenous synthesis and exogenous uptake of fatty acids, which are needed by cells for membrane biogenesis, energy production and protein modification.

Squamous cell carcinoma of the oral cavity mucosa grows under conditions of poor oxygenation and nutrient scarcity.

Reprogramming of lipid biosynthesis accompanies tumour growth, but the conditions under which it occurs are not fully understood. Alterations in lipid metabolism and, consequently, lipid composition have important therapeutic implications, as they affect the survival, membrane dynamics and therapy response of cancer cells.

In this article, we provide an overview of recent insights into the regulation of lipid metabolism in cancer cells under metabolic stress and discuss how this metabolic adaptation helps cancer cells thrive in a harsh tumour microenvironment.

Keywords: Fatty Acid, Tumour, Lipid, Metastasis

Introduction

In the course of cancer pathogenesis, normal cells progressively acquire a sequence of biological abilities, known as the hallmarks of cancer, which comprise the six established hallmarks of sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. There are also two emerging hallmarks, namely the programming of energy metabolism and evading immune destruction[1].

In order to meet the needs of biosynthesis during high levels of proliferation, the reprogramming of fatty acid (FA) metabolism becomes essential in cancer cells. At present, a number of previous studies have investigated the effects of cancer on fatty acid metabolism during progression, demonstrating the increased de novo biogenesis and β-oxidation of FAs in these transformed cells. However, whether this influence is unilateral remains to be fully elucidated[2].

In the present review, evidence regarding the contribution of the change in fatty acids in cells during

the acquisition and development of the hallmarks of cancer is discussed.

In addition, the review provides a comprehensive insight into the underlying roles of fatty acids in tumour genesis that go beyond their function in membrane phospholipid synthesis, signal transduction and energy production.

Due to the diversity of cancer phenotypes and limitations of existing evidence, results on the associations may not be universal. However, the aim of the present review was to provide a diverse perspective in order to obtain a better understanding of the pathogenesis of cancer and to highlight potential novel treatment targets and therapies.

Fatty acid metabolism and angiogenesis

The induction of angiogenesis, including the sprouting of existing blood vessels and tubular arrangement of endothelial cells (ECs), is crucial for metastatic spread and for primary and metastatic tumour growth.

The overstimulation of angiogenic growth by induced signals in tumour progression results in various tumour vasculature abnormalities, which in turn induces hypoxia, nutrient deficiency, reduced drug delivery, and more aggressive tumour growth; this forms a vicious circle of event[3,4].

Tumour angiogenesis has long been recognised as an important target for anticancer therapy, and evaluation from the perspective of fatty acid metabolism is an interesting area to evaluate first.

Fatty Acid Synthase (FASN), an enzyme associated with the endogenous synthesis of palmitic acid, is overexpressed in various types of human cancer, and its expression level is associated with prognosis and invasion depth. Increased knowledge of its connection with angiogenesis is gradually being obtained.

Fatty Acid Synthase can affect the expression of a series of vasculogenesis-related factors, including promotive growth-regulated protein family members, angiogenin and interleukin (IL)-6, and suppressants tissue inhibitor of metalloproteinase-1 (TIMP-1) and tissue inhibitor of TIMP-2[5,6].

The significant impact of Fatty Acid Synthase inhibitors on angiogenesis has also been demonstrated in previous studies; by inhibiting the proliferation of ECs, they induce the inhibitory effect of angiogenesis[7].

The role of another factor closely associated with angiogenesis, Fatty Acid oxidation (FAO), is gradually being elucidated. During vessel sprouting, Fatty Acid Oxidation is involved in the growth and differentiation of vascular Endothelial Cells [8,9,10]

Fatty Acid-binding protein (FABP), an intracellular fatty acid carrier protein, has also been observed to correlate with this hallmark of cancer. Elmasri et al identified that Fatty Acid Binding Protein was closely associated with the proliferation and migration of Endothelial cells, in addition to vessel sprouting[11].

These results are indicative of an important association between Fatty acid metabolism and angiogenesis; they provide a basis for novel potential therapeutic strategies for targeting angiogenesis in cancer at different stages.

Fatty acid metabolism in invasion and metastasis

Several types of cancer gradually obtain the characteristics of invasion and metastasis with deterioration, an ability that is associated with the development and poor prognosis of cancer. Through an invasion-metastasis cascade, cancer cells infiltrate nearby blood vessels and lymphatic ducts, or are transferred to distant tissues[12].

During this progression, an important mode is epithelial-mesenchymal transition (EMT). Through this process, cancer cells reverse to an undifferentiated state and

possess the abilities of invasion, transmission and resistance to apoptosis.

In this reversible process, the majority of enzymes associated with these epigenetic modifications require the involvement of cofactors including acetyl coenzyme A (acetyl-CoA), the intermediate products in FA metabolism, which causes EMT to become susceptible to the changing intracellular metabolite levels.

FA transporter [FAT; also known as cluster of differentiation (CD)-36], a membrane glycoprotein involved in transporting FAs, provides certain groups of cancer cells with unique metastasis-initiating potential and, particularly in human squamous cell carcinoma[13].

CD36 has been identified as the inducer of distant metastasis. CD36 is also involved with poor, long-term outcomes in several types of cancer, including melanoma and breast carcinoma, due to its prometastatic characteristics.

CD36 also compromises the development of metastasis. A previous study suggested that inhibiting CD36 using neutralising antibodies resulted in a decrease in metastasis in mice with deficient immune systems. Furthermore, the induction of EMT requires complex remodelling of cellular lipid composition in order to alter the membrane fluidity required for cell migration, thereby highlighting the possibility of targeting membrane fluidity for the suppression of metastasis[14,15]

Fatty acid metabolism and resisting cell death

Apoptosis. A mechanism that maintains homeostasis through programmed cell death controlled by genes, has long been considered the biggest challenge in the onset of cancer since it was first suggested by Kerr et al in 1972.

With regulation of different B-cell lymphoma 2 (Bcl-2) members, cells can initiate this program in response to DNA damage and insufficient growth factors.

Correspondingly, cancer evades this cell death mechanism via p53 deletion, thereby lowering the expression of pro-apoptotic factors or increasing the expression of anti-apoptotic factors and survival signals.

FA metabolism is also involved in this transformation[16,17]

In addition, as expected, successful FAO is associated with the anti-apoptotic ability of cancer. Samudio et al revealed that human leukemia cells with inhibited FAO were more susceptible to apoptosis induced by ABT-737, an activator of Bcl-2, resulting from the fact that FAO acts as a regulator of Bcl-2 antagonist/killer 1-dependent mitochondrial permeability[18].

Autophagy, an important form of cell death, is a self-digestive process in which intracellular organelles or proteins are degraded in order to meet the needs of cell metabolism or the reprogramming of certain organelles.

However, the role of autophagy in the development of tumours is complex and multifaceted. At present, autophagy is considered to function as a tumour suppressive process in the early stages of tumourogenesis by eliminating cytotoxic substrates, however, it also contributes to tumour cell resistance to apoptosis under energy stress conditions in established tumour autophagy.

The triggering mechanism of autophagy in tumours is complicated, and FA metabolism is involved in this process. As important products in FA synthesis, the accumulation of palmitic acids in cells can trigger autophagy through lipotoxic effects via the mammalian target of rapamycin (mTOR)-independent signaling pathway[19,20]

Fatty acid metabolism and avoiding immune destruction

The immune system is considered to be the greatest challenge for tumours to overcome in order to develop. The well-established theory of immune surveillance states that, through constant examination, the immune system is responsible for the recognition and elimination of nascent transformed cells via various means of monitoring, which is vital for prevention of the emergence, development and metastasis of cancer.

However, through immunoediting processes, in which weak immunogenic tumour cells are allowed to evade and undergo further expansion while the immune system inhibits tumour growth, or the absence or inhibition of a link in the immune system, this mechanism is avoided and solid tumours form. In this process, FA metabolism leads to the promotion of immune evasion through effects in different sites[21].

Alterations in FAs are also closely associated with the sensitivity of cancer cells to immune system-induced cell death. In humoral immunity, regulation of the biosynthesis of cell membrane FAs and lipids can affect the sensitivity of tumour cells to antibody-mediated lysis[21].

In addition, immunity against the cytotoxicity mediated by natural killer cells can be enhanced by an increase in oleic acid and linoleic acid in the membrane of HCC cells[22].

Macrophages, including tumour-prohibitive M1 type and tumour-promoting M2 type macrophages, are involved in the phagocytosis, antigen presentation and the secretion of cytokines and are important parts of the immune system. The M2 polarization of tumour-associated macrophages, an immunosuppressive phenotype, is known to be associated with an increase in FAO[23].

Fatty acid metabolism and enabling replicative immortality

In the ongoing replication process, the telomere length of normal cells gradually reduces and aging or cell death can be induced to a certain extent. Therefore, for the majority of cancer cells, this mechanism requires avoidance in order to permit infinite reproduction.

In the regulation of the appearance of the senescence state, the formation and activity of telomerase is the most promising method. During this progression, FAs are directly or indirectly involved in the emergence of this important hallmark

Cellular aging, an irreversible state in which the physiological function and proliferation and differentiation abilities gradually decline, is an important obstacle that requires avoidance by tumour cells in order to survive. Previous studies have suggested that the appearance of senescence is closely associated with the de novo synthesis and desaturation of FAs.

The inhibition of FASN and SCD1, induced by telomere shortening and the subsequent activation of P53, results in increased levels of palmitic acid, reduced levels of monounsaturated FAs and phospholipids, and the induction of senescence[24,25].

Therefore, it is hypothesised that the modification of FA metabolism is vital in the aging process. In addition, carnitine palmitoyl transferase 1C, an enzyme associated with the transportation and oxidation of FAs, is also associated with proliferation and senescence; therefore, altering the metabolism of FAs to delay or eliminate cell aging is beneficial for cancer progression[26].

Furthermore, oleic acid, a monounsaturated FA, can competitively inhibit telomerase activity through its

specific structure and molecular length. The ability to duplicate without limit is essential for tumour development. Therefore, regulating FA metabolism or using unsaturated FAs to treat a wide variety of solid tumours and malignancies may be an effective strategy.

Fatty acid metabolism and sustaining proliferative signaling

The maintenance of proliferative signaling is a prerequisite for the formation, development and deterioration of tumours. Intracellular or extracellular ligands activate a sequence of signaling pathways, including the mitogen-activated protein kinase (MAPK) kinase/extracellular signal-regulated kinase (ERK) or phosphoinositide 3 kinase (PI3K)/protein kinase B (Akt)/mTOR signaling pathways, to have a regulatory function in the proliferation of transformed cells, mainly via the regulation of cell cycle.

The pharmacological inhibition of FASN has also been confirmed to be closely associated with pro-proliferative pathways. In addition, most notably, the antiproliferative effects of omega-3 FAs are also as a result of the regulation of cell cycle[27,28].

Fatty acid metabolism and evading growth suppressors

In the process of tumour progression, in order to combat potent negative regulators, tumour cells must obtain the ability to evade growth inhibitive factors, which are mainly composed of proteins encoded by tumour suppressor genes, the inhibition mechanism and TGF signaling pathways.

Through the absence of associated gene expression or the destruction of inhibitory programs, tumours are able to evade the reactions that are responsible for the response to internal and external signals and the subsequent regulation of proliferation, senescence and apoptosis[2].

P53 protein, which is expressed by the p53 gene, is an important established tumour suppressor and is an important growth inhibitive factor as it functions as a regulator of transcription and the cell cycle; the loss of expression or mutations in P53 are known to contribute to the development of several types of cancer[29].

Therefore, p53 is able to regulate lipid metabolism and respond to stressors.

Fatty acid metabolism and the tumour microenvironment

The tumour microenvironment is important for transformed cells. The effect of the microenvironment on tumour metabolism is an important factor to consider. Hypoxia, inflammation, and the metabolism of adjacent cells can affect the occurrence and development of cancer. In this process, FA metabolism is synergistically or negatively involved in the interactions between tumours and the microenvironment[30].

Hypoxia. Due to the rapid growth of cancer cells and uncontrolled angiogenesis, hypoxia represents a significant environmental state. Furuta et al demonstrated that hypoxia upregulates the expression of SREBP-1, an important transcription factor in the anabolism of FAs, which in turn promotes breast cancer progression. The inhibition of hypoxia in FAO also facilitates the survival, proliferation and metastasis of cancer cells[31].

Inflammation. Cancer-associated inflammation, which is usually caused by the necrosis of tumour cells or oncogenic changes and the subsequent chronic stimulation induced by immune cells, is a favorable environment for the growth or malignant transformation of tumour cells; tumour cells are also able to tolerate cell

necrosis for the increase in growth factors during the immune response. The production of mediators that contribute to inflammation are also associated with the metabolism of FAs[31]

Stromal cells. Cancer progression is associated with interactions between stromal and cancer cells. As an important part of the tumour microenvironment, stromal cells promote the proliferation and invasion of cancer cells by providing metabolic substrates or signaling molecules.

A previous study on colon cancer revealed that transformed cells are able to absorb the FFAs released by surrounding adipocytes to activate FAO and autophagy in order to facilitate cancer development Similar auxo-action has been confirmed in ovarian cancer (90). In addition, in terms of the changing modalities, exosomes derived from adipocytes are considered to be associated with the invasion of melanoma through FAO [32]

Potential drug targets in cancer therapy

Targeting abnormal tumour metabolism is an attractive potential avenue for future direct medicines. Due the importance of FA metabolism in protein modification, the synthesis of the cell membrane and the localization of oncogenic molecules, pharmacological inhibitors that target the key enzymes in these processes may be effective in future therapies.

The early generation of FASN inhibitors, including cerulenin and C75, are limited in their application, despite their confirmed induction of apoptosis in cancer cells, due to side effects associated with weight and appetite[33].

As an anti-obesity drug, orlistat has also been shown to exert inhibitory effects on lipid metabolism and a certain degree of tumour suppression; however, its poor selectivity and membrane permeability prevent it from being an ideal antineoplastic agent clinically. In addition, several novel generations of molecules targeting FASN, including GSK837149A, TVB2640, and plant-derived polyphenols, are currently in development; among these, TVB2640 has now moved into the human trials phase. Therefore, the accurate and efficient inhibition of tumour lipid metabolism offers promise as a novel therapeutic strategy[34].

Conclusion

The previous few decades of experimental results have indicated that cancer is similar to a metabolic disease that involves disordered energy metabolism in tumour cells. The abnormal metabolism of FAs is known to be crucial in cancer biology and pathology[35,36,37].

In general, any limitations on the essential capabilities of cancer cells can have an inhibitory effect on tumourigenesis and tumour progression. However, due to the diversity of cancer types and characteristics, the same therapeutic method tends to have different effects between different types of cancer.

Further investigations are required on the association between FA metabolism and the various hallmarks of different types of cancer in order to determine the angiogenesis tendency or how cancer invasion and metastasis is facilitated. Targeting the corresponding intermediate products of a signaling pathway may have a good response, which in turn may highlight novel strategies and potential therapies[38].

This targeted treatment is likely to be more effective and have fewer toxic side effects towards normal tissues, therefore, non-toxic metabolic therapy may become the primary method for treating cancer in the future. Furthermore, due to the correlation between FAs and cancer, other sources of FAs, including dietary habits,

obesity and hyper lipidaemia, also require consideration in addition to the regulation of metabolic processes[39,40].

In future precision medicine, FA metabolism offers significant potential. However, due to the diversity of tumour types, the flexibility of tumour metabolism and complex interactions in the tumour microenvironment, drugs or therapies that may be effective and appropriate for clinical treatments require further verification.

Abbreviations

FA - Fatty Acid

FASN - Fatty Acid Synthase

VEGF - Vascular Endothelial Growth Factor

VEGFR2 -Vascular Endothelial Growth Factor Receptor 2

FAO - Fatty Acid Oxidation

ECs - Endothelial Cells

CPT1 - Carnitine Palmitoyl Transferase 1

PGE2 - Phenyl Glycidyl Ether 2

FABP - Fatty Acid-Binding Protein

PPARγ - Peroxisome Proliferator Activated Receptor γ

EMT - Epithelial-Mesenchymal Transition

Acetyl-CoA - Acetyl coenzyme A

FAT - Fatty Acid Transporter

FFA - Free Fatty Acid

SCD1 - Stearoyl-CoA Desaturase-1

ACS - Acetyl-CoA Synthase

HCC – Hepato Cellular Carcinoma

27HC - 27-Hydroxy Cholesterol

LXR - Liver X Receptor

PUFAs – Poly Unsaturated Fatty Acids

TIMP1 - Tissue Inhibitor of Metallo Proteinase-1

TGF - Transforming Growth Factor

FAK - Focal Adhesion Kinase

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