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EDITORIAL

Functions of metabolic enzymes in the development of non-small cell lung cancer

Lung cancer is the leading cause of cancer death globally.[1] Non-small cell lung cancer (NSCLC), the most common lung cancer, is known to have various genetic and metabolic alterations, which directly contribute to growth and malignancy.[2,3] Although there are several targeted NSCLC treatments including the epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), anaplastic lymphoma kinase (ALK) inhibitors and several antibodies, the effects of NSCLC treatments remain unsatisfactory.[4–6]

Cancer metabolism is an emerging source of novel targets for NSCLC treatment, as it is now regarded as one of the hallmarks of cancer.[7,8] Cancer cells alter their metabolism in order to facilitate proliferation, migration and survival in the tumor microenvironment.[9] Metabolic enzymes carry out a wide range of catalytic activities and are responsible for a variety of cellular functions necessary for cancer survival. A growing body of evidence indicates that metabolic enzymes possess both metabolic and non-metabolic activities that are critical in the development of NSCLC.[10,11]

NSCLC undergo metabolic reprogramming by dysregulating metabolic enzymes

Glycolysis

In the early twentieth century, Otto Warburg observed that that tumor cells depend solely on glycolysis for energy production, even with an ample quantity of oxygen.[12] This phenomenon is now known as the Warburg effect. Marked progress has been made in understanding the molecular mechanisms leading to constitutive upregulation of glycolysis in NSCLC. Various glycolytic enzymes are often increased in this cancer type. For example, hexokinase (HK, the enzyme that converts glucose to glucose 6-phosphate), has been identified to be upregulated in NSCLC.[13] Phosphofructokinase (PFK, the enzyme that catalyzes the rate limiting step of glycolysis), is involved in transcription regulation, and its expression is often upregulated in NSCLC cells.[14] Subsequently, the well-known classic glycolytic enzyme, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has been demonstrated to be overexpressed in NSCLC patients.[15] Another critical regulator of glycolysis is pyruvate kinase (PK, the enzyme which catalyzes the irreversible phosphoryl group transfer from phosphoenolpyruvate to pyruvate, yielding pyruvate and ATP), appears to be involved in cancer. Previous studies have demonstrated that the type M2 isoform (PKM2) activity is higher in patients with NSCLC than in healthy subjects.[16]

Tricarboxylic acid (TCA) cycle

The tricarboxylic acid (TCA) cycle is a central hub for energy metabolism. It fulfills the bioenergetic, biosynthetic, and redox balance requirements of cells. Even a minor alteration in TCA cycle markedly influences energy production. Mutations in genes that encode enzymes isocitrate dehydrogenase (IDH)[17] and succinate dehydrogenase (SDH)[18] may lead to NSCLC. Fumarate hydratase (FH) is the enzyme that converts fumarate to malate. Previous survival analysis indicated that FH: rs1414493 was the primary risk factor contributing to overall survival of NSCLC patients.[19]

Pentose phosphate pathway (PPP)

The pentose phosphate pathway (PPP) is the major catabolic pathway of glucose for nucleotide synthesis in cancer cells.[20] Through this pathway, cancer cells produce large quantities of ribose-5 phosphate and glyceraldehyde-3-phosphate dehydrogenase (NAPDH). The activation of PPP is a common hallmark of tumor cells.[21] The 6-phosphogluconolactone hydrolase irreversibly hydrolyzes 6-phosphogluconolactone into 6-phosphogluconate (6PG). 6PG is then oxidatively decarboxylated by 6-phosphogluconate dehydrogenase (6PGD), leading to the synthesis of ribulose-5-phosphate (Ru5P), CO_2 and a second molecule of NADPH. Upregulation of 6PGD activity has been identified in NSCLC.[22]

Amino acid metabolism

Amino acids are essential for cancer cell proliferation. Even a slight alteration in the biosynthetic pathways may have an impact on amino acid synthesis. Cancer cells are characterized by glutamine addiction. Glutamine catabolism or glutaminolysis is elevated in NSCLC.[23] Emerging evidence indicates the role of glutamate and glutamate receptors in NSCLC cell lines A549 and SK-LU-1.[24] Glycine is a significant constituent of proteins in the body, which build tissues and organs. Glycine metabolism has also been demonstrated to be upregulated in NSCLC.[25] Another important nonessential amino acid that participates in nucleotide synthesis is serine which has been shown to be upregulated in NSCLC.[26]

Lipid metabolism

Over the past decade, the increased rate of lipid metabolism in cancer cells is being recognized as one of the prominent hallmarks of cancer. Cancer cells demonstrate a high dependence on lipids.[27] One of the enzymes involved in the synthesis of de novo fatty acids is ATP citrate lyase (ACLY). In human NSCLC samples, ACLY activity was found to be significantly higher than in normal lung tissue, suggesting that ACLY is involved in NSCLC pathogenesis associated with metabolic abnormality and might offer a novel therapeutic target.[28] Acetyl-CoA carboxylase (ACC) is the rate-limiting enzyme in fatty acid synthesis. Genetic and pharmacological evidence have shown that ACC is required to maintain de novo fatty acid synthesis needed for growth and viability of NSCLC.[29] Fatty acid synthase (FAS), the enzyme that catalyzes the final step in fatty acid synthesis, is often upregulated in NSCLC[30] and increased FAS activity in NSCLC tissue is a predictor of patient survival.[31]

Metabolic enzymes possess nonmetabolic activities critical in development of NSCLC

Metabolic enzymes promote development of NSCLC by using nonmetabolites as substrates to catalyze reactions

Recent studies have determined that some enzymes, originally classified as metabolic enzymes, possess nonmetabolic activities that are critical in the development of cancer,[11] such as gene transcription and epigenetic regulation.[32] Some of them were found to use proteins as substrates and function as protein kinases to phosphorylate these protein substrates, thereby regulating diverse functions in many types of cancer include NSCLC.[33] For example, PKM2 is involved in histone H3 phosphorylation in the nucleus promoting the cancer cell proliferation in NSCLC.[34] It can bind to Bub3 (a spindle checkpoint protein) and phosphorylate it at Tyr207 enabling the interaction of the Bub3-Bub1 complex with kinetochores, which is necessary for the mitotic checkpoint and tumorigenesis.[35] Moreover, FH localized in the nucleus promotes driver gene-mediated transcription by inhibiting H3K36me2 demethylation, and thereby promotes the proliferation of NSCLC cells.[36]

Metabolic enzymes regulate the cellular activities of NSCLC via their metabolite products

Metabolic enzymes can form complexes with other proteins and regulate the function of these proteins through their metabolites. Acetyl-CoA synthetase 2 (ACSS2) is a nonmitochondrial source of acetyl-CoA that localizes in the cytosol and nucleus, and catalyzes the attachment of acetic acid to CoA from exogenous and recirculating histone deacetylase reactions to produce acetyl-CoA.[37,38] In response to hypoxia, the conditions common in the tumor microenvironment, ACSS2 translocate to the nucleus, where it forms a complex with the transcription factor EB (TFEB) and locally produces acetyl-CoA for histone H3 acetylation in the promoter region of TFEB-regulated autophagosome and lysosomal genes. Expression of these genes promotes autophagy, cancer cell survival and proliferation.[38]

Perspective

Current studies have demonstrated that metabolic enzymes involved in the development and progression of NSCLC have both metabolic and nonmetabolic activities. Selectively targeting metabolic enzymes in cancer cells and blocking their metabolic and nonmetabolic activities may present as an effective approach for the treatment of NSCLC.

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