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Tumor Metabolic Reprogramming: Mechanisms, Regulatory Networks, And Therapeutic Opportunities

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Abstract: Metabolic reprogramming is one of the basic hallmarks of malignant tumors—that is, a whole set of adaptive responses by which tumor cells organize their metabolism in a way that suits fluctuating microenvironments, permits unchecked growth, and helps them withstand treatment pressures. Contrary to normal cells, which in general depend upon mitochondrial oxidative phosphorylation for energy generation under aerobic circumstances, tumor cells usually get their energy via glycolysis even if they are exposed to large amounts of oxygen (a situation called the Warburg effect).But now it is clear that tumor metabolic reprogramming is not just an exaggerated form of glycolysis, nor merely a localized change—rather, it entails an organized readjustment of several pathways (of glucose, of lipids, of amino acids, or of nucleotides). From the molecular standpoint, the basic regulatory factors HIF-1, MYC, p53, and mTORC1 are part of a complex signaling system which brings together nutrient sensing and signals for cancer as well as for transcriptional control. At the microenvironment level, interactions of all three kinds—tumor cells, immune cells, and fibroblasts linked to cancer—help to shape (often unfavorably) the local immunological situation. From the standpoint of clinical translational research, a number of approaches—lactate transporter inhibitors, fatty acid synthase inhibitors, and glutaminase inhibitors—related to metabolic vulnerability are now being tested clinically. The present work analyzes in detail the molecular bases, control circuits, interactions with the microenvironment, and treatment options for tumor metabolic reprogramming, as well as the main difficulties and likely developments connected with this area of study.

Keywords: metabolic reprogramming; Warburg effect; tumor microenvironment; metabolic targeted therapy; immunometabolism

1. Introduction

Cancer has long been considered primarily a genetic disease—one involving an accumulation of mutations affecting oncogenes or tumor suppressors [1]. Yet now, after two decades of investigation, it is becoming clear that cancer is also of great metabolic importance. Metabolic changes of a systematic type arise in tumors during malignant transformation, and such changes are not to be viewed merely as an actively chosen survival strategy. The notion of tumor metabolic reprogramming seems to date back to the 1920s, for at that time German biochemist Otto Warburg noted an unusual degree of glycolytic activity and of lactate formation even by tumors under aerobic conditions [2,3]. This “Warburg effect” has long been considered one of the central features of tumor metabolism [4]. Yet, after more careful study, it has become gradually clear that the complexity of tumor metabolism goes well beyond what Warburg originally supposed. The metabolic reprogramming of tumor cells is not merely a matter of increased glycolysis but also of altered TCA-cycle function (i.e., of tricarboxylic acid metabolism), of activation of the pentose phosphate pathway, of higher glutamine consumption, of boosted lipid biosynthesis from scratch, or of specific nucleotide-related changes. The various metabolic changes operate together—i.e., they are

synergetic—to yield energy, biosynthetic materials, and redox control for the fast growth of tumor cells [5]. Even more importantly, tumor metabolic reprogramming is not a stand-alone phenomenon; it joins with stromal elements (such as immune or fibroblast-like cells) in the tumor's microenvironment in a complex metabolic interaction that is strongly connected to epigenetic regulation at the molecular level is one of the important factors contributing to resistance of tumors to therapeutic treatment at the clinical level [6,7]. An all-encompassing analysis of the various mechanisms and regulatory networks of tumor metabolic reprogramming may yield substantial theoretical and practical guidance for the design of new anticancer approaches. The present work intends to give a systematic account of prior studies of tumor metabolic reprogramming—considering, separately or together, metabolic pathway changes, molecular control, microenvironmental metabolism, epigenetic cross - effects, and clinical applications.

2. Alterations in Core Metabolic Pathways during Tumor Metabolic Reprogramming

Reprogramming of glucose metabolism is now the first and best developed area of tumor metabolism study [8]. The tumor cell takes up a much larger amount of glucose and—even with oxygen available—favors glycolysis rather than mitochondrial respiration for its energy needs [9]. Though glycolysis gives rise to only 2 ATP molecules per glucose molecule (instead of 36 ATP molecules pr with oxidative phosphorylation as its basis, this kind of metabolic strategy is uniquely useful for tumor cells: the various glycolytic intermediates may be redirected to the pentose phosphate pathway, with production of ribose-5-phosphate needed for nucleotides and NADPH (to keep the redox state stable); the lactic acid made by glycolysis has a means of exit—secretion into the microenvironment—which may help to control pH or to regulate immune cell behavior; the very fast ATP generation of glycolysis helps tumor cells to meet energy needs promptly. A number of important enzymes of the glycolytic pathway—such as phosphoglycerate kinase 1 (PGK1)—are expressed abnormally in tumors (e.g., in gliomas of the brain), with a substantial rise in their levels that favors glycolysis rather than mitochondrial oxidative phosphorylation; the higher activity of PFKFB3 seems to help tumor cell biosynthesis occurs through upregulation of the non-oxidative pentose phosphate pathway and of de novo serine synthesis [10,11]. More recent work has begun to question the traditional view of mitochondria in tumor metabolism, with a growing body of data pointing out that mitochondrial oxidative phosphorylation need not be wholly absent from tumor cells but may be highly relevant in special situations (for example, under treatment or at metastatic sites). Tumor cells display notable metabolic plasticity—they can shift, as needed, between glycolysis and oxidative phosphorylation [12]. Even some of the earlier studies now seem to indicate that the basic cause of the Warburg effect lies in the "overload" oftumor cell mitochondria—the nuclear migration of TCA enzymes sets off adaptive responses in mitochondrial function.

Reprogramming of lipid metabolism is now attracting a growing amount of attention [13]. For tumor cells, lipids are not merely passive elements of the membrane structure, but also sources of fuel or of signals. The three principal means by which they meet their lipid needs are:an enhanced capacity to absorb exogenous lipids from the local environment, an increased rate of de novo lipid synthesis, and increased lipid storage and mobilization [9,14,15]. The fatty acid synthase (FASN) is one of the main enzymes in de novo lipid biosynthesis and is highly expressed—across many tumors—as a possible therapeutic target for metabolic therapy. Fatty acid oxidation (FAO) —regulated by carnitine palmitoyltransferase 1A (CPT1A)—is unusually active in tumor stem cells, helping to maintain them and to resist therapeutic attack.

Reprogramming of cholesterol metabolism is by no means unimportant-cholesterol contributes not only to membrane construction but also to nuclear receptor signaling through its own metabolites (as ligands) in transcriptional control. Lipid metabolic reprogramming has major importance for the formation of immune microenvironments [4,16,17]. Changes in lipid metabolism promote tumor growth and yet may transform the tumor's surroundings profoundly, thus creating intricate metabolic relationships that favor immune escape.

Metabolic reprogramming of amino acids is yet another important factor in tumor metabolism [18]. There is substantial evidence of dependence by tumor cells on glutamine, called "glutamine addiction". Glutamine functions not only as a precursor to proteins but also as a major contributor of carbon or nitrogen to the tricarboxylic acid cycle (anaplerosis). With regard to a glutamine-deficient environment of the tumor microspace, tumor cells meet their needs by means of several strategies—either by improving membrane transporter function or by upregulating endogenous synthesis. Glutaminase (GLS1) is one of the central enzymes for glutamine breakdown, and its inhibitor CB-839 now stands in clinical trials. With regard to glutamine itself, other amino acids also undergo marked metabolic alterations in tumors, involving branched-chain amino acids, arginine, methionine, tryptophan as well as one-carbon compounds figure in the metabolic reprogramming of tumors [19]. One-carbon metabolism—or the folate-connected amino acid pathway—is central to the production of nucleotides, to

epigenetic stability, and to redox balance; accordingly, it now occupies a key place in tumor metabolism studies. Reprogramming of the urea cycle and of arginine-related pathways favors biosynthesis by controlling both ammonia and nitrogen availability.

Tumor cells that multiply very quickly show an extremely high need for nucleotides. To satisfy such a need they modify enzyme expression—both in salvage and in de novo synthesis pathways—to raise nucleotide levels. The pentose phosphate pathway yields ribose-5-phosphate and stands in close relation to nucleotide metabolism. Reprogramming of nucleotide metabolism turns out to be helpful not only for DNA replication and RNA transcription but also for four pathways—of glucose, of lipids, of amino acids, and of nucleotides—are each affected by cell cycle processes and by DNA damage, and are closely connected to genomic instability and to tumor treatment resistance. To summarize: systematic rewiring of these four pathways does not take place independently but is strongly linked by shared precursors (metabolites), by cofactors, and by energetic conditions —a fact that defines a tightly regulated metabolic network helpful to malignancy.

3. Molecular Regulatory Network of Metabolic Reprogramming

Metabolic reprogramming of the tumor is no mere change in individual metabolic enzymes, but a complex remodeling controlled jointly by several transcription factors and signaling pathways. Hypoxia-inducible factor-1 (HIF-1) is one of the basic molecules that link the hypoxic microenvironment to altered metabolism. With hypoxia present in the cell, HIF-1 promotes higher levels of expression for glycolytic enzymes, encourages the transcription of the glucose transporter GLUT1 and at the same time inhibits mitochondrial respiration—a fact central to the Warburg effect [20]. MYC is a significant regulatory transcription factor for metabolism; it controls a whole range of metabolism-linked genes (in terms of transcription) and deals with glycolysis, glutamine use, nucleotide production, or mitochondrial biogenesis [21]. Abnormal activation of this kind can directly cause the expression of glutamine transporters and of glutaminases, which are central to the molecular setup of “glutamine addiction”. Among tumor suppressors, p53 is by far the most important one and plays a “braking” role with regard to metabolism—it keeps metabolic processes under control by means of several phenomena: glycolytic inhibition, stimulation of oxidative phosphorylation, and management of lipids or amino acids.

A defect or mutation of p53 is one of the main causes of tumor metabolic deregulation. mTORC1 is central to integration of the cell’s nutrient signals and of its metabolic state, and it combines information about amino acids, glucose, and growth factors in order to direct anabolic phenomena—protein building, lipid production, or nucleotide formation; AMPK, as an energy sensor, blocks anabolism and encourages catabolism if energy is lacking. SREBP1 and PPARs are important regulators of lipid metabolism, with SREBP1 controlling expression of genes that drive de novo fatty acid or cholesterol biosynthesis [22,23]. Its faulty activation is a major factor behind tumor lipid metabolism reprogramming.

Over the past few years, the non-canonical roles of metabolic enzymes—not dependent on their standard metabolic catalytic functions—have come to be widely studied. Such non-canonical functions may pertain to transcriptional control by metabolic enzymes or to epigenetic modulation or to the management of intracellular signals. As one example, PGK1, in addition to catalyzing ATP production during glycolysis, this enzyme is involved in tumor progression (non-canonically). Such findings help us to understand better the functional roles of metabolic enzymes and to design new therapeutic approaches based on them. Generally speaking, the multiple regulatory levels—transcription factors, signal transducers, and metabolic enzymes—form an exact yet redundant system of control. That precision allows tumor cells to alter their metabolism promptly under varying conditions, which explains the difficulty of single-target therapy.

4. Metabolic Symphony in the Tumor Microenvironment

The tumor microenvironment may be considered a battlefield with regard to metabolism—here tumor cells and immune cells struggle intensely for scarce nutrients [24]. Among the nutrients taken up by tumor cells, glucose and glutamine are especially favored (they are captured via high-affinity transporters of both types), which leads to local nutrient shortages and later to diminished metabolic performance of the immune function of effector T cells [25]. At the same time, the various metabolites secreted by tumors—notably lactic acid—seem to be capable of altering immune-cell function locally (in the microenvironment). An acidic environment induced by lactic acid favors tumor spread and at the same time suppresses the activity and cytotoxicity of $CD8^+$ T cells. Tumor-linked macrophages (TAMs) undergo major metabolic reprogramming of the tumor microenvironment—especially of glycolysis, of lipid metabolism, of the tricarboxylic acid cycle, or of amino acid metabolism—may lead to polarization of the cells toward immunosuppression [26]. Cancer-associated fibroblasts (CAFs) constitute the main class of stromal elements in the tumor microenvironment [27]. They help to advance tumor growth through

cytokine secretion and through exosome release, and they play an important part in tumor development due to their own metabolic reprogramming. The metabolic reprogramming of CAFs includes, among other things, glycolytic activity, lipid handling, and amino acid metabolism. Even in an environment that is hypoxic or low in nutrients, CAFs keep their energy needs met by means of altered metabolism; more importantly, they are able to give tumor cells “metabolic support” via secretion of metabolically useful. Among the products formed (lactic acid or ketone bodies). The coupling of tumor and stromal metabolism is called the “Warburg effect in reverse”. Metabolic reprogramming of CAFs—whether partial or complete—has bearing on tumor growth, movement, and drug resistance. With regard to the heterogeneity and adaptability of CAFs, treatment involving targeted metabolic interference may offer a novel approach to the problem of tumor resistance.

Among the frontier topics in tumor metabolic reprogramming is the interaction of neural signals with tumor metabolism. A number of recent reports have identified a bidirectional regulatory loop—between neural signals and tumor metabolism—which seems to promote malignant progression. Neurotransmitters and neurotrophic substances help to direct or control the metabolic changes of tumor cells, while tumor metabolites may in turn influence neural function. This “neuro-metabolic symphony” presents an alternative viewpoint with regard to the global regulation of tumors. Briefly stated, metabolic interactions within the tumor microenvironment are not one-sided nutrient deficits, but rather complex dialogues involving all four types of cell (tumor, immune, fibroblast, nerve), with major implications for both growth and therapy.

5. Cross-regulation of metabolic reprogramming and epigenetics

Among the recent major advances in tumor research is the realization of a close interplay between metabolic reprogramming and epigenetic regulation. Metabolites serve not only as fuel or raw materials for biosynthesis but also as cofactors influencing the functional activity of enzymes that modify epigenetic states. The “oncometabolites” secreted by tumor cells—for example, 2-hydroxyglutaric acid (2-HG), succinate and fumarate may act as competitive inhibitors of epigenetic regulatory enzymes. 2-HG is a metabolite—arising from certain mutations of isocitrate dehydrogenase (IDH)—which can disturb normal epigenetics by blocking histone and DNA demethylases. Among the metabolites known to be relevant here are acetyl-CoA, S-adenosylmethionine, and α-ketoglutarate; they help supply substrates or cofactors for histone acetylation, methylation, or similar changes, respectively, one may consider direct coupling of cellular metabolism with epigenetic status [28,29]. The metabolic-epigenetic-immune triaxial relationship is central to an understanding of tumor adaptability and plasticity: tumor cells adjust chromatin (and hence gene) expression by metabolic means to avoid immune detection; metabolic rivalry promotes epigenetic exhaustion of the cytotoxic T cell compartment; tumor-linked myeloid cells gain immunosuppressive or pro-angiogenic features due to metabolite-driven histone modification. Such triaxial thinking offers a foundation for combination strategies involving multiple targets and implies that when metabolism is targeted, its effect upon the epigenetic state must not be neglected.

6. Therapeutic Strategies and Challenges of Targeted Metabolic Reprogramming

With an accurate grasp of tumor metabolic reprogramming, targeted metabolic therapies are now advancing quickly. As far as glucose is concerned, inhibitors of major glycolytic enzymes—hexokinase 2, PFKFB3, lactate dehydrogenaseA—and of lactate transporters (MCT1/MCT4) are under investigation (preclinical or early clinical); for lipid metabolism, the fatty acid synthase inhibitor TVB-2640 is now under study in clinical trials; with regard to amino acid metabolism, the glutaminase inhibitor CB-839 too is being considered for such trials. Targeting AMPK is thought to be one of the possible metabolic strategies of therapeutic value, since AMPK agonists help to normalize metabolism—by reducing biosynthesis and favoring catabolism [30]. As far as metabolic reprogramming of tumor cells brings about survival benefits, but also creates certain metabolic vulnerabilities. A single conceptual framework of “mechanism-strategy-translation”—as developed by Xue et al.—treats two principal types of metabolic vulnerability: inflexibility and synthetic lethality. Metabolic inflexibility is a case of too great an attachment of tumor cells to given metabolic routes, with no or little redundancy among alternatives; synthetic lethality is a pairing of specific metabolic defects (in the tumor) with targeted therapeutic actions. Such a dual-axis model offers theoretical help in analyzing and making use of tumor metabolic vulnerabilities.

With regard to the marked plasticity and adaptability of tumor metabolism, single therapeutic agents targeting one metabolic pathway may fail because of resistance—hence combination approaches are now studied more closely. It is possible to combine metabolic inhibitors with chemotherapy, targeted treatment, or immunotherapy for synergy. Other auxiliary means (dietary ones like ketogenic regimens or caloric restriction) might also be worth considering in metabolic regulation seems to offer much promise. Yet metabolic targeting therapy has not been wholly free of major difficulties. One such difficulty is metabolic heterogeneity: individual areas of a tumor or

certain cell subgroups may differ greatly in their metabolism. This heterogeneity is now being studied more closely by means of single-cell profiling and of spatial metabolomics (in both senses).

Secondly, we must consider the problem of normal tissue toxicity—because normal cells make use of the same metabolic processes, drugs directed at metabolism may cause major off-target side effects. Thirdly, the issue of metabolic plasticity-driven resistance-arises: tumor cells may escape a given target by switching their metabolic patterns. To meet these challenges it is necessary to bring together many disciplines, and now artificial intelligence-aided multi-omics approaches (such as patient-derived organoids or spatial transcriptomics) and proteomics help to shape precise metabolic therapies.

7. Summary and Outlook

Metabolic reprogramming of tumors has moved on from being just one observation—namely the Warburg effect—to an intricate situation involving multiple dimensions of glucose, lipid, amino acid, and nucleotide remodeling. On the molecular scale, regulatory factors including HIF-1, MYC, p53, and mTORC1 are joined in an exact signaling network; with regard to the microenvironment, competition or cooperation between tumor cells occurs in terms of metabolism, immune cells, and cancer-related fibroblasts (CAFs); at the systemic level, metabolic reprogramming is closely connected to epigenetic control and to neural signals. A multi-level, multi-dimensional conceptualization of this sort is beginning to change people' s ideas about the nature of cancer. With a view to the future, these several directions deserve attention: first, metabolic studies at the single-cell and spatial levels will help to define both the pattern and the clinical relevance of metabolic heterogeneity in tumors; second, an improved grasp of the metabolic-epigenetic-immune triad may lead to ideas about multi-target combination therapies; third, the identification of metabolic biomarkers promises better patient stratification and more individualized treatment; fourth, new delivery systems (nanomedicines among them) seem likely to raise the tumor specificity and therapeutic window of metabolic-targeted agents. The study of tumor metabolic reprogramming now stands at a crucial point—it moves toward application rather than mere description. Despite the many unresolved issues, metabolic weakness—the Achilles' heel of tumors—offers startling new opportunities for anticancer work.

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