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Molecular Mechanisms of Tumor Metabolic Reprogramming and Progress in Bioinformatics Research

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Abstract. Tumor metabolism reconstruction is a core marked feature of malignant tumors, which is characterized by overall rebuilding of energy metabolism, biological synthesis, and oxidation-reduction balance. This review, in a systematic way, makes a summary of the molecular foundation of important pathways which include glycolysis, mitochondrion metabolism, glutamine-pushed anaplerosis, fat metabolism, and one-carbon metabolism. We further carry out division on hierarchical control mechanisms that are intermediated by signal–transcription axes, for example hypoxia-inducible factors (HIFs), MYC, the PI3K–AKT–mTOR pathway, and AMP-activated protein kinase (AMPK). In addition, we carry out discussion on metabolite-mediated mutual communication and immunity-suppressing influences inside the tumor microenvironment (TME), hence we emphasize the core function of metabolites like lactic acid and kynurenine in metabolic interactions and immune escaping. From a clinical view angle, we carry out evaluation on the translational worth of metabolic phenotypes in imaging and liquid biopsy, summarize evidence from clinical tests of targeted metabolic agents (e.g., glutaminase blocking agents and IDO1 blocking agents), and carry out analysis on treatment heterogeneity and combination-treatment difficulties. At last, we make a summary of recent advancement in bioinformatics methods—including integration of multiple omics, metabolomics pathway analysis, and transcriptome-based co-expression networks—for depiction of metabolic heterogeneity, finding targets that drugs can act on, and forecasting the reaction of treatment. We put forward that future researches should keep on pushing forward metabolic flux verification, space-time resolved metabolic measurements, and accurate layering strategies to help the transformation of metabolic targeting from concept verification to clinical meaningful benefits.

Keywords: Tumor metabolic reprogramming, Cancer metabolism, Tumor microenvironment, Metabolic-targeted therapy, Multi-omics bioinformatics

1. Introduction

The starting and developing of malignant tumors are closely connected with complicated metabolism change. Already in the 1920s, Otto Warburg discovered that tumor cells have a tendency to change glucose into lactic acid even when oxygen is sufficient, this phenomenon was afterwards called "aerobic glycolysis" or the Warburg effect [1]. Since quite a long period,metabolic reprogramming has been regarded by people as a passive result that goes with the growth of tumors.

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But, the evidence which people collected through the past thirty years shows that metabolic changes are active propelling factors for malignant transformation and the progress of tumors. It is worth pointing out that the adjusting network of metabolic change is deeply combined into cancer-causing signal paths, and forms two-directional feedback together with the TME [2].

The metabolic reprogramming of tumor is not a switch-shaped transformation of one single pathway; on the contrary, it embodies a system-level reconstruction that contains many modules, containing glycolysis, mitochondrial oxidative phosphorylation, glutamine catabolism, fatty-acid synthesis and oxidation, and one-carbon metabolism [2]. Under the united pressing forces of anoxia, nourishment restriction, and carcinogen signal conduction, tumor cells reallocate carbon and nitrogen flowing through layered control which is mediated by signal-transcription axes including HIFs, MYC, PI3K–AKT–mTOR, and AMPK. This reconstruction meets many needs simultaneously —energy provision, biosynthesis predecessors, and oxidation-reduction equilibrium. It is important that the results of metabolic change go further than the internal processes of the tumor: small molecules like lactate and kynurenine can be transported out into the TME, they directly adjust the function of immune cells and the behavior of stroma, therefore thus setting up an immunosuppression network driven by metabolism that forms the development of the tumor and the reaction to treatment.

The clinical importance of metabolism re-arrangement is more and more clear thus. From one aspect, imaging methods which are based on tumor metabolic characteristics—such as ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT)—and circulating metabolic markers which are like serum lactate dehydrogenase (LDH) have been already widely applied in oncology daily work. On the other hand, the exploitation of medicines that hit key metabolic nodes, involving glutaminase (GLS) and indoleamine 2,3-dioxygenase 1, has gone forward in a steady way. Although a number of phase III trials have not reached expected results, therefore these experiences have given important inspirations for the precision classification of metabolic therapy. At the same time, large-scale multi-omics projects which take The Cancer Genome Atlas (TCGA) and the Clinical Proteomic Tumor Analysis Consortium (CPTAC) as representatives have produced very many molecular data sets, which for system-level description of metabolic heterogeneity, finding of drug-targetable weaknesses, and forecast of treatment reaction provide key resources and method support.

Under this background, this review paper puts together viewpoints from "molecular mechanisms —regulatory networks—microenvironment mutual communication—clinical transformation—bioinformatics usages." We at first sum up the molecular foundation of core metabolic paths and their hierarchical control networks, then we analyze metabolic interactions and immunology results inside the TME, subsequently we assess translational uses of metabolic phenotypes and proof for representative targeted treatment methods, and finally we outline progresses in bioinformatics approaches that are applied to metabolic research. Through this comprehensively integrated summary, we have the objective to offer a structured theoretical framework for fundamental and translational researches on tumor metabolism, and therefore to discuss key future research directions and breakthrough opportunities that people may obtain.

2. Molecular basis of tumor metabolic reprogramming

2.1. Enhanced glycolysis and lactate metabolism

Hypoxia and "pseudohypoxia" are able to make HIF signaling keep stable and bring out the expression of genes linked to glycolysis, which includes glucose transporters, key enzymes of

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glycolysis, and pathways that produce lactate. At the same time, the rising adjustment of pyruvate dehydrogenase kinase (PDK) that hypoxia causes holds back pyruvate from going into the tricarboxylic acid (TCA) cycle, therefore it further turns carbon flow to the making of lactate and non-oxidative biosynthesis branches. This tactic assists the production of ATP when oxygen supply is low or changes unsteadily, and meanwhile it decreases the oxidative stress of mitochondria [2].

Lactate ought not be regarded only as a "metabolic waste product." In the inside of tumor tissues, the output of lactate and the partial acid environment change the shape of immune and stroma functions, and therefore affect the invasion, blood vessel growth and the reaction of treatment through the connection between metabolism and signal conduction. Furthermore, lactate and the epigenetic modifications that come from lactate (e. g., lysine lactylation) are put forward by people to take part in transcriptional regulation which has connection with immune evasion. Hence, the lactate axis can by us be regarded as a multi-function module that acts as (i) one energy base material, (ii) one micro-environment signal molecule, and (iii) one immune adjustment factor.

2.2. Mitochondrial metabolism and remodeling of oxidative phosphorylation

The function of oxidative phosphorylation (OXPHOS) inside cancer is more accordant with a "switchable module" than a capability that is globally turned off. In a number of tumor tissues or particular cell conditions, mitochondrion generation and electron-transport chain function can be kept or even strengthened to support continuous ATP production, making of metabolic middle products, and redox steady state. The transcription synergistic activation factor PGC-1α is a key adjusting factor of oxidative metabolism and mitochondrion generation; through the adjustment of gene programs of mitochondria which are encoded by nucleus, PGC-1α is able to exert influence on the intensity of OXPHOS. It is worth pointing out that, its function seems to have very strong dependence on context in all kinds of tumor types and microenvironment situations.

There exist two-directional mutual actions between the function of mitochondria and the HIF signal pathway. Under the condition of hypoxia, the regulation which is driven by HIF makes carbon flux divert away from mitochondrial oxidation and move toward glycolysis. On the opposite side, the final products of glycolysis and the Warburg-type metabolic states can therefore in turn strengthen the pathways related to HIF, hence forming a positive feedback loop which makes the metabolic phenotypes of tumors become stable.

2.3. Glutamine metabolism and anaplerotic pathways

Numerous tumor cells display very obvious glutamine reliance ("glutamine addiction"). From the mechanism perspective, glutamine can offer both carbon and nitrogen: after it is changed into glutamate by glutaminase (GLS), glutamate can be further processed through metabolism into α-ketoglutarate (α-KG), which enters the tricarboxylic acid (TCA) cycle and supplements metabolic intermediates (anaplerosis). The metabolism resultings of IDH mutations upon glutamate making and oxidation-reduction balance are concluded in Fig. 1. This mechanism is especially of great importance when glucose-originated carbon flow is under restriction or the demand for biosynthesis becomes higher, therefore hence it supports the production of amino acids and nucleotides [1].

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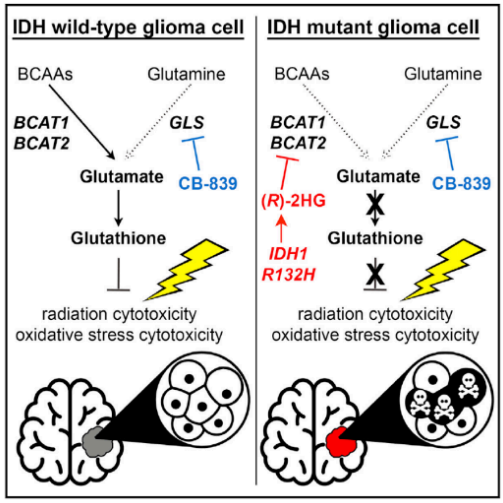

Figure 1. Schematic model of IDH-mutation-driven metabolic rewiring linking BCAT inhibition, glutamine metabolism, and redox imbalance in glioma [3]

In the regulation part, MYC can enhance glutamine intake and decomposition through transcriptional and post-transcriptional mechanisms, hence therefore building metabolic programs that take glutamine as the center inside tumor cells. In the meanwhile, glutamine metabolic process is closely linked to oxidative stress regulation, anti-oxidation systems (e. g., glutathione biological synthesis), and nutrient contest in the TME.

2.4. Lipid metabolic reprogramming and upstream transcriptional control

The changed lipid metabolism in tumor cells usually includes fatty acid synthesizing, lipid taking in and storing, membrane lipid refitting, and fatty acid oxidizing. Beside the rising expression of key lipid produce enzymes such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), up-stream transcription factors take core positions in the promotion of lipid produce processes. Especially, the sterol adjusting element-binding proteins (SREBPs) can together increase the expression level of genes that take part in fatty-acid and cholesterol biosynthesis, and they function as transcriptional "switches" for the lipogenesis module.

Carbohydrate response element combination protein (ChREBP) acts as one nutrition feeling transcription factor which connects glucose inflow with gene expression. In concrete organization and cancer circumstances, ChREBP can control both glycolysis- and lipogenesis-related genes, therefore therefore building a straight transcription connection between "glucose metabolic process" and "lipid production." This indicates that carbon arrangement inside cancer cells is not only a passive outcome of supply and requirement but can be actively reorganized by nutrient-perceiving transcription networks.

Lipid metabolism also possesses hierarchical connection with PI3K–AKT signaling: the PI3K–AKT–mTOR axis facilitates SREBP-led lipogenic plans, hence pulling metabolism from catabolic energy generation toward anabolic proliferation assistance. On the opposite side, alterations in fatty-acid desaturation and membrane lipid components may indirectly adjust growth factor signal transmission and survival paths through changing membrane structure and signal transmission platforms. These mutual actions also mold ferroptosis sensibility, which reflects a metabolism–signaling connection that joins lipid reshaping to adjusted cell death schemes.

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2.5. Transcriptional regulation of one-carbon metabolism and redox homeostasis

Serine–glycine–one-carbon (SGOC) metabolic process provides one-carbon units for nucleotide synthetic production and affects the supply of methyl donors (S-adenosylmethionine, SAM) via the folate and methionine cycles, hence it thus influences epigenetic homeostasis (Fig. 2). Under the condition of rapid proliferation, the one-carbon pathways of mitochondria can be connected with the biosynthesis of purine and pyrimidine, thus satisfying the requirements for the replication and repair of DNA.

The key ferments including SHMT2 and MTHFD2, they are continuously raised in expression in many kinds of tumors. The regulation of their upstream parts is not pushed forward by only one single pathway. For an example, mTORC1 can cause the expression of MTHFD2 through ATF4 and hence promote the synthesis of purine. In the cells of tumor, it has also been reported that MYC is an upstream regulator of mitochondrial one-carbon enzymes—these include MTHFD2, MTHFD1L, and SHMT2—therefore it shows promoter occupancy and transcriptional activation in many different cancer models [4].

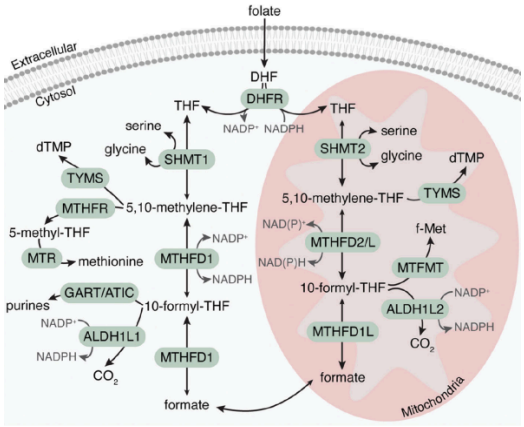

Figure 2. Schematic overview of the serine–glycine–one-carbon metabolic pathway and its compartmentalization between cytosol and mitochondria [4]

One-carbon metabolisms are also very important for redox balance: the reactions of folate cycle influence the supply-demand equilibrium of NAD(P)H, they support the antioxidant systems like glutathione and buffer the reactive oxygen species (ROS). When being in metabolic stress condition, the influence of one-carbon pathways upon the allocation of reducing equivalents between the mitochondrion group and the cytosol can thus become a core deciding factor of tumor tolerance toward oxidative stress and therapy-caused damage.

2.6. Key transporters and the core regulatory network

The metabolism adjustment of tumor may be regarded as a layered structure that contains "environmental input—signal feeling—transcription implementation—metabolic working factors." The oxygen pressure degree, the nourishment supply condition and the energy consumption pressure can activate the signal paths which are like HIF and AMPK. The signal conduction of growth factors and the programs that cause cancer push forward anabolism metabolism through modules such as PI3K–AKT–mTOR and MYC. In the end, alterations display themselves on the level of transporters (e. g., glucose and amino acid conveyors) and enzyme collections as redistribution of pathway current intensities.

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Inside this level order, PI3K–AKT–mTOR can at the same time push glucose use, fat making, and one-carbon metabolism-connected gene plans, and hence indirectly help the making-needs that are put by MYC through strengthened material supply. AMPK, which acts as an energy stress sensor, has a tendency to inhibit energy-consuming anabolic processes and facilitate pathways that generate ATP like fatty-acid oxidation (e. g., through the phosphorylation of ACC, it makes malonyl-CoA decrease, so that the inhibition of CPT1-mediated fatty acid transportation/oxidation is relieved).

The connection between HIF and MYC is possessed of both "competition" and "cooperation." In some anoxic environments, HIF limits carbon getting into mitochondria and rearranges core carbon metabolism, hence MYC—according to expression degree and cell condition—can work together with HIF to push forward adaptive metabolism recombination. This complex situation shows that single adjusting factors seldom can explain metabolic appearance characters when they are considered alone; Networks that integrate cross-pathway and cross-level are required for enhancing the explanatory power of mechanisms [5].

2.7. Metabolic crosstalk and immunological consequences in the tumor microenvironment

The tumor micro-environment may be regarded as a small position in which "nutrient lack" exists together with "accumulation of metabolic substances." The high-efficiency glucose taking-in by tumor cells limits the nutrient supply for tumor-infiltrating T cells, therefore it restricts mTOR activity, glycolytic ability, and interferon-γ (IFN-γ) output, hence finally it weakens the anti-tumor immunity. In several models, the blockading of immune checkpoints can resume T-cell glycolysis and function partially through increasing metabolic accessibility within the TME, hence it indicates an operable connecting surface between metabolism and immunotherapy.

Besides the contention for nutrients, "metabolic restraining axes" including lactic acid gathering and the tryptophan-kynurenine path can additionally enlarge the immune suppression. The accumulation of lactic acid is generally acknowledged by people to affect the effector function and the differentiation states of many kinds of immune cells, and it has a connection with the resistance to immunotherapy. The kynurenine pathway, which is driven by rate-limiting enzymes like IDO1 and tryptophan 2,3-dioxygenase (TDO), therefore can suppress immunity through both tryptophan depletion and generation of metabolites that suppress immunity, hence it represents a main research focus in the interactions between metabolism and immunity.

With respect to intercellular metabolic coupling, the "reverse Warburg effect" model puts forward that tumor cells are able to make cancer-associated fibroblasts (CAFs) carry out aerobic glycolysis and generate substrates for example lactate and pyruvate, which afterward are used by neighbor tumor cells to give support to OXPHOS and anabolic metabolism. This model enlarges metabolic reprogramming from an event that is inherent to tumor to a cooperative tactic of cell groups and offers theoretical basis for aiming at transporters and metabolite-exchange paths [6].

3. Clinical significance and applications of tumor metabolic reprogramming

3.1. Imaging and liquid-biopsy applications of metabolic phenotypes

^{18}F-FDG PET/CT uses the rising glucose absorbing ability of tumor tissues to conduct metabolic imaging, and it has been widely applied in staging, recurrence evaluation, and treatment watching in many kinds of cancers. From the mechanism point of view, the increased glucose conveying and

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phosphorylation in tumor cells are what underlie tracer "absorbing and holding" inside malignant lesions.

Beyond the imaging technique, serum LDH and other indicators related to metabolism display comparatively consistent connections with the prognosis among many kinds of solid tumors. Systematic reviews and meta-analyses on the whole hold the tendency that the rising baseline LDH has connection with worse survival results. Notwithstanding that, clinical explanation must take in tumor category, treatment rank, and dynamic alterations through time.

Regarding metabolite-specific biological markers, 2-hydroxyglutarate (2HG) which is generated by tumors that have isocitrate dehydrogenase mutations (e. g., IDH1/IDH2) can be detected in non-invasive way through the use of magnetic resonance spectroscopy (MRS). The former comprehensive integration research result of data indicates that 2HG-MRS possesses high diagnosis ability for forecasting IDH-mutant gliomas, while the unification of collection procedures and threshold arrangements still is an important obstacle to wider clinical application [3].

3.2. Clinical evidence for representative metabolic-targeted therapies

The clinical proof of treatment methods that aim at metabolic targets is frequently depicted as "powerful biological logic, restricted clinical profit, and reliance on classification." In regard to glutamine metabolism, early-period research that combines a GLS inhibitor together with immune checkpoint inhibitors (open-label, multi-cohort expansion) has 118 patients enrolled. Among patients that can be evaluated, the total objective response rate (ORR) was 8. Four percent, whereas the sub-cohort of clear-cell renal cell carcinoma (ccRCC) which has not contacted immune checkpoint inhibitor (n = 25) displayed an ORR of 24%, thus this indicates the obvious heterogeneity of the cohort and the potential dependence on population.

In a random test that is nearer to a registration route, the CANTATA study offered important proof for a GLS inhibitor in kidney cancer. This randomization control experiment has brought into 444 patients that have metastatic ccRCC; The main observation end point was the progression-free survival, namely PFS, which was evaluated through independent image examination. The median value of PFS was 9. Two months in the combination treatment group and 9. Three months lie in the placebo-combination control group (hazard ratio [HR] 0. 94; P has the value of 0. 65), with ORRs being 31% and 28% in respective order, therefore it displays no beneficial effect on the primary endpoint. This experiment emphasizes the difficulty that metabolic goals may not give stable increasing advantage in non-selected groups [7].

3.3. Evidence and limitations of metabolism–immunity combination strategies

Metabolism–immunity combined strategies which take the IDO1–kynurenine pathway as core were once very expected, therefore their clinical developing path shows a classical "early signal—late failure" risk. ECHO-301/KEYNOTE-252 was one international random, double-blind, placebo-control third-phase experiment that included patients having unresectable or transfer melanin tumor, and analyzed the main end points in the population of treated-intention. This test randomly divided 706 patients into groups and discovered that epacadostat together with pembrolizumab did not bring improvement to PFS (median 4. 7 versus 4. Nine calendar months; Human Resources ~1. 00) or whole lifetime survival (OS; Human Resource ~1. 13); Our research work was brought to a halt when we conducted the interim analysis. These findings indicate that, under the tested dosage and administration mode, the inhibition of IDO1 did not bring about repeatable clinical benefit.

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By contrast, ECHO-303/KEYNOTE-698 for urothelial carcinoma gave number ORR differences, but enrollment was stopped early because of the ECHO-301 result. Although the prearranged target recruitment number was 648, merely 84 sick people were randomly arranged (42 in each group), and the main observation endpoint was altered to researcher-evaluated ORR after the recruitment work was stopped. Under brief follow-up observation, the non-confirmed objective response rate was twenty-six. 2% is in the combination group when compared with 11. Nine percent is in the control group arm. From the perspective of research methods, this should be considered as a hypothesis-producing signal, it is not definitive evidence therefore; The limited sample size and the change of endpoint thus restrict the extension of the real clinical benefit.

From a method angle, these past things tell us that metabolism–immunity together need at least three pre-conditions: (i) the confirmation that path suppression attains enough strength inside living body; (ii) formulation of operable biological markers to screen "patients who rely on metabolism"; and (iii) the verification on the level of immune microenvironment, that metabolic intervention really can promote the nutrient acquisition ability and functional status of effective T cells.

4. Bioinformatics applications in tumor metabolic reprogramming

4.1. Genomics

One big tendency in tumor metabolism study is to make use of big public resources to depict, on the population level, connection structures that connect "mutation—expression—pathway activity—clinical results." The layer-level structure of biological information in each different omics level is shown in the Fig. 3. TCGA has systemically carried out characterization of molecular features on more than 10,000 tumor samples that cover 33 kinds of cancer, therefore it provides foundational data sets for analysis on metabolic gene changes, pathway enrichment and prognostic connection. CPTAC, which has a strong emphasis on proteomics and proteogenomics, offers complementary proof to connect "genetic change" and "functional protein-level output" [8].

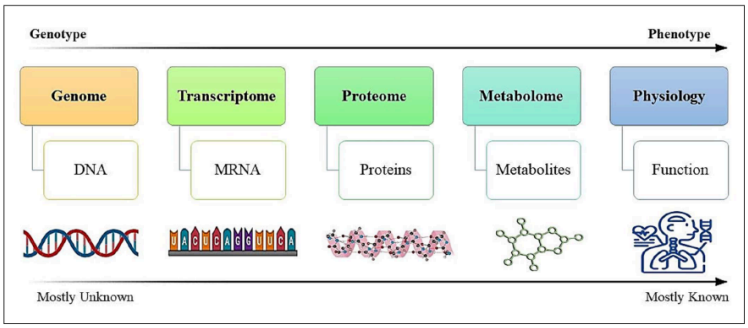

Figure 3. Hierarchical organization of multi-omics layers illustrating the flow of biological information from genome to phenotype [8]

In actual work, metabolism-related genome research usually contains: confirmation of driver mutations and copy-number changes, abundance analysis of metabolism gene sets, connection of key nodes with clinical outcomes (survival, stage, therapy reaction), and cross-layer verification with proteomic/phosphoproteomic data. A frequently encountered trap is to directly regard statistical connection as equal to causal flow changes. Hence, mechanism-related assertions should be additionally finalized via metabolomics data and/or isotope-tracking flow experiments, for the establishment of causal consistency [9].

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4.2. Metabolomics

Metabolomics has the unique closeness to phenotypic endpoints but is frequently more difficult to explain than transcriptomics or proteomics. Newly appeared droplet microfluidic platforms make possible high-throughput multiscale biological research analysis of nucleic acids, microorganisms, and tumor cells (Fig. 4). A more accurate academic statement than "data interpretation has difficulty" is what follows: untargeted metabolomics usually gives a static picture of metabolite quantity, while one single metabolite may sit at the cross point of many different paths. Without time-series measure works, stable isotope track method, or flux magnitude calculation, stably assigning different metabolites to specific reaction steps and constructing cause chains from molecular change to pathway flux and phenotype still has uncertainty. Such kind of inference is moreover further affected by the metabolite identification confidence and the analytical biases [10].

On the aspect of resource and tool, high-quality data banks and working procedure platforms give support to annotation work and data sharing. The Human Metabolome Database (HMDB) is the one that offers structure and note messages. MetaboLights is an open storehouse that holds raw data and metadata. The network platforms such as MetaboAnalyst and the software tools such as XCMS Online give support to the flow line processing that begins with peak extraction and alignment and ends with statistical analysis and pathway explanation. Beside this, microfluidic droplet experiment platforms can let highly parallel reaction systems and on-spot examination be realized, thus providing engineering schemes for high-throughput, multi-scale analysis of biological samples [11].

As for pathway explanation, enrichment methods such as over-representation analysis (ORA) can be disturbed by "coverage deviation in found metabolites," "metabolite wrong annotation," and "unsuitable background set definition," hence leading to unsteady or misleading outcomes. Hence, it is suggested that people should report metabolite identification degrees, background definitions, and key parameters together with pathway results, and, when possible, add cross-method consistency checks and experimental verification.

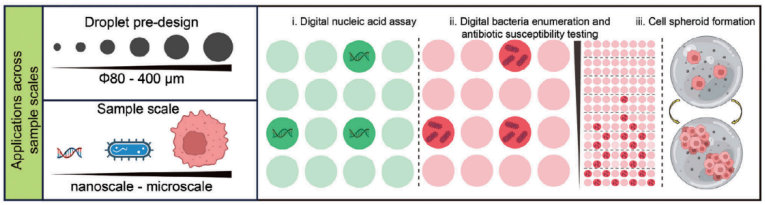

Figure 4. Droplet microfluidic platforms enable multiscale biological analysis ranging from nucleic acids to microorganisms and tumor cells [11]

4.3. Transcriptomics

On the transcriptome level, the co-expression networks and immune-infiltration deconvolution can be helpful to the interpretation of metabolic phenotypes. Weighted gene co-expression network analysis which is called WGCNA can find modules and core genes that have relation with clinical phenotypes or metabolic characteristics. Deconvolution approaches like CIBERSORT are able to compute immune-cell component from bulk transcriptome data, hence allowing assessment of core questions like if metabolic reprogramming happens together with enrichment of immunosuppressive cell groups.

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4.4. Multi-omics integration

The core aim of multi-omics combination is to project signals coming from genomics, transcriptomics, proteomics, and metabolomics into one united low-dimensional space, therefore finding out molecular subtypes and potential driving factors. Non-supervised factor analysis methods such as Multi-Omics Factor Analysis (MOFA) are able to pull out main sources of change from incompletely matching multi-mode datasets and assist in explanation of shared structures connecting "metabolic phenotypes—molecular marks—clinical results." Combined hidden-variable models like iCluster offer statistic frameworks for multi-omics combined clustering and sub-type finding.

5. Conclusions and perspectives

The metabolic reprogramming of tumors is a dynamic and adaptive process which is together driven by environment pressures, oncogenic signals, and transcriptional network systems. This review makes a summary of the molecular bases of important passages including glucose decomposition, mitochondrion metabolism, glutamine filling replenishment, fat composition, and one-carbon metabolism; gives elaboration on the hierarchical control which is mediated by HIFs, MYC, PI3K–AKT–mTOR, and AMPK; and makes clear the core function of interactions which are mediated by metabolites (e. g., lactic acid and kynurenine) inside tumor microenvironment for the immunosuppression function. In clinical practice, metabolic imaging (^{18}F-FDG PET/CT) and fluid biological markers (LDH, 2HG) are broadly used, however phase III tests of metabolism-targeted medicines (GLS inhibitors and IDO1 inhibitors) [12] have not gotten the anticipated results, therefore it points out the real-world difficulty of "strong biological theory basis, weak clinical benefit, and dependence on accurate stratification." Beside biomarkers from blood, newly appeared noninvasive sampling methods like volatile organic compounds (VOCs) emitted from skin which are collected by patches or headspace sampling have hopefulness for diagnostics based on metabolomics [13].

The success of translation, it is very likely, needs breakthroughs in three bottleneck problems: (i) in vivo checking of target suppression strength, (ii) building of stable biomarkers for metabolic dependence, and (iii) experimental proof that metabolic intervention can promote the function of immune microenvironment. Bioinformatics gives the support that cannot be lacked for solving the complexity of metabolism. Multi-omics data sources like TCGA and CPTAC draw connection structures among "mutation—expression—pathway—outcome", meanwhile, metabolomics instruments (e. g., HMDB, MetaboAnalyst) and multi-omics integration frames (e. g., MOFA, iCluster) help the finding of molecule sub-types and pushing factors. Even so, metabolomics is still restricted by its property of "static snapshot", and causal inference still must rely on stable isotope tracking and flux verification.

The research of future tumor metabolism ought to go on to make progress in the next directions: (1) the standardization of technologies for metabolic flux verification [14]; (2) the exploitation of measurement methods for metabolism with high time-space resolution [15]; (3) the finding and confirmation of biomarkers which reflect the metabolic dependence; (4) deeper mechanism explanation on the synergy between metabolism and immune; and (5) the ripening of multi-modal data combination work flows. Under the coordinated advancing on these directions, the research of tumor metabolism can change from the description which is based on correlation to the testing of causality, therefore it can enable the metabolic target therapy to move from the proof of concept to the accurate clinical benefit.

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