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Mechanisms and Therapeutic Potential of Lipid Metabolic Reprogramming in Regulating the Colorectal Cancer Microenvironment

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Abstract. Lipid metabolic reprogramming is an important mechanism by which colorectal cancer adapts to nutritional stress, maintains a malignant phenotype and affects treatment response, and its action involves both tumor cells and the immune and stromal components of the microenvironment. This review centers on fatty acid uptake, de novo synthesis, oxidative utilization, lipid droplet storage and cholesterol signaling, and summarizes representative studies on how abnormal lipid metabolism participates in colorectal cancer progression, with emphasis on its regulation of immune cell function, cancer-associated fibroblasts, peritumoral adipose tissue and the gut microbiota. Current evidence shows that lipids are both the material basis of cell proliferation and stress adaptation and the signaling mediators connecting tumor and host cells; their pro-cancer effect depends on cell type, molecular background and anatomical site. Interventions targeting CD36, fatty acid synthase, cholesterol-related pathways and lipid droplet formation have preclinical value, but treatment benefit and the applicable population still require clinical validation. Future work should combine spatial lipidomics, metabolic flux analysis and functional experiments to establish reproducible stratification biomarkers, and should optimize combination therapy on the basis of protecting normal tissue and antitumor immune function.

Keywords: colorectal cancer, lipid metabolic reprogramming, tumor microenvironment, immunosuppression, metabolically targeted therapy

1. Introduction

Colorectal cancer (CRC) is one of the important global burdens of malignant tumors [1]. Identifying the factors that can be intervened in during tumor progression is an important research question for improving its diagnosis and treatment. In recent years, lipid metabolism has drawn attention: lipid droplet related proteins can take part in the invasion programs of tumor cells, fatty acid synthesis can change the composition of the gut microbiota, and lipid signals can connect tumor cells with stromal and immune cells [2-5]. Abnormal lipid metabolism is therefore expressed in changes of intracellular lipid content and in the remodeling of lipid origin, mode of utilization and intercellular allocation.

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The cells in the tumor microenvironment (TME) have different metabolic requirements. The same lipid or metabolic pathway may produce different effects in different cells, and it is difficult to determine its functional source and intervention value on the basis of the overall expression level of tumor tissue alone. This paper adopts a narrative review format, takes colorectal cancer as its subject, and discusses the topic around "tumor cell metabolic adaptation-microenvironment remodeling-clinical translation", focusing on fatty acid metabolism, lipid droplet homeostasis and cholesterol-related signaling, and distinguishing patient-sample associations, causal evidence from experimental models and prospects for therapeutic application.

2. Main links of lipid metabolic reprogramming in colorectal cancer

2.1. Exogenous fatty acid uptake and transport

Exogenous lipid utilization provides colorectal cancer cells with a supply route other than de novo synthesis. CD36 combines lipid uptake with signal regulation, and its pro-cancer effect needs to be understood in the context of a specific molecular background. Yang et al. found that the lipid droplet coating protein PLIN2 stabilizes CD36 by inhibiting proteasomal degradation, enhancing epithelial-mesenchymal transition and the migratory and invasive capacity of cells; blocking CD36 weakened these phenotypes [2]. The result connects lipid droplet related proteins with lipid transport on the membrane surface, but it does not justify the conclusion that all colorectal cancers depend on the same lipid uptake mechanism.

Besides CD36, the long-chain fatty acid transporter SLC27A1 is also related to colorectal cancer metastasis. Studies based on patient-related data and cell experiments indicate that SLC27A1-mediated utilization of long-chain fatty acids can promote diacylglycerol-3-phosphate synthesis and enhance migratory and invasive phenotypes [6]. When evaluating the role of fatty acid uptake, one should therefore examine transporters, the types of available lipids and downstream metabolic fates at the same time, and avoid equating increased expression of transporter-related molecules directly with increased uptake flux.

2.2. De novo fatty acid synthesis and its regulation

Sterol regulatory element-binding protein (SREBP) coordinates the expression of genes related to fatty acid and cholesterol synthesis. Wen et al. found that knocking down SREBP1 or SREBP2 reduced fatty acid levels in colon cancer cells, lowered cell proliferation, tumor sphere formation and xenograft growth, and was accompanied by changes in glycolysis and mitochondrial metabolism [7]. This indicates that the lipid synthesis program is linked to overall cellular metabolism and to the maintenance of stemness.

Fatty acid synthase (FASN) is the key enzyme of the de novo synthesis pathway. Coleman et al., combining human tissue, mouse and organoid studies, found that activation of signaling related to activating transcription factor 6 (ATF6) can be accompanied by changes in FASN and long-chain fatty acid metabolism; in the corresponding mouse models, FASN inhibition and microbiota transplantation experiments further support the involvement of lipid changes in tumorigenesis [3]. Its significance lies in connecting epithelial stress, lipid synthesis and microbial adaptation, rather than only showing that FASN is an enzyme required for cell proliferation.

The mechanism also suggests that metabolic changes in tumor cells can reshape the external nutritional environment, and then affect the interaction between host and microbes. However, tumorigenic dependence in a specific transgenic model is not equivalent to a shared weakness of

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tumors in all patients. FASN-related interventions still need to specify tumor molecular features, lipid supply conditions and the stage of treatment, in order to explain the differences in sensitivity between different models.

2.3. Fatty acid oxidation and metabolic adaptation

Fatty acid oxidation (FAO) supplies cells with energy and metabolic intermediates, and its action is subject to nutritional and microenvironmental conditions. Research by Su et al. on a high-fat diet indicates that carnitine- and acetylcarnitine-related changes can participate in colorectal cancer metabolic reprogramming through carnitine palmitoyltransferase 1A (CPT1A), and are intervenable in the experimental system [8]. The result supports studying FAO dependence under a specific exposure background, but this does not suffice to deduce that a persistently elevated FAO exists in all colorectal cancers.

Diet-induced metabolic adaptation also involves tumor initiation. Beyaz et al. found in mice that a high-fat diet can enhance the stemness and tumorigenic potential of intestinal stem and progenitor cells through programs related to peroxisome proliferator-activated receptor δ (PPARδ) [9]; Mana et al. further demonstrated by genetic and pharmacological interventions that FAO mediated by CPT1A downstream of PPARα/δ participates in this adaptation, and that inhibiting CPT1A can weaken high-fat diet-related intestinal tumor formation [10]. These studies provide causal clues among diet, lipid sensing and early tumorigenesis, but their mouse intestinal model still differs from the tissue context and disease stage of human colorectal cancer.

Understanding this link requires distinguishing enzyme expression, substrate level and actual flux. FAO and glucose metabolism may be compensatory or synergistic, and cannot be reduced to a fixed "imbalance". Functional validation of related targets should combine stable isotope tracing, mitochondrial function testing and genetic intervention, in order to judge whether tumor cells truly depend on fatty acid oxidation, and whether they can turn to other energy sources after this process is inhibited.

2.4. Lipid droplet formation and lipotoxicity buffering

Lipid droplets are dynamic organelles that store neutral lipids and regulate the allocation of fatty acids. Liu et al. found in colorectal cancer cells long adapted to an acidic environment that enhanced autophagy and lipid droplet formation constitute a continuous adaptive process: lipid droplets temporarily store autophagy-related fatty acids, buffer the damage of excess free fatty acids to mitochondria, and help maintain cell survival [11]. Increased lipid droplets may therefore reflect increased lipid supply, or may represent a protective mechanism against stress.

Lipid droplets are also related to tumor cell stemness. Tirinato et al. used Raman spectroscopy and cell sorting to find that colorectal cancer stem cells contain more lipid droplets, which correlates with CD133 expression and Wnt pathway activity, and that lipid droplet-rich cells showed strong tumorigenic capacity in xenograft experiments [12]. These findings support lipid droplets as a candidate characterization of functional state, but an increase in lipid droplets alone is not enough to determine that they drive stemness.

Lipid droplet research should attend to formation, mobilization and fatty acid utilization at the same time. Merely observing the number of lipid droplets cannot tell whether cells are in a state of high uptake, high synthesis or low consumption. Therapeutic ideas targeting lipid droplets also have to take their buffering role into account: disrupting the storage step may increase lipotoxicity, but

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whether a selective antitumor effect is produced needs to be verified in normal epithelium and other microenvironmental cells at the same time.

2.5. Cholesterol distribution and signal transduction

The function of cholesterol depends on its total amount and its intracellular distribution. Huang et al. found that ATP6V0A1 promotes cholesterol uptake by colorectal cancer cells, increases cholesterol accumulation in the endoplasmic reticulum and the generation of 24-hydroxycholesterol, and thereby activates immunosuppression-related signaling [5]. Sharma et al., in the APC-truncated-mutant colorectal cancer models they examined, found that increased cholesterol in the inner plasma membrane can maintain abnormal β-catenin signaling through interaction with Dishevelled (Dvl) [13]. The two studies point to the intracellular transport and the membrane signaling function of cholesterol respectively, which shows that "lowering cholesterol" is not a sufficiently precise description of the therapeutic mechanism and that intervention design still needs to specify the site of action and the molecular interaction.

3. Mechanisms by which abnormal lipid metabolism remodels the tumor microenvironment

3.1. Lipid utilization and functional differentiation of immune cells

The influence of lipid metabolism on immune function depends on the cell subset and the organ environment. In a study of colorectal cancer liver metastasis, activated hepatic stellate cells secrete interleukin-33 (IL-33), promoting the formation of DGAT1/2-dependent lipid droplets in mature low-density neutrophils and maintaining their survival and immunosuppressive function. Lipid-rich neutrophils can also supply lipids to tumor cells and take part in the reactivation of dormant cells; blocking IL-33 reduced intrahepatic colonization in mouse models and enhanced the effect of immunotherapy [14]. The mechanism indicates that stromal cells in the organ of metastasis can change immune cell function through metabolic support, and its range of application should first be limited to the corresponding liver metastasis context.

Different γδ T cell subsets also have different metabolic programs. Lopes et al. observed in several mouse tumor models, including colon cancer, that IL-17-producing γδ T cells have a stronger capacity for lipid uptake and storage, and that a lipid-rich environment favors their expansion; the interferon-γ-producing subset presents different metabolic requirements [15]. This indicates that the immunological consequences of metabolic intervention cannot be assessed by counting immune cells alone; subset composition, effector function and nutritional dependence should also be analyzed.

The CD36-related mechanism further shows that lipid uptake does not act in the same way on different T cells. Wang et al. found in several solid tumor models that CD36 maintains the mitochondrial adaptation and suppressive function of regulatory T cells in the tumor through PPARβ-related signaling [16]. Xu et al. found that after $CD8^+$ T cells take up oxidized low-density lipoprotein through CD36, lipid peroxidation and p38 signaling increase and effector function is impaired [17]. These cross-tumor-type studies suggest that evaluating CD36 intervention should consider immunosuppressive cells and effector cells together; the strength of its action in different colorectal cancer subtypes still needs verification.

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3.2. Cancer-associated fibroblasts and matrix remodeling

Cancer-associated fibroblasts (CAFs) are important mediators connecting tumor metabolism with changes in tissue structure. Hsu et al. found that oncogenic KRAS upregulates BMP4 and WNT5B through the transcription factor TFCP2, driving CAFs into a lipid-rich phenotype; these cells then secrete vascular endothelial growth factor A (VEGFA) and promote angiogenesis. Targeting TFCP2 reduced lipid-rich CAFs and tumor vessel formation in the related mouse models [4]. Such a process reveals how changes in tumor genes shape stromal metabolism through paracrine signaling.

Beyond secreting pro-angiogenic factors, CAFs can also supply lipid support directly. Gong et al. found that fatty acid and phospholipid metabolism in colorectal cancer CAFs is remodeled, that the lipids they secrete can be taken up by tumor cells and enhance migration, and that inhibiting FASN in CAFs or interfering with CD36-related uptake in tumor cells weakens this effect [18]. This study links stromal lipid synthesis with the exogenous supply to tumor cells and provides a basis for intervening on the lipid source and the receiving end at the same time.

Another mechanism takes the form of matrix stiffening caused by fatty acid accumulation. Deng et al., in research related to obstructive colorectal cancer, found that palmitic acid can activate NF-κB signaling in tumor cells, promote the secretion of CSF1, TGF-β1 and CXCL8, indirectly induce normal fibroblasts to shift into matrix-type CAFs, and enhance extracellular matrix deposition and stiffening [19]. The mechanism and the KRAS-related pro-angiogenic pathway act on different functions of CAFs respectively. CAFs as a whole should therefore not be regarded as a uniform pro-cancer population; subsequent intervention should pay attention to their origin, subtype and spatial location.

3.3. Cancer-associated adipocytes and peritumoral adipose tissue

Adipose tissue in colorectal cancer both supplies metabolic substrates and takes part in changes of cell identity and immune distribution. Song et al., in a study that included a colon cancer model, found that YAP/TAZ activation in dysfunctional adipocytes is related to dedifferentiation, an inflammatory phenotype and the formation of cancer-associated adipocytes [20]. However, dedifferentiation of mature adipocytes and transdifferentiation of adipose stromal cells are different processes, and the two should not be used interchangeably.

The substrates provided by adipocytes can also be converted into an oxidative dependence of tumor cells. Xiong et al. found that exposure to adipocytes or fatty acids can upregulate CPT1A in colon cancer cells; knocking down CPT1A weakened survival under nutrient shortage, organoid formation and adipocyte-promoted xenograft growth [21]. Together with the FAO studies described above, this shows that external lipid supply and intracellular utilization capacity jointly determine metabolic adaptation, and that analysis of one side alone easily underestimates intercellular interaction.

Research by Wang et al. on peritumoral visceral adipose tissue in colorectal cancer further found that tumor-derived factors can induce adipose stromal cells to form adipose-derived CAFs through adipose mesenchymal transition. These cells secrete CXCL12 and, through CXCR4-related chemotaxis, make tumor-specific $CD8^+$ T cells accumulate in the peritumoral adipose tissue, thereby taking part in tumor immune escape [22]. This finding indicates that a high local immune cell infiltration does not necessarily correspond to an effective intratumoral immune response and that the anatomical position of the cells matters as well; peritumoral adipose tissue should be evaluated as an independent spatial unit in tumor immunology research.

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3.4. Lipid mediators and immunosuppressive signaling

Lipid metabolism can be turned into intercellular signaling through specific products. After ATP6V0A1-related cholesterol uptake increases, 24-hydroxycholesterol activates the liver X receptor (LXR) and upregulates TGF-β1 secretion in tumor cells; the latter acts on the SMAD3 pathway of memory $CD8^+$ T cells and inhibits antitumor activity [5]. This forms a mechanistic chain from lipid transport in tumor cells to changes in immune cell function.

Prostaglandin E2 (PGE2) connects lipid metabolism with myeloid cell remodeling. Han et al. found that colorectal cancer-derived PGE2 acts on tumor-associated neutrophils through EP2/EP4 receptors, accompanied by increased reactive oxygen species and suppressed FOXO3a expression, promoting the expression of molecules such as ARG1 and MMP9 and pro-tumor function [23]. The "N2 type" in the literature is suitable for describing the functional phenotype under those experimental conditions, but it has difficulty covering all the states of patient neutrophils. Compared with marking cells by a binary scheme alone, combining functional testing and single-cell analysis is more helpful for determining the truly intervenable subgroup.

PGE2 can also act on antigen-presenting cells. Bayerl et al. found in tumor models and human-derived cell studies that PGE2 lowers the IRF8 expression of conventional type 1 dendritic cells (cDC1) through downstream cyclic adenosine monophosphate signaling of EP2/EP4, making it difficult for these cells to organize $CD8^+$ T cell responses effectively at the tumor site [24]. This cross-tumor-type mechanism and the neutrophil studies above together indicate that lipid mediators may affect several immune links at the same time, and that related combination therapy needs to determine which cell populations are actually affected.

3.5. Metabolic links between tumor epithelium and intestinal microbes

Colorectal cancer also has the tissue characteristic of being directly adjacent to luminal microbes. The ATF6 study indicates that epithelial lipid changes can provide selective conditions for specific tumor-associated bacteria, and that long-chain fatty acid exposure is linked with changes in the growth and function of the related bacteria [3]. Lipid metabolism research should therefore not be limited to tumor parenchyma and stroma; it should also consider intestinal ecology. However, lipid differences in tissue or stool may be affected at the same time by host metabolism, microbial activity and diet, and organoids, germ-free animals or microbiota transplantation are needed to tell source from causal direction.

4. Clinical translation potential and boundaries of the evidence

4.1. Conditions for the application of lipid-related biomarkers

Lipidomics and metabolism-related proteins provide candidate indicators for risk stratification. Ecker et al. analyzed the lipid profiles of colorectal cancer tissue in three retrospective cohorts at two centers and found that some triglyceride and sphingomyelin features can distinguish tumor from non-tumor tissue, and that triglyceride features are also related to postoperative disease-free survival and lymphovascular invasion [25]. The PLIN2 study also provided clues that expression levels are related to patient prognosis [2]. These results support further validation, but classification ability at the tissue level cannot be directly carried over to blood or stool screening performance, and prognostic correlation does not mean that drug benefit can be predicted.

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Biomarker development should specify its intended use in advance and adopt the corresponding clinical endpoints. Screening studies need to include controls such as adenoma and benign inflammation; prognostic models need to evaluate their incremental value over clinical variables such as stage; treatment-predictive biomarkers need to test their relationship with the effect of intervention. Sampling time, storage conditions, diet, weight status and medication should all be included in a standardized procedure. Achieving rather high classification performance within a single data set is not yet enough to demonstrate clinical usability.

4.2. Metabolic targets and combination therapy

The two main routes for intervening in fatty acid supply are reducing uptake and inhibiting synthesis. An anti-CD36 antibody showed inhibition of tumor growth in humanized CD36 mice bearing MC38 tumors, which provides a basis for efficacy evaluation [26]. FASN-related studies put more emphasis on the resistance background: Geisen et al. found that after BRAF V600E-mutant colorectal cancer cells acquire resistance to PLX8394, lipid synthesis is enhanced, and combining the FASN inhibitor TVB-3664 with BRAF-targeted intervention enhances the inhibition and delays the formation of resistance [27]. The result supports designing combination regimens on the basis of molecular subtype and metabolic dependence, and the patient benefit still requires dedicated verification.

The effect of FASN inhibition is also subject to metabolic compensation. Zaytseva et al. observed the antitumor activity of FASN inhibitors in primary colorectal cancer cells and patient-derived xenografts, and at the same time found that sensitivity differs between models [28]. Drury et al. further confirmed that CD36 expression can be compensatorily upregulated after FASN is suppressed, and that joint intervention on CD36 and FASN enhances the inhibition in cell experiments [29]. Lipid synthesis and uptake should therefore be evaluated as mutually complementary supply routes, and the metabolic changes before and after treatment may explain resistance better than target expression measured once.

Cholesterol intervention also has different strategies. Blocking the interaction between cholesterol and Dvl can inhibit β-catenin signaling and tumor growth in APC-truncated-mutant-related models [13]. Dalal et al. found that the HIF-2α inhibitor PT2385 alone had limited effect in the colorectal cancer models studied, but combined with statins to inhibit cholesterol biosynthesis it can enhance lipid peroxidation and ferroptosis-related effects [30]. The latter indicates that metabolic inhibition sometimes has to target a dependency formed after treatment; statins are already used for other indications, and this does not constitute evidence that the combination regimen is effective or safe for treating colorectal cancer.

What the above strategies share is the need to specify the target cells, the molecular background and the efficacy endpoints. The therapeutic effects discussed in this paper come mainly from cell and animal experiments, and patient sample analysis is mainly used to support mechanistic relevance or candidate stratification features. Representative targets and their translational limitations are listed in Table 1.

Table 1. Representative evidence and translational limitations of interventions related to lipid metabolism in colorectal cancer

Intervention target	Main research context	Representative finding	Main translational limitation
CD36 [26]	MC38 xenograft in humanized CD36 mice	Antibody treatment inhibits tumor growth	Cell selectivity and human safety need to be established

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Table 1. (continued)

FASN [27]	Model of BRAF V600E mutation-related resistance	TVB-3664 combined with BRAF-targeted intervention enhances the effect and delays resistance	Depends on specific molecular background; clinical validation needed
Interaction between cholesterol and Dvl [13]	APC-truncated-mutant cells and xenografts	Blocks β-catenin signaling and inhibits tumor growth	Long-term toxicity and pharmacokinetic properties need evaluation
HIF-2α and cholesterol synthesis [30]	Colorectal cancer cells and xenografts	PT2385 combined with statins enhances ferroptosis-related effects	Limited effect as a single agent; combined benefit still awaits clinical testing
IL-33 and lipid droplet formation [14]	Mouse model of colorectal cancer liver metastasis	Inhibits neutrophil lipid support and reduces intrahepatic colonization	Dependent on organ and cell subset
ATP6V0A1 [5]	Colorectal cancer cells and mouse models	Intervenes in cholesterol-related signaling and improves memory $CD8^+$ T cell function	Drug selectivity and human efficacy remain to be confirmed

Note: The "findings" in the table are all results obtained within the corresponding experimental systems and do not represent clinical treatment regimens that have already been established.

4.3. Microenvironment intervention and therapeutic selectivity

Interventions targeting the microenvironment can start from reducing pro-cancer lipid support or restoring immune function. IL-33-related lipid droplet formation, ATP6V0A1-related cholesterol transport and CXCL12-mediated distribution of peritumoral immune cells offer research directions at the level of organ specificity or of intercellular communication [5, 14, 22]. The evaluation of such strategies should not observe tumor volume only; it should also test effector T cell function, immunosuppressive subsets and changes in lipid distribution at the same time, to establish whether the efficacy is achieved through the expected mechanism.

Therapeutic selectivity is the key to translation. Normal intestinal epithelium, liver and immune cells need lipid metabolism as well, and broadly inhibiting one pathway may weaken the adaptive capacity of normal tissue. Follow-up studies should preferentially verify target cell selectivity, reasonable administration timing and the window of benefit for combination regimens, and should set endpoints for normal tissue and immune function. For dietary or microbial intervention, the mechanistic results obtained in animal models should also not be turned directly into nutritional or therapeutic regimens for patients.

5. Research limitations and future directions

First, the molecular backgrounds and tissue sites covered by the available evidence are not balanced. The metabolic relationships in the primary tumor, liver metastases and peritumoral adipose tissue cannot simply be merged. Some studies rely on cell lines, subcutaneous xenografts or a single genetic model, and still need verification in patient-derived organoids, models with an intact immune system and independent clinical cohorts. This paper is a narrative synthesis of representative studies; no systematic literature screening or quantitative meta-analysis was carried out, and the conclusions should be read with that scope in mind.

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Second, metabolic phenotypes need to move from static association to dynamic causal verification. Single-cell transcriptomics can help identify cell subsets, but transcriptional level cannot directly represent lipid content or flux. In the future, spatial lipidomics should be combined with single-cell and spatial transcriptomics, and isotope tracing together with cell-type-specific genetic intervention should be used to track the origin, direction of transfer and mode of utilization of lipids. Only when it is clear which cells depend on which pathway under which conditions can the treatment target be chosen reasonably.

Finally, combination therapy research should start from testable biological hypotheses. Around models of insufficient single-agent effect or of resistance, comparing different combinations of interventions and evaluating metabolic compensation, immune effects and tissue toxicity at the same time is more convincing than inferring synergy from related gene expression alone. Clinical studies need to define the population, the testing procedure and the endpoints in advance, and to confirm through independent validation whether the biomarker can improve the accuracy of patient selection, so that mechanistic findings gradually become repeatable diagnostic and therapeutic evidence.

6. Conclusion

Lipid metabolic reprogramming in colorectal cancer involves fatty acid uptake, synthesis, oxidation and lipid droplet homeostasis, and influences immune and stromal functions through cholesterol and lipid mediator signaling. Its core feature is the interaction among tumor cells, host cells and the local environment, and the specific effect depends on cell type, molecular background and lesion location. Current research has proposed several intervenable mechanisms, but going from preclinical activity to patient benefit still requires solving the problems of selectivity, metabolic compensation and biomarker validation. Stratified studies and combination therapy based on clear metabolic dependence are a reasonable direction for advancing the clinical translation of this field.

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