Tumor metabolism at the center of the cancer hallmarks

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In January 2026, Douglas Hanahan published a third major update to his conceptual framework of "cancer hallmarks" in *Cell*.[1] Among these hallmarks, tumor metabolic reprogramming, as a classic hallmark incorporated in 2011,[1-2] has been significantly expanded and refined within the updated framework. Rather than being viewed as an isolated characteristic of cancer cells, tumor metabolism is now a complex network integrated with genomic instability, tumor microenvironment interactions, neural regulation, and systemic interactions. This commentary argues that examining tumor metabolism within the multidimensional hallmark framework not only deepens our understanding of cancer biology but also provides a theoretical basis for developing more effective combinational therapies.

TUMOR METABOLIC REPROGRAMMING FROM WARBURG EFFECT TO MULTIDIMENSIONAL REGULATION

The concept of tumor metabolic reprogramming can be traced back to Otto Warburg's discovery in the 1920s, later termed the "Warburg effect". Even with sufficient oxygen, cancer cells tend to convert glucose to lactate rather than efficiently producing energy through oxidative phosphorylation.[3] While less efficient in ATP production, this metabolic strategy provides cancer cells with multiple survival advantages. This is achieved through several key mechanisms: (1) supplying biosynthetic precursors (such as nucleotides, amino acids, lipids) to support vigorous cell proliferation; (2) providing essential cofactors (such as ATP, SAM, and acetyl-CoA) that drive protein post-translational modifications (PTMs); and (3) modulating the microenvironment via lactate-mediated acidification to enhance invasion and immune evasion.

Tumor metabolic reprogramming extends beyond a simple shift toward aerobic glycolysis. It links the cancer cell's internal state to its external microenvironment and ultimately to its gene expression profile. Central to this process is the accumulation of metabolites such as acetyl-CoA, 2-hydroxyglutarate (2-HG), and succinate, which can act as critical signaling nodes by directly inhibiting a family of epigenetic regulators. Through these regulations, metabolic changes alter the landscape of PTMs, especially for modifications of histones and DNA.[4] Simultaneously, the unique metabolic features of the tumor, characterized by hypoxia, nutrient deprivation, and acidosis, affect the composition of the intratumoral microbiome. Metabolites produced by these intratumoral bacteria, such as short-chain fatty acids and polyamine, further integrate with cancer-cell-derived metabolites, to modulate the host cell's PTM machinery. In this way, the tumor metabolome acts as a master conductor of PTMs, translating metabolic cues directly into stable epigenetic changes that define cancer cell plasticity, immune evasion, and therapy resistance (Figure 1).

THE "BEHIND-THE-SCENES DRIVER" AND "FRONTLINE EXPRESSION" OF METABOLIC REPROGRAMMING IN PHENOTYPIC PLASTICITY

The most striking new hallmark in the 2026 framework is "unlocking phenotypic plasticity", the ability of cancer cells to transition between different cellular states. This characteristic contributes to intratumorally cellular heterogeneity and enables n cancer cells to adapt to various therapeutic pressures. There is also a profound, reciprocal relationship between metabolic reprogramming and phenotypic plasticity (Figure 1). From a metabolic perspective, transitions between cellular states are invariably coupled with metabolic shifts. For example, when cancer cells undergo epithelial-mesenchymal transition (EMT) or MET, their metabolic characteristics will shift from glycolysis and certain amino acids to the new microenvironment. Thus, metabolic reprogramming is not only a result of phenotypic

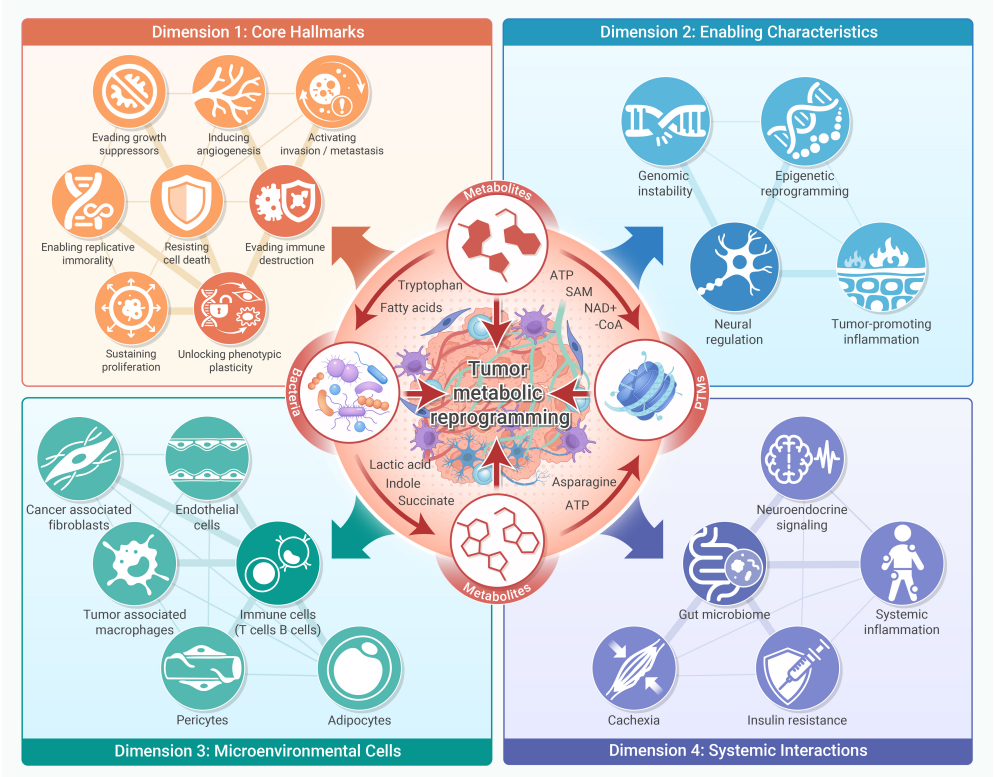

Figure 1. Central integrating node of metabolism in tumor hallmarks

Conversely, phenotypic plasticity adds new dimensions to our understanding of metabolic reprogramming. It is now widely recognized that the metabolic states of cancer cells are highly plastic. Throughout different stages of tumor progression and in response to shifting microenvironmental stressors, cancer cells can flexibly adjust their metabolic patterns. For example, highly proliferative cancer cells in primary tumors often rely heavily on glycolysis, while in nutrient-poor metastatic foci, cancer cells may switch toward more efficient oxidative metabolism or activate other nutrient scavenging mechanisms. This metabolic flexibility reflects phenotypic plasticity at the metabolic level. However, the dynamic regulation of metabolism within specific organelles, such as mitochondria, the endoplasmic reticulum (ER), lysosomes, and the nucleus, is far more complex. How these organelle-specific processes coordinate with broader cellular functions remains to be elucidated in future investigations.

NEURAL REGULATION ADDS A NEW DIMENSION TO TUMOR METABOLISM

Hanahan's 2026 framework identifies neural regulation as an independent enabling phenotypic characteristic of cancer. The emergence of cancer neuroscience in recent years has brought to light a fundamental yet historically neglected dimension of tumor biology. Nerves are not only passively distributed around tumors but also actively communicate with tumor cells. Researchers have found that some cancer cells can even form pseudo-synaptic connections with neurons, enabling them to receive neurotransmitter-derived growth signals. These findings expand our understanding of how neural signaling influences tumor metabolism. Neurotransmitters can function not only as growth signals but also regulators of metabolism. For example, norepinephrine activates β-adrenergic receptors and downstream cAMP-PKA pathway, resulting in influencing glycolysis and mitochondrial metabolism. More importantly, the formation of pseudo-synapse interfaces suggests that cancer cells may reprogram their metabolism to respond rapidly to neurotransmitter-induced electrical or calcium signaling. On the other hand, metabolic communication may also occur in the opposite direction. Tumor-derived metabolites can feed back to affect the nervous system (Figure 1). For example, lactate produced by cancer cells functions not only as an energy substrate but also a signaling molecule, potentially promoting neural innervation and remodeling into tumors by affecting the metabolic state of tumor-associated neurons. These bidirectional interactions position neural regulation and tumor metabolism as an emerging frontier for future research.

METABOLIC CROSSTALK AMONG DISTINCT CELLS IN THE TUMOR MICROENVIRONMENT

Another dimension of the updated Hanahan's framework emphasizes interactions among various cell types in the tumor microenvironment (TME), such as cancer-associated fibroblasts (CAFs), macrophages (TAMs), neutrophils, and other stromal components. From a metabolic perspective, the TME can be viewed as a metabolic ecosystem characterized by cooperative interactions among different cell populations (Figure 1).[5] Among them, cancer cells typically exhibit enhanced glycolysis, consuming large amounts of glucose and secreting lactate. In contrast, stromal cells such as CAFs may use lactate, converting it to pyruvate, to support "fuel" for cancer cells. This phenomenon, often referred to as the "reverse Warburg effect", reveals metabolic collaboration between cancer cells and stromal cells. The metabolic state of TAMs is also closely related to their function. For instance, classically activated (M1-like) macrophages are typically associated with glycolytic metabolism, while alternatively activated (M2-like) macrophages rely more on oxidative phosphorylation. As such, regulating the metabolic state of macrophages can reshape their functional phenotype, thereby changing the immune state of the entire tumor microenvironment. Therefore, tumor metabolism should be understood not only at the level of individual cancer cells but also as a multicellular metabolic ecosystem.

RE-EXAMINING CANCER AS A METABOLIC DISEASE

The fourth dimension of Hanahan's updated framework highlights systemic interactions, emphasizing the complex interplay between tumors and organism-wide metabolic regulation. This perspective expands the study of tumor metabolism from local sites to the level of the whole organism (Figure 1). Cancer patients often show systemic metabolic disturbances, including cachexia, insulin resistance, systemic inflammation, etc. These systemic metabolic changes can in turn feedback to affect tumor evolution and progression. For example, lipid breakdown products and inflammatory factors released during cachexia may be utilized by circulating tumor cells, promoting their distant colonization. The gut microbiome has emerged as an important regulator of systemic metabolism, and has been implicated in tumor development and response to immunotherapy. Alternatively, a growing number of novel metabolites derived from host-microbiota interactions have been identified and shown to play critical roles in tumorigenesis, invasion, and metastasis (Figure 1). Together, these findings highlight the importance of considering tumor metabolism within the context of systemic physiology. Effective therapeutic strategies require not only targeting cancer cells locally but also correcting systemic metabolic disturbances and restoring the overall homeostasis of the organism.

THERAPEUTIC IMPLICATIONS OF HALLMARK CO-TARGETING AND METABOLIC INTERVENTION

In his 2026 review, Hanahan proposed the concept of mechanism-guided hallmark co-targeting, in which multiple cancer hallmarks are targeted simultaneously to achieve more durable therapeutic responses. This approach has shown initial success in clinical practice by combined application of anti-angiogenic drugs and immune checkpoint inhibitors in certain cancers. Tumor metabolism represents a key node for co-targeting strategies, as metabolic interventions can synergize with targeted therapies against other hallmarks. For instance, the metabolic state in the TME is an important determinant for immunosuppression. Targeting metabolic pathways (such as targeting IDO, or arginase), may help reverse the immunosuppressive microenvironment and enhance the efficacy of immune checkpoint blockade. Although metabolic interventions hold promise for restricting phenotypic plasticity and preventing therapy resistance, the field must now consider a new layer of complexity. It is worth noting that implementing hallmark co-targeting strategies requires a precise understanding of the "hallmark landscape" of individual tumors. Defining patient-specific hallmark profiles may therefore guide therapeutic decision-making. Thus, "Hallmark-guided personalized therapy" based on such maps will represent an important future direction of precision oncology.

Over the past 26 years, the cancer hallmarks framework has undergone a clear conceptual evolution: from focusing cancer-cell intrinsic capabilities, to incorporating tumor microenvironmental interactions, and more recently to integrating the neural regulation, microbiome, and systemic physiology. Within this expanding landscape, tumor metabolism has remained a central theme. By providing both a necessary substrate for acquiring other cancer hallmarks and a shared pathways for enabling characteristics, metabolic reprogramming occupies a unique central position in cancer biology. Metabolism is the essential medium for dialogue among cells in the microenvironment and for systemic communication between the tumor and the organism. We propose that metabolism constitutes a "universal language", a common denominator linking the various dimensions of cancer (Figure 1). Understanding this central role may unlock new opportunities for translational research and therapeutic intervention.

The current framework, while more integrative, remains a simplification of the complex, dynamic, and context-dependent nature of tumor biology. Our understanding of the precise mechanistic connections linking metabolism, the microbiome, and epigenetic regulation remains incomplete, with many interactions inferred from correlative rather than causal studies. We also acknowledge the considerable challenge of translating these complex, multi-dimensional interactions into effective targeted therapies, given the profound heterogeneity of tumors and the remarkable plasticity of metabolic reprogramming.

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DECLARATION OF INTERESTS

The authors declare no competing interests.