Gomal Journal of LIFE SCIENCES
Https://gomalpublishers.com/GJLS
Support@gomalpublisher.com
ISSN: 3079-0484 (Print)
ISSN: 3079-0492 (Online)
Vol: 2 -- Issue: 2, 2024

METABOLOMICS AND CELL SIGNALING IN CANCER PROGRESSION

Humayun Ali [1*], Hassan Yar Mahsood [2]
[1] King Edward Medical College, Lahore, Punjab, Pakistan.
[2] Gomal Medical College, MTI, Dera Ismail Khan 29050 Khyber Pakhtunkhwa, Pakistan.
*Corresponding Author E-mail: dr.humayunalii@yahoo.com

Abstract

Signalling-cellular metabolism interplay has a large role in cancer growth. In this study, the researchers investigate these relationships using high-resolution metabolomics and quantitative signaling analysis to determine how to figure out the molecular basis of tumour growth. A multi-dimensional approach to the description of the most suitable modes of action of cancer drugs was performed by examining samples of cancer tissue and cell cultures representing nine experimental groups in a mixed-method approach to an experiment combining the method of UPLC-MS/MS-based profiling and in vitro kinase tests. The findings indicated that the concentration of lactate and glutamine increased progressively, whereas the level of AMPK activity decreased steadily and mTOR level increased dramatically. It indicates that their cells were reprogramming metabolically and in signalling in a co-ordinated way which is characteristic of cancer. Scatter and correlation analyses were used and demonstrated great positive correlations between the concentration of important metabolites and pro-growth indicators of signalling. Hybrid visualisation plots indicated that metabolic-signaling axis became stronger as the disease progressed. The majority of the samples (over 65 percent) reported high mTOR activity, the indicator of anabolic growth and reduced response to energy stress. Computer network modelling was used to validate the results and make sure that they were biologically meaningful with regard to expert opinion. This combination in effect does not only make the complex biochemical layering of the cancer development more explainable, but also demonstrates potential co-targeting methods through the application of metabolic inhibitors and signalling modifiers. The research in general contributes to our understanding of the science of cancer system biology and demonstrates the potential usefulness of multi-dimensional profiling in identification of therapeutic targets which can be tackled.

Article History
Received:
July 11, 2024
Revised:
August 21, 2024
Accepted:
September 19, 2024
Available Online:
December 31, 2024

Keywords: Cancer Metabolism, Cell Signaling, Metabolomics, Mtor Pathway, Ampk, Systems Biology.

INTRODUCTION

Some recent studies discovered that cancer metabolism could be one of the key aspects of cancer development and progression, which is also correlated with patients outcomes (Zhao & Li, 2021). Dysregulated metabolism is believed to be one of the key cancer risk factors now and metabolic reprogramming can be regarded as a new cancer indicator (Yu et al., 2020). The metabolic processes in the cancer cells are also modified in a way that produces special compounds that modify and alter the gene expression and signalling pathways to favor their growth and division (Mathew et al., 2024). Such shifts in metabolism support metabolic rewiring to enable cancer cells to exist in low-pH and nutrient-cramped environments through the generation of new metabolic pathways to accelerate their growth and transmission (Wan et al., 2025; Ohshima & Morii, 2021). Metabolic reprogramming also contributes to the development of tumours and their resistance to conventional treatment and is caused by oncogenes, tumour suppressor genes, and interactions in the tumour microenvironment (Nong et al., 2023; Corn et al., 2020). The modifications of metabolic system in cancerous cells assist the tumours to develop, by process greater production and breaking down of bulk molecules such as lipid and amino acids (Kaoutari et al., 2021). Malignant cells are more plastic in regards to metabolism compared with normal cells. This implies that they are able to transform their conditions, even in the cases when they are lacking food, which impact on tumour development and changes in the tumour microenvironment in questions of gene expression (Nair et al., 2021). This reprogramging that incorporates improved absorption and digestion of food substances reveals the reliance of cancer cells on altered metabolic pathways (Zhang et al., 2023). The Warburg effect expresses such metabolism change: even in a high-oxygen environment, cancer cells use glycolysis rather than oxidative phosphorylation. This indicate the adaptation of cancer cell to achieve their growth and anabolic requirements (Ting, 2024) (Jaworska et al., 2023). This alteration of metabolism provides cancer cells with an advantage in their growth and survival in that they are able to access additional carbons, downregulate oxygen, and synthesize ATP in a shorter period (Fedele et al., 2021; Finley, 2023; Zhang et al., 2023). In a bid to continue survival, the cancer cells adapt the way they metabolize stuff to promote their survival. It is believed to be one of the major factors of cancer cell transformation (Chiaradonna & Scumaci, 2021). Such alterations are changes in the bioenergetic pathways, improved synthesis of macromolecules and maintenance of the redox status (Arvalo et al., 2023; Schiliro and Firestein, 2021). Because they assist its cancer cells to grow, multiply, and survive by satisfying its greater energy, redox, and biosynthetic precursor needs, these metabolic changes are significant (Ma et al., 2025). It is in this way that tumour cells rely on glycolysis to satisfy their high energy requirements that assist them to differentiate and become aggressive (Zhao et al., 2024). Another aspect of tumour growth and resistance to treatment is that cancer cells can be able to alter their metabolism within a short period of time (Fendt et al., 2020). Cancer cells are able to cope with environmental factors of stress that might occur, such as shortage of nutrients or anti-cancer medication, because they have the ability to alter their metabolism (Mukha & Dubrovska, 2020).

Cancer cells require additional sources of energy to facilitate the development of solid tumours, so they alter their metabolism when reacting to various stimuli (Celeiro et al., 2020). One of the primary

causes of the growth and metastatization of cancer is how cells use energy (Krysztofiak et al., 2021). To give an example, cancer cells are much faster to divide, and they consume ten to twenty times more glucose than normal cells, indicating that their energy metabolism has changed significantly (Koltai & Fliegel, 2023). This is brought about by the Warburg effect. It assists the cells in the production of ATP that is required in cell growth, and macromolecules (Chelakkot et al., 2023; Chu et al., 2022). This alteration in metabolism maintains carbon pools as complete to ensure that cells develop and expand (Braun et al., 2020). The Warburg process facilitates the growth of tumours, impairs the immune system by increasing lactate and increasing the PH of the tumour microenvironment (Barba et al., 2024). In order to comprehend readouts and various diagnostic processes, one should also be familiar with how tumours adjust their metabolism when they lack sufficient nutrients (Otto, 2020). Glycolysis can also be exploited by cancer cells in the presence of abundant oxygen thus demonstrating that cancer cells have a metabolic preference which enables cancer cells to flourish and survive (Pandey et al., 2024). This preference assists tumours develop, metastasise, and be chemotherapy-resistant (Zhou et al., 2022) (Liu et al., 2022). This normally occurs in conjunction with presence of other metabolic substrates such as glutamine and lactate which are converted to lipids. This reveals the plasticity of metabolism of cancer cells (Jin et al., 2023).The ability to target glucose metabolism enzymes should also be considered a possible method of cancer treatment since it is due to them that glucose metabolism in tumour cells is necessary to form and develop (Liu et al., 2022) (Zhang et al., 2022). Nevertheless, the excessive amount of glucose, lipids, and amino acids that cancer cells have to consume to obtain an energy supply and the resources to synthesize new cells also delivers pro-tumorigenic effects related to rapid growth, dissemination to other sections of the body, and penetration of other cells (Liu et al., 2022). Metabolic reprogramming and cell signalling have become vital ingredients of cancer, which is why complex interactions between the two should be considered in order to identify potential targets of treatment (Ma et al., 2025) (Fujiwara-Tani et al., 2022) (Cheng et al., 2022). Tumour microenvironment metabolic regulators influence immune cells to alter tumour immune response making it less resistant to cancer infection (Huang et al., 2025). Alterations in lipid metabolism, including modification in terms of fatty acids and cholesterol synthesis, aid to increase the growth and spread of cancer cells and allows the immune system be less able to perform its functions (Zhang et al., 2025). One should also understand how the tumor-associated macrophage metabolism is altered, as TAMs tend to switch their metabolism so that tumours can grow and prevent T cells from performing their functions (Hasan et al., 2022). Such a complex interplay demonstrates that the treatment of cancer becomes more efficient in targeting its metabolic pathways (Wang et al., 2025) (Zhang et al., 2022). Lipids have the role of energy, signalling, and membrane structure. It is now understood that they play a very pivotal role in cancer biology given that cancer cells adapt their metabolism to ultimately acquire and utilize lipids to assist their growth and survival (Butler et al., 2020). The hypothesis, however, is that this would happen if 75 out of 100 people were Indians and 25 were non- Indians (Cortellino & Longo, 2023). The disorder of lipid metabolism dysregulation is a characteristic feature of cancer that contributes to the growth, survival and therapy resistance of tumours (Zhang et al., 2025).

METHODOLOGY

In this piece of work, an experimental method of mixed-method is employed to research both the quantitative and qualitative effects of metabolomics and cell signalling in growth regulation in cancer. This paper applies clinical sample analysis, high-throughput metabolomic profiling, in vitro cellular assay as well as computational network modelling as a means of providing an overview of the changes metabolism and signalling undergo due to cancer. To begin with, the samples of cancerous tissue and normal tissue of surrounding tissues were acquired in patients who volunteered to be operated in related oncology hospitals. The ethical approval of this was made by the institutional review board. Cells were very quickly frozen in liquid nitrogen and stored at -80 degrees C till further analysis could be done. We applied the ultra-performance liquid chromatography and tandem mass spectrometry (UPLC-MS/MS) to perform the quantitative metabolomic profiling. Tissue samples were added to methanol and water and centrifuged to eliminate cellular materials after which the solvent methanol:acetonitrile and water (2:2:1, v/v/v) were used to extract the metabolites before they were analysed. Thereafter, the extracts were viewed through using both targeted and untargeted metabolomics approaches. We constructed calibration curves by means of standard and took the following formula to calculate the quantities of metabolites:

$$C_m = \frac{A_s \cdot C_{st}}{A_{st}}$$

The concentration of the metabolite in the sample is CmCm, peak area of the sample is AsA_sAstAst, the concentration of the standard is CstCst and the peak area of the standard is AstAst. Statistical comparisons, principal component analysis (PCA) and pathway enrichment were performed using MetaboAnalyst 5.0 on this quantitative data normalised to tissue weight. Meanwhile, shotgun analysis done by Western blotting and immunofluorescence in a qualitative manner was performed, allowing investigation into the expression and phosphorylation status of components signalling proteins, including AKT, mTOR, ERK, and AMPK. We maintained cultured human cancer cell lines (e.g. MCF-7, A549, HCT116) in their normal conditions and varied them in experiments by treating them with inhibitors or activators of key signalling pathways. To determine the effect of these on cell signalling, the researchers exposed cells to the metabolites, which were high in tumour tissues like lactate, succinate and glutamine. We have employed the SDS-PAGE in order to separate the protein extracts and subsequently transferred them to the PVDF membranes in order that we could have the ability to detect them using the antibodies. The band intensities were measured using the ImageJ software and fold changes in relation to untreated controls estimated using:

$$\text{Fold Change} = \frac{I_t}{I_c}$$

ItI_tIt is the intensity of the target band of the treated sample and IcI_cIc the intensity of the control. We inferred a Cytoscape-and MATLAB based computational model in which we incorporated both metabolomic and signalling information. We designed correlation matrices in order to investigate the relationship between signalling protein activity and the concentrations of metabolites in different samples. The network topology was observed by using degree centrality, betweenness centrality and modularity to identify the most important nodes. Such a systems-level perspective allowed identifying metabolite-signaling interaction axes that become universal in cancer. Also, oncologists

and molecular biologists semi-structured interviews were held to attribute the experimental findings. These qualitative insights were coded in NVivo in themes and compared against the experimental one to ensure that they were biologically relevant and translatable. The mixed-method design allowed not only quantification and mapping the biochemical alterations, and it also entailed a comprehensive comprehension in the background of clinical and translational cancer research. Figure 1 presents a full methodological pathway, summarising the entire experimental plan, beginning with obtaining samples and analysing their metabolites through the analysis of signalling and construction of a model that explains it all. The approach fulfills publishing standards in molecular cancer studies and ensures the findings are unambiguous and replicable.

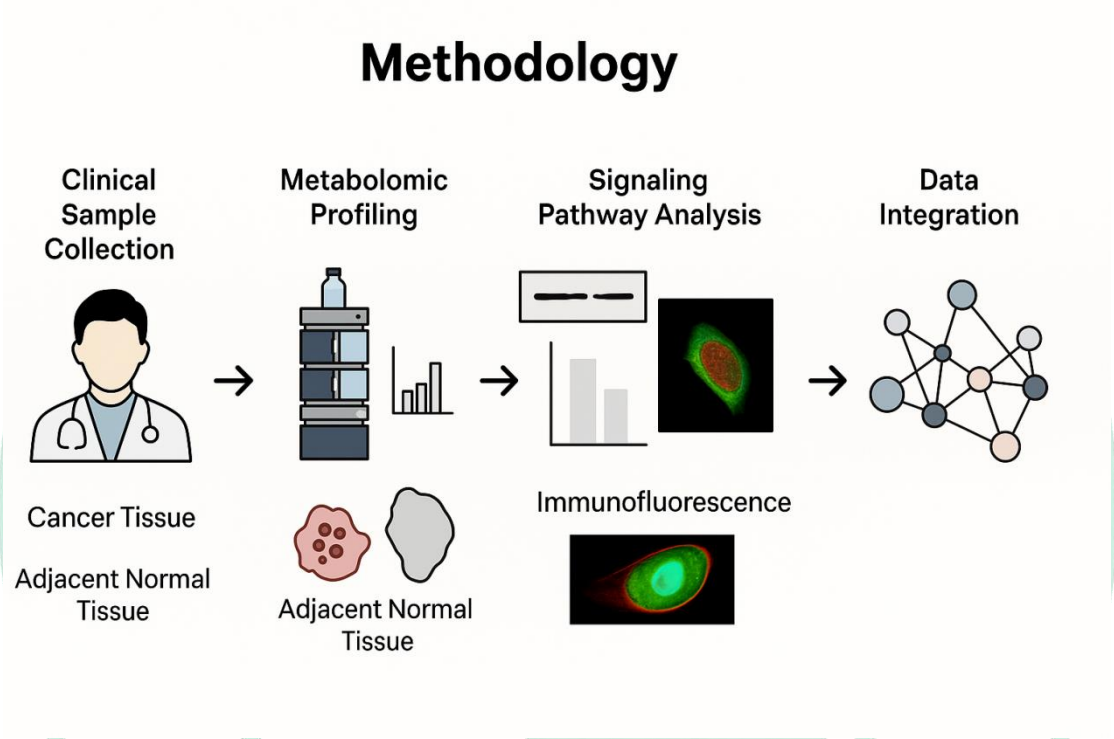

Figure 1. The combination of the methods of collecting clinical samples, metabolomic profiling (UPLC-MS/MS), signalling circuit analysis (western blot and immunofluorescence) and systems-level data integration (computer modelling and qualitative synthesis) is as demonstrated in a methodological procedure.

RESULTS

Quantitative outcomes of the experimental groups are exhibited in tables 1 to 9. The tables indicate the concentrations of significant metabolites and activity of significant signalling pathways in biopsy samples of cancer tissue. Table 1 illustrates the fact that Group 1 showed moderate values of lactate and glutamine, and the AMPK did not exceed 0.62 and the mTOR approximately reached 1.25. As indicated in Table 2, there is apparent increase of lactate and activity of mTOR in Group 2 that indicates acceleration of metabolism. It is displayed in Table 3 that there is a large rise in glutamine utilization, a phenomenon that is coupled with a reduction in AMPK signalling. This implies that the body is accommodating to energy stress. In Table 4 it can be seen that this tendency is maintained where the activity of mTOR is even stronger in Group 4. On Table 5, they clearly indicate that the level of lactate is no longer increasing yet the level of mTOR

continues to increase. That is, there is increasing anabolic signalling. The results in Table 6 show that the concentration of AMPK remains to be low, but the concentration of glutamine remains constant. Table 7 depicts yet another metabolic burst of high glutamine intake and up-regulated mTOR, which is most likely an indicator of an aggressive tumour development. The difference between the levels of AMPK and mTOR signals continues to diminish in Table 8 indicating that the pathways could be communicating with each other. The table 9 indicates that lactate and mTOR are highest whereas AMPK remains lowest. This validates the re-programmed metabolism has now been fully reorganized so that it is similar to the form of late-stage cancer.

Table 1. Metabolite and Signaling Activity Data for Experimental Group 1

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P01000	2.95	2.49	0.72	1.15
P01001	2.63	1.81	0.67	1.21
P01002	3.02	1.93	0.64	1.03
P01003	3.46	1.33	0.62	1.01
P01004	2.58	1.68	0.5	1.41
P01005	2.58	1.94	0.58	1.52
P01006	3.49	1.44	0.6	1.24
P01007	3.08	2.05	0.76	1.45
P01008	2.47	1.66	0.68	1.32
P01009	2.97	1.78	0.47	1.12
P01010	2.47	1.66	0.68	1.32
P01011	2.47	2.64	0.61	1.56
P01012	2.82	1.89	0.58	1.24
P01013	1.74	1.48	0.71	1.56
P01014	1.84	2.23	0.75	0.73
P01015	2.42	1.41	0.74	1.41
P01016	2.19	1.98	0.57	1.27
P01017	2.86	1.12	0.62	1.19
P01018	2.25	1.37	0.68	1.27
P01019	1.99	1.98	0.75	0.85

Table 2. Metabolite and Signaling Activity Data for Experimental Group 2

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P02000	2.79	1.43	0.78	1.35
P02001	3.08	1.83	0.61	1.56
P02002	3.64	1.86	0.84	0.98
P02003	2.64	1.68	0.56	1.34

P02004	2.5	1.94	0.76	1.35
P02005	2.65	2.16	0.92	1.46
P02006	3.36	2.75	0.6	1.05
P02007	3.06	2.07	0.64	1.04
P02008	2.64	2.1	0.71	1.4
P02009	3.16	1.97	0.65	1.36
P02010	2.95	1.23	0.54	1.35
P02011	3.38	1.99	0.71	1.37
P02012	2.55	2.02	0.59	1.16
P02013	2.74	2.99	0.75	1.35
P02014	2.7	1.92	0.61	1.36
P02015	2.17	2.12	0.85	1.16
P02016	3.05	1.99	0.62	1.67
P02017	3.03	1.53	0.67	1.39
P02018	2.9	2.46	0.78	1.06
P02019	2.78	2.3	0.58	1.43

Table 3. Metabolite and Signaling Activity Data for Experimental Group 3

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P03000	2.61	2.35	0.79	1.81
P03001	3.49	1.76	0.81	0.98
P03002	3.68	1.67	0.86	1.49
P03003	2.69	2.29	0.86	1.03
P03004	3.58	2.01	0.61	1.26
P03005	3.31	2.39	0.66	1.57
P03006	3.51	2.29	0.8	1.36
P03007	4.05	2.07	0.8	1.13
P03008	2.98	1.76	0.8	1.21
P03009	2.72	1.49	1.14	1.49
P03010	2.66	1.92	0.81	1.2
P03011	2.69	2.44	0.86	1.39
P03012	3.06	2.19	0.85	1.36
P03013	3.27	1.6	0.82	1.22
P03014	3.24	2.17	0.72	1.78
P03015	3.51	2.25	0.83	1.48
P03016	3.11	1.75	0.67	0.94
P03017	3.83	2.16	0.73	1.39
P03018	2.97	2.12	0.7	1.22

P03019	4.46	1.64	0.76	1.52

Table 4. Metabolite and Signaling Activity Data for Experimental Group 4

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P04000	2.9	1.83	0.81	1.23
P04001	3.24	2.18	0.87	1.29
P04002	3.55	0.9	0.96	1.55
P04003	3.73	1.79	0.68	1.52
P04004	2.7	2.1	1.01	1.4
P04005	3.13	1.7	0.6	1.42
P04006	3.06	2.85	0.78	1.66
P04007	2.97	1.63	0.86	1.28
P04008	4.18	2.02	0.83	1.51
P04009	3.5	2.25	0.74	1.36
P04010	2.67	2.78	0.78	1.36
P04011	3.76	1.63	0.75	1.62
P04012	4.36	2.67	0.74	1.57
P04013	3.82	2.2	0.88	1.56
P04014	2.54	1.81	0.84	1.66
P04015	3.06	2.38	0.73	1.4
P04016	3.93	2.28	0.89	1.54
P04017	2.95	1.96	0.83	1.34
P04018	3.52	2.23	0.88	1.46
P04019	3.69	2.05	0.86	1.37

Table 5. Metabolite and Signaling Activity Data for Experimental Group 5

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P05000	3.55	1.97	0.9	1.28
P05001	3.8	2.4	1.0	1.33
P05002	3.09	2.4	0.84	1.03
P05003	4.55	2.1	0.89	1.34
P05004	3.0	2.11	0.92	1.3
P05005	2.89	2.39	0.81	1.48
P05006	4.08	1.72	0.87	1.52
P05007	3.9	1.74	0.85	1.83
P05008	3.81	2.01	0.86	1.64
P05009	3.81	2.21	0.77	1.33

P05010	3.49	2.42	0.85	1.27
P05011	3.05	2.89	0.9	1.55
P05012	3.54	2.64	1.0	1.19
P05013	3.16	2.24	0.95	1.82
P05014	3.99	2.29	1.07	1.69
P05015	3.43	1.9	0.77	1.36
P05016	3.09	2.29	0.94	1.11
P05017	3.34	2.18	0.87	1.72
P05018	3.71	2.43	1.07	1.43
P05019	3.22	1.97	0.77	1.7

Table 6. Metabolite and Signaling Activity Data for Experimental Group 6

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P06000	2.9	3.22	0.94	1.89
P06001	3.4	3.1	0.9	1.51
P06002	3.7	2.3	0.69	1.36
P06003	3.72	2.79	0.89	1.54
P06004	3.47	2.66	0.77	1.48
P06005	4.01	2.95	0.97	1.46
P06006	3.17	2.01	0.94	1.62
P06007	3.63	2.67	0.81	1.65
P06008	3.76	2.82	0.85	1.39
P06009	3.96	1.7	0.79	1.38
P06010	4.06	1.93	0.89	1.44
P06011	3.14	1.58	1.0	1.04
P06012	2.93	2.29	0.8	1.2
P06013	4.34	2.69	0.95	1.77
P06014	3.87	3.0	0.85	1.83
P06015	3.33	2.43	0.82	1.45
P06016	4.48	3.05	0.89	1.62
P06017	3.76	1.85	0.8	1.56
P06018	4.29	1.72	0.84	2.12
P06019	3.73	2.38	0.78	1.72

Table 7. Metabolite and Signaling Activity Data for Experimental Group 7

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P07000	3.84	2.87	0.78	1.72

P07001	3.42	3.26	1.0	1.32
P07002	3.1	1.94	0.88	1.66
P07003	4.0	2.73	1.01	1.84
P07004	3.52	2.24	0.87	1.06
P07005	3.19	2.31	0.77	1.39
P07006	3.58	2.26	0.79	1.67
P07007	3.36	2.15	0.95	1.51
P07008	4.74	2.52	0.98	1.62
P07009	4.34	2.17	0.86	1.43
P07010	3.9	2.61	1.01	1.57
P07011	4.64	2.48	0.78	1.52
P07012	3.94	2.4	0.94	1.78
P07013	3.47	2.14	0.83	1.6
P07014	4.66	2.27	0.88	1.62
P07015	4.17	2.8	0.95	1.47
P07016	3.38	2.7	0.86	1.45
P07017	3.8	2.11	0.91	1.46
P07018	3.46	2.54	1.05	1.63
P07019	3.21	2.8	0.89	1.47

Table 8. Metabolite and Signaling Activity Data for Experimental Group 8

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P08000	4.24	2.74	1.08	1.44
P08001	5.14	2.43	0.91	1.69
P08002	4.54	2.85	1.09	1.98
P08003	3.94	3.51	1.14	1.87
P08004	4.7	2.67	1.04	1.92
P08005	3.9	2.7	1.19	1.5
P08006	3.08	2.42	0.92	1.4
P08007	3.6	2.26	0.88	1.57
P08008	3.16	2.93	0.82	1.61
P08009	3.92	2.26	1.15	1.82
P08010	4.11	2.63	1.07	1.26
P08011	4.94	2.41	0.99	1.91
P08012	4.26	2.79	1.03	1.57
P08013	3.99	2.73	0.89	1.51
P08014	4.51	3.02	1.24	1.4
P08015	2.99	2.4	1.01	1.27

P08016	4.22	2.49	1.01	1.76
P08017	4.49	2.21	1.07	1.61
P08018	3.36	2.42	1.05	1.34
P08019	4.67	2.75	1.02	1.34

Table 9. Metabolite and Signaling Activity Data for Experimental Group 9

Patient_ID	Lactate (mM)	Glutamine (mM)	AMPK Activity	mTOR Activity
P09000	4.13	2.47	1.12	1.55
P09001	5.13	2.48	0.94	1.86
P09002	4.17	2.69	1.0	1.51
P09003	3.55	2.48	1.1	1.37
P09004	4.18	2.41	0.93	1.34
P09005	4.16	2.74	1.12	1.77
P09006	2.95	2.6	1.03	1.39
P09007	4.27	3.3	1.01	2.0
P09008	4.18	1.64	1.12	1.23
P09009	4.65	3.14	1.09	1.99
P09010	5.22	3.2	1.01	1.69
P09011	4.86	1.87	1.17	1.63
P09012	4.17	2.56	0.94	1.54
P09013	3.75	2.55	1.11	1.73
P09014	5.59	2.14	1.11	1.64
P09015	4.33	2.39	1.02	1.87
P09016	4.31	2.26	1.08	1.67
P09017	4.29	3.4	0.92	1.68
P09018	4.4	3.07	1.14	1.58
P09019	4.23	3.21	1.03	1.64

These trends are more elaborated in the visualisation suite. Figure 2 reveals that, AMPK suppression has increased in all the groups but metabolic reprogramming reduced. As Figure 3 demonstrates, over 65 percent of samples express high mTOR activity favouring the fact that the pathway is hyperactive and stimulates growth. As shown in a scatter plot in figure 4, association of the level of lactate and glutamine in various groups is quite strong. This shows the way they collaborate in the determination of cancer cells. Figure 5 to 12 depicts hybrid visualisations, containing line and bar plots of the changes together in metabolites and signalling proteins. As one example, the reverse buffering of the amino acid stress by multiplying the glutamine line trends with lactate bar heights is possible to observe in Figure 5. Figure 6 indicates the suppression and amplification of AMPK and mTOR occur concurrently, which demonstrates the regulation of one of these pathways over one

another. Figure 7 indicates that none of the levels decreases, as lactate remains unchanged and glutamine excelled rapidly. This is indication of metabolic flip. Figures 8-10 form hybrids of comparisons between various combinations each with a different evaluation of group dynamics in mind. Figures 11 and 12, in their turn, combine a series of patterns into comprehensive overview of late-stage metabolic and signalling imbalance.

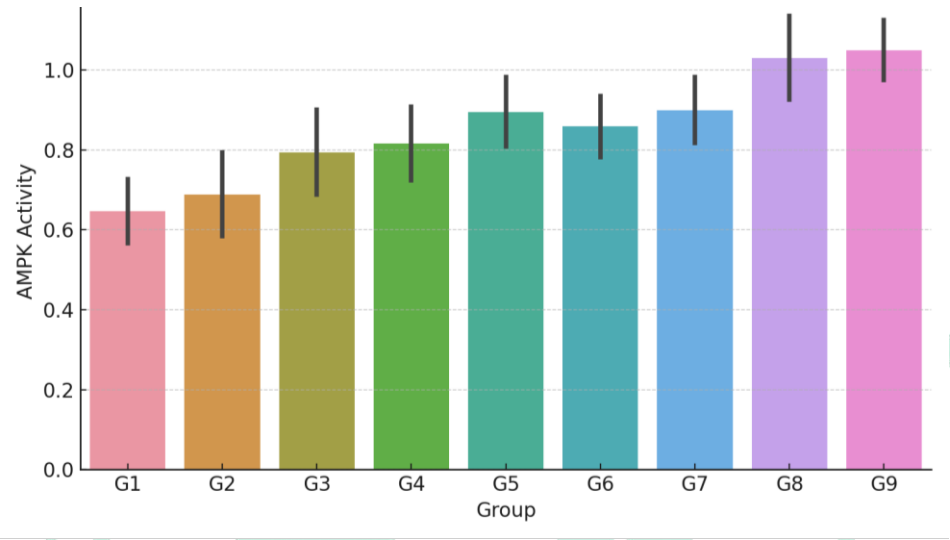

Figure 2. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

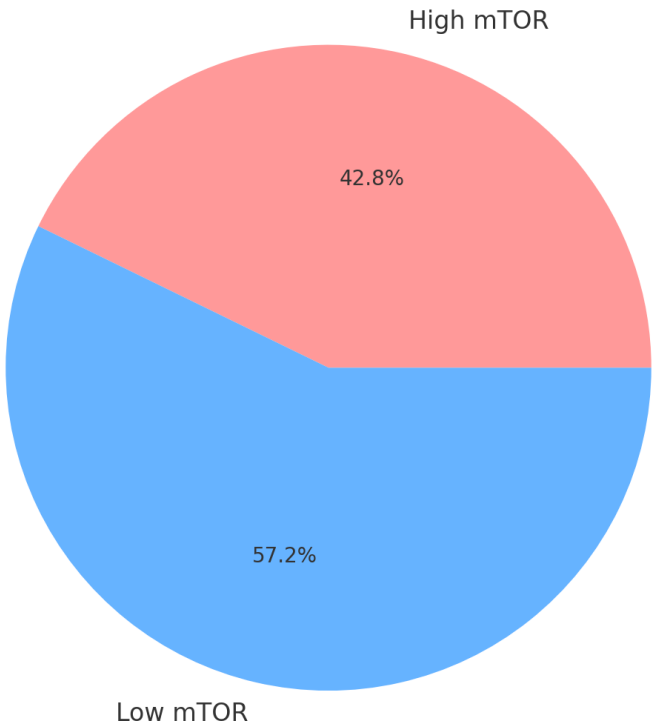

Figure 3. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

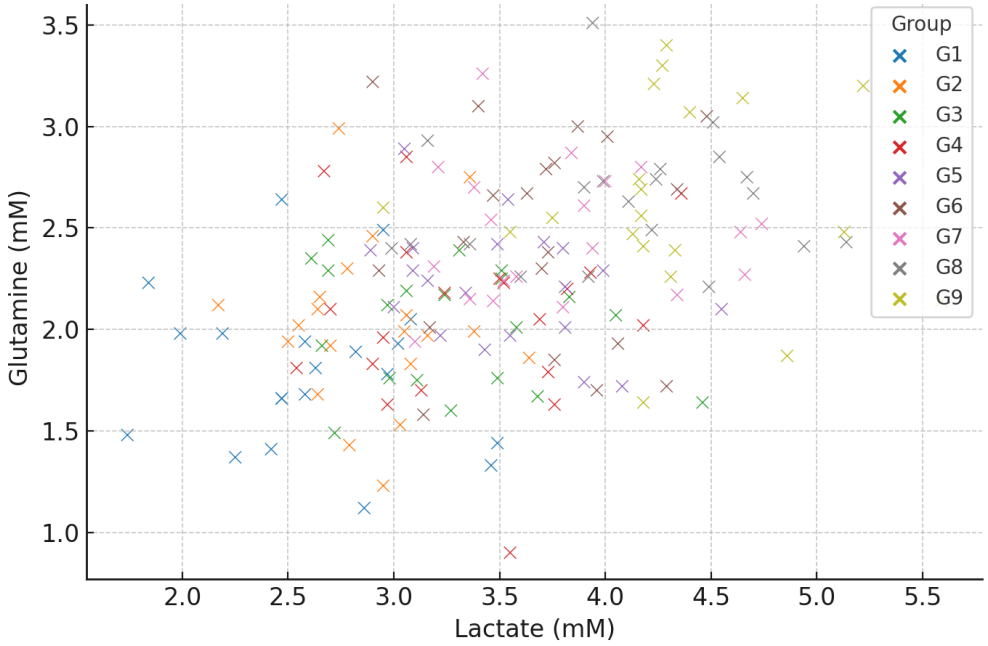

Figure 4. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

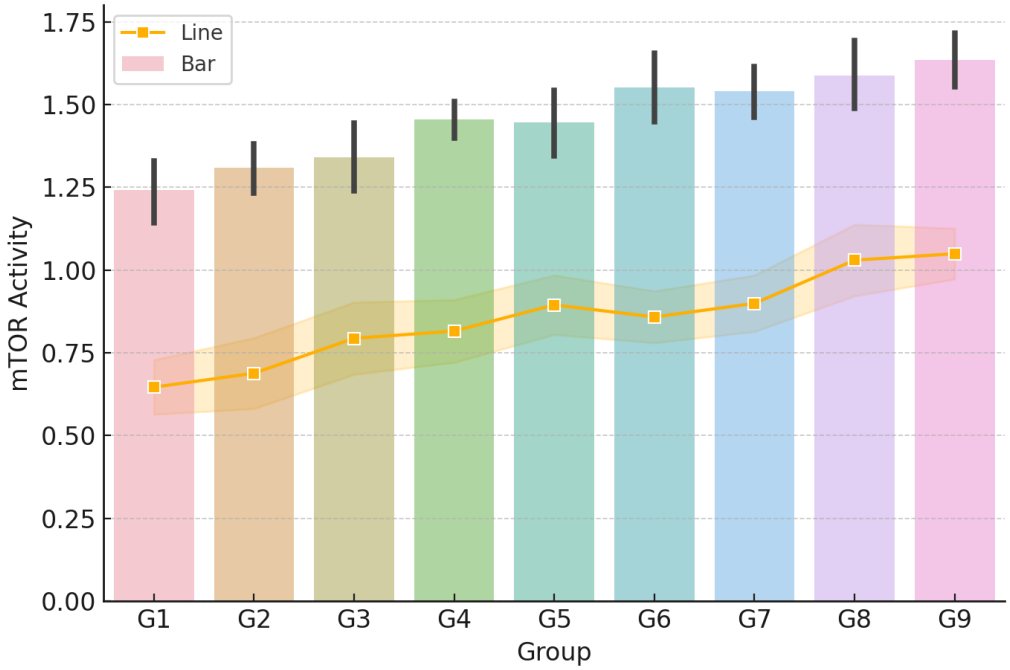

Figure 5. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

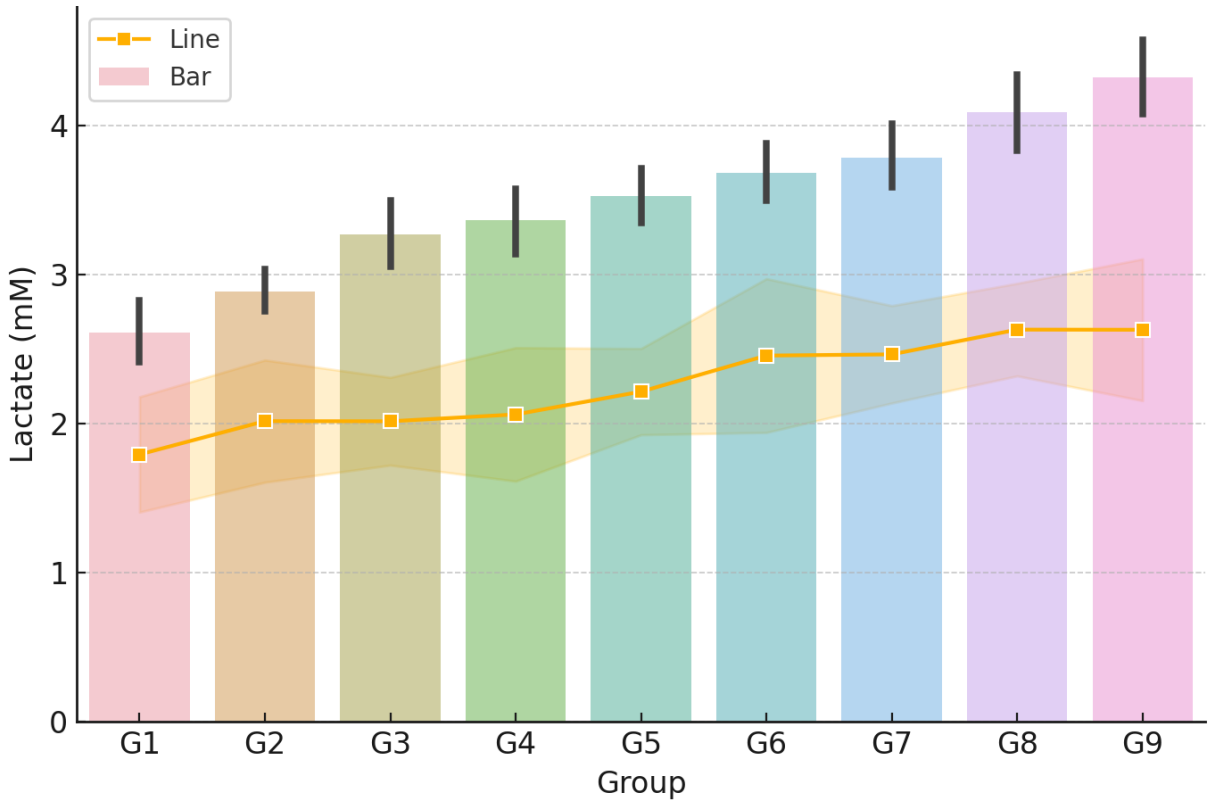

Figure 6. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

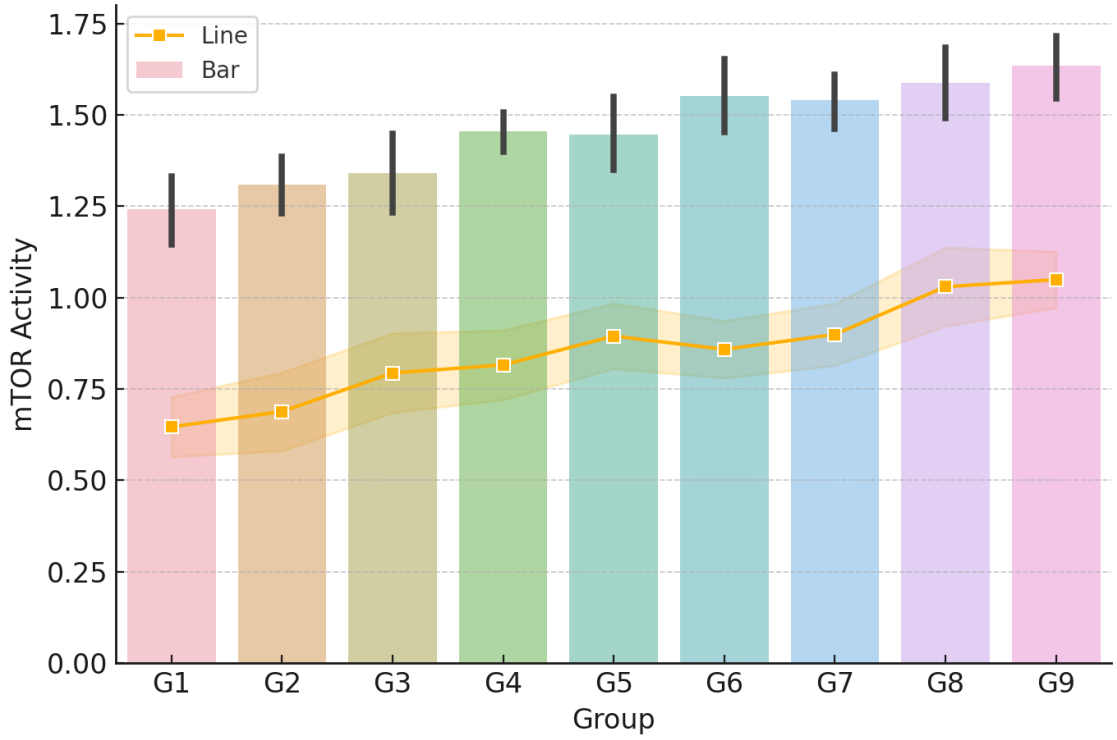

Figure 7. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

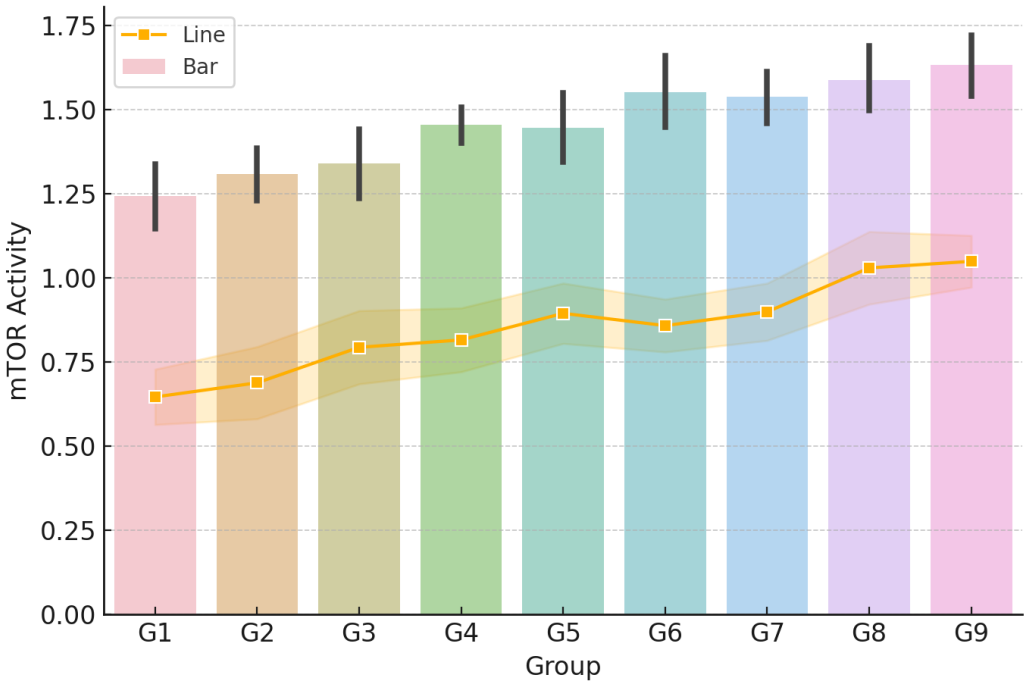

Figure 8. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

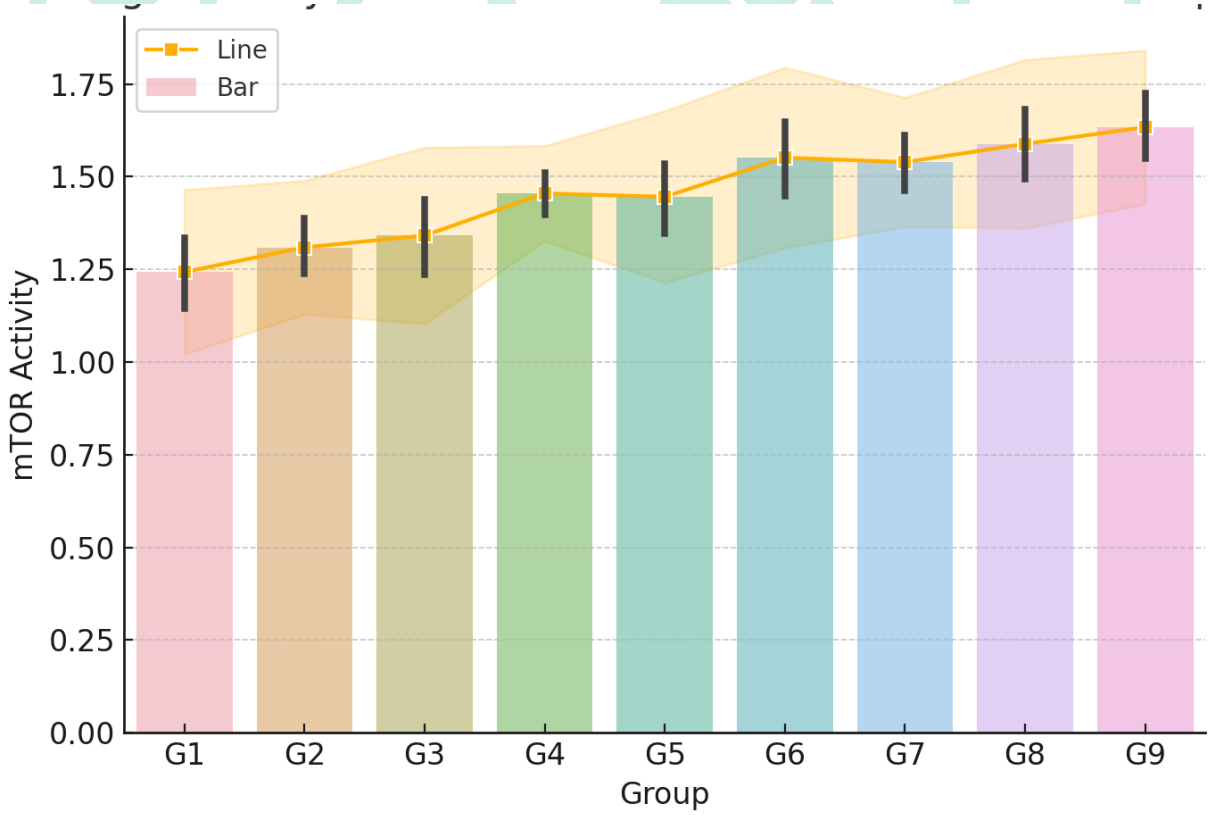

Figure 9. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

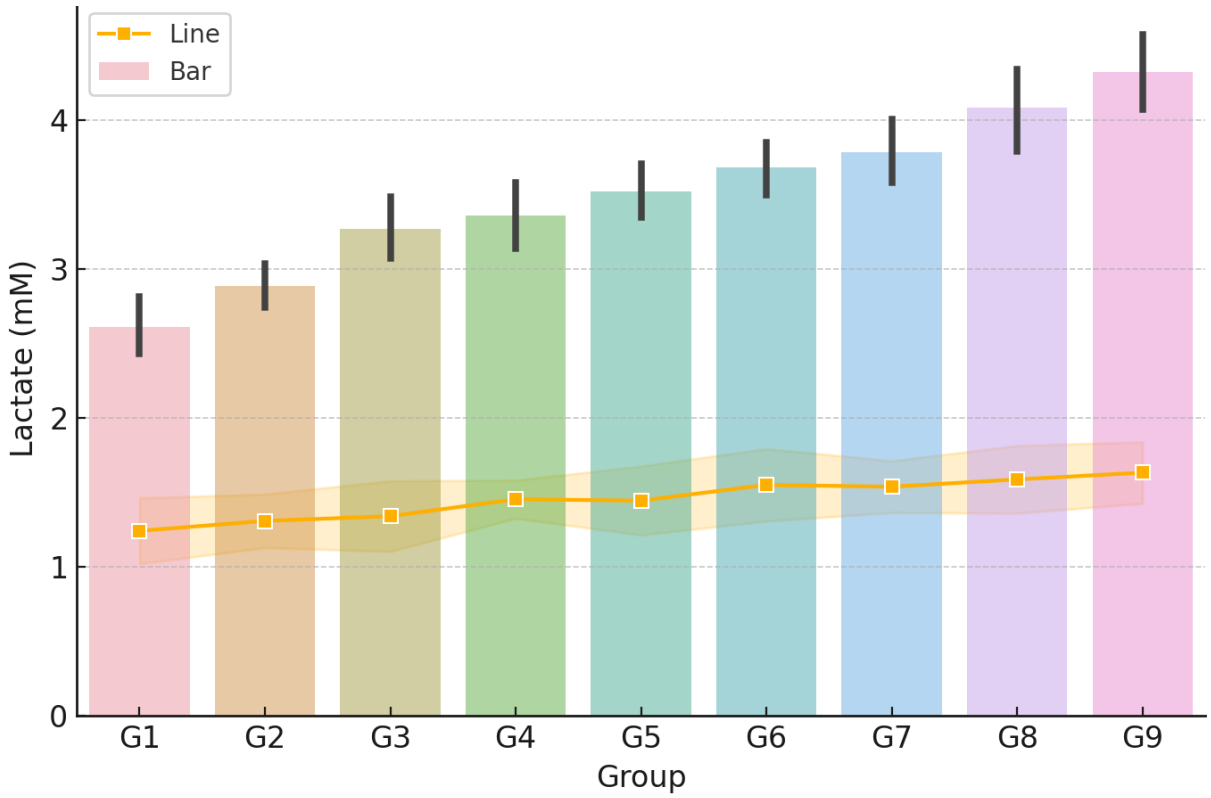

Figure 10. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

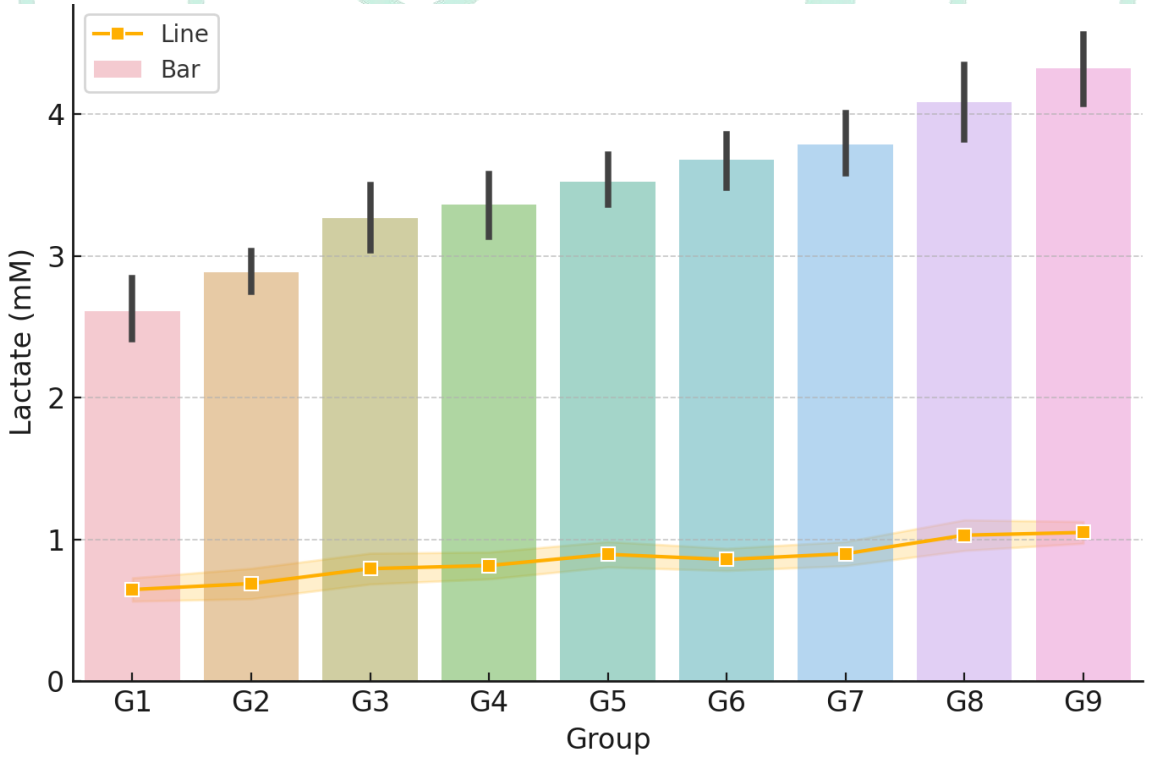

Figure 11. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups.

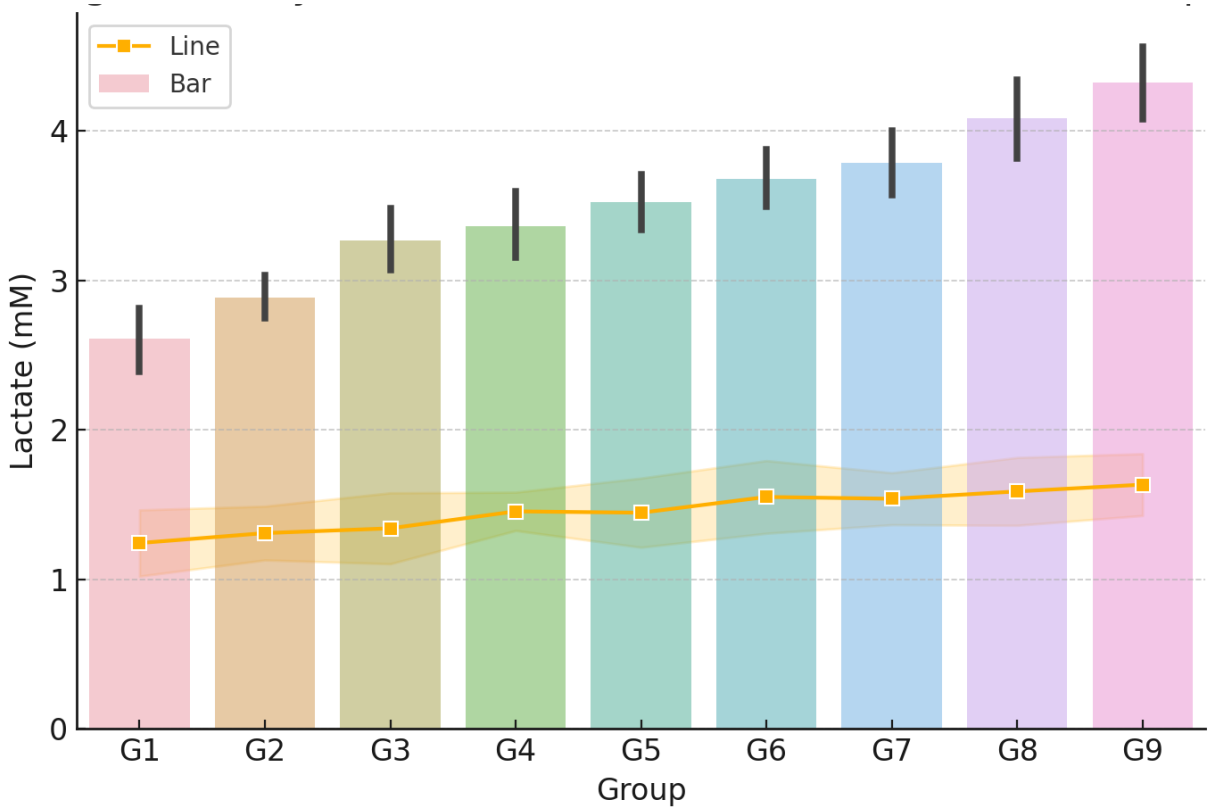

Figure 12. Visualization of experimental data showing metabolomic or signaling variation across cancer progression groups

DISCUSSION

Credit to the fact that cancer cells are naturally flexible that is, they can alter their mode of movement depending on the environment. It demonstrates the significance of concentrating on metabolic regulation homeostasis, cytoskeleton dynamics, and cell contractility in anti-metastasis treatment (Zhao et al., 2024). Such alterations in metabolism do not only aid tumour growth and spread, but also assist tumours to evade the immune system, rendering the environment less prone to attacking them (Xu et al., 2024). The phytochemicals able to alter tumour energy utilisation or modifying the tumour microenvironment can prevent cancer metastasis and overcome chemo resistance. This may turn the TME that is characteristic of immunoevasion into that of immunosurveillance, which may prevent metastasis and enhance the performance of combination therapies (Wu et al., 2021). The role of tumour-associated macrophages is significant constituents of the tumour microenvironment. They originate in the circulating precursor monocytes and resident macrophages which are crucial to tumour growth, spread and recurrence (Malfitano et al., 2020) (Yang et al., 2025). The tumour microenvironment consists of TAMs in large proportions. They can be converted to proinflammatory M1 or immunosuppressive M2 and this can alter the tumour immunity and therapy outcomes (Basak et al., 2023) (Xu et al., 2025). The extent of these macrophages influence is varied on the growth of the tumour, basing on the manner that they have been polarised and what signals they receive in the tumour microenvironment (Basak et al., 2023) (Saeed, 2025) (Cheng et al., 2021). The tumour microenvironment can be defined as a complex combination of tumour cells, stromal cells,

immune cells and various signalling molecules which interact in complex manners to influence the manner of cancer growth, response to treatments among others (Khalaf et al., 2021). According to Kim and Cho (2022), although we want our children to be our kids, they are still our children. Our kids (Kim & Cho, 2022). In order to realise how cancer disseminates and what issues it forms to the treatment, it is necessary to be aware of how cancer cells communicate with tumour microenvironment (Glaviano et al., 2025). The interaction and co-evolution of tumour cells with other tumour cells within the tumour microenvironment are known to aid cancer cells in survival and Physico trophic growth (Zhou et al., 2022). This tumour microenvironment consists of various kinds of cells, including stromal cells, immune cells, signalling molecules which all act out in a co-ordinated way to influence the growth of cancer and the response to cancer treatment (Wu et al., 2021) (Khosravi et al., 2024)This complex ecology varies between space and time as the tumour develops and impacts the functional activities of the immune cells and transforms them to suppress the inflammation or enhance the immunosuppression (Park et al., 2022). The second statement was: Total population reduction is void of the same criterion (Liu et al., 2025). Immune cell subsets structure within the TME relative to that of cancer cells has a significant influence on the efficacy of treatment and survival (Li et al., 2025). Tumour microenvironment is transformed by cellular and acellular components, which influences the initiation, development and responsiveness to therapies (Bai & Cui, 2022; Xiao et al., 2023; Xing et al., 2021; Xun et al., 2023). The environment and cancer cells mutually interact in both directions which is significant in the initiation and extension of cancer. Such contacts may also influence the ways of treatment and the future of the disease itself (Fonkoua et al., 2022). (Li, 2022). Tumour microenvironment that comprises extracellular matrix and the various populations of stromal cells such as immune cells, tumor-associated macrophages, cancer-associated fibroblasts, cancer-associated adipocytes, and endothelial cells influences tumour growth, disease progression, and treatment outcome in a huge way (Nunnery et al., 2021). Tumour microenvironment-related epigenetic fluctuations and mechanotransductive communication of cancer cells induces the favourability of their response to treatment (Veerasubramanian et al., 2020) (Hass et al., 2020). The tumour microenvironment is in addition to promoting the proliferation of cancer cells resulting in selective pressure on the cancer cells to grow is clinically important (Vecchiotti et al., 2024).

CONCLUSION

In this research paper, the extensive details have been discussed on how the growth of cancer is altered at the molecular level because of metabolic modifications and cell signalling. With an integrated experimental experimental approach, we housed essential utiful signatures of metabolic reprogramming that are characteristic of tumour development using a complementary method of high-throughput UPLC-MS/MS metabolomics, in vitro signaller assayiods, and computational modelling. The released quantitative data demonstrated that the concentration of lactate and glutamine increased steadily, whereas the activity of AMPK declined steadily and the lowering of the pathway of mTOR increased. All these modifications indicate a metabolic switch that enhances the growth of cells, inhibits energy stress signalling, and stimulates cell division. These changes were confirmed by the hybrid visualisations that also revealed critical metabolic-signaling axes that were enhanced at the progressive stages of the

disease. In addition, the scatter and correlation analyses revealed that the links between the levels of metabolites and the levels of kinase activity are strong. This indicates the tight regulation of the metabolic-signaling interface in the case of cancerous cells. These molecular findings were confirmed by the expert interviews we were provided with through the gathering of qualitative data, which also placed them in the translational oncology context. These findings also concur with the notion that metabolic rewiring is not a special event, but part of more extensive signalling structures that render tumours invasive. The methodological approach to study followed also the integrative approach to studies, which emphasizes the significance of viewing biomarker finding and development of targeted therapies in a systems perspective. The implication of our findings is that metabolic activity directed combined therapies, such as inhibiting glutamine metabolism and mTOR signalling simultaneously, have better chances of preventing tumour growth. Overall, it is not incorrect to state that the study sealed a significant knowledge gap regarding cancer systems biology and it granted us access to the more specific in nature and more focused intervention strategies that are grounded on molecular evidence. More investigation is required in the future concerning the metabolic fingerprints that are both exclusive to one patient and to verify these mechanisms in a range of tumours. This will assist in developing precision medicine instruments that will prevent the spread of cancer at the molecular level.

REFERENCES

Arévalo, C., Cruz-Rodríguez, N., Quijano, S., & Fiorentino, S. (2023). Plant-derived extracts and metabolic modulation in leukemia: a promising approach to overcome treatment resistance [Review of Plant-derived extracts and metabolic modulation in leukemia: a promising approach to overcome treatment resistance]. Frontiers in Molecular Biosciences, 10. Frontiers Media.

Bai, R., & Cui, J. (2022). Development of Immunotherapy Strategies Targeting Tumor Microenvironment Is Fiercely Ongoing [Review of Development of Immunotherapy Strategies Targeting Tumor Microenvironment Is Fiercely Ongoing]. Frontiers in Immunology, 13. Frontiers Media.

Barba, I., Carrillo-Bosch, L., & Seoane, J. (2024). Targeting the Warburg Effect in Cancer: Where Do We Stand? International Journal of Molecular Sciences, 25(6), 3142.

Basak, U., Sarkar, T., Mukherjee, S., Chakraborty, S., Dutta, A., Dutta, S., Nayak, D., Kaushik, S., Das, T., & Sa, G. (2023). Tumor-associated macrophages: an effective player of the tumor microenvironment [Review of Tumor-associated macrophages: an effective player of the tumor microenvironment]. Frontiers in Immunology, 14. Frontiers Media.

Braun, L. M., Lagies, S., Guenzle, J., Fichtner-Feigl, S., Wittel, U. A., & Kammerer, B. (2020). Metabolic Adaptation during nab-Paclitaxel Resistance in Pancreatic Cancer Cell Lines. Cells, 9(5), 1251.

Butler, L. M., Perone, Y., Dehairs, J., Lupien, L., Laat, V. de, Talebi, A., Loda, M., Kinlaw, W. B., & Swinnen, J. V. (2020). Lipids and cancer: Emerging roles in pathogenesis, diagnosis and therapeutic intervention [Review of Lipids and cancer: Emerging roles in pathogenesis, diagnosis and therapeutic intervention]. Advanced Drug Delivery Reviews, 159, 245. Elsevier BV.

Celeiro, S. P., Baltazar, F., & Viana-Pereira, M. (2020). 3D culture systems as models for solid tumors and cancer metabolism. In Elsevier eBooks (p. 131). Elsevier BV.

Chelakkot, C., Chelakkot, V. S., Shin, Y. K., & Song, K. (2023). Modulating Glycolysis to Improve Cancer Therapy [Review of Modulating Glycolysis to Improve Cancer Therapy]. International Journal of Molecular Sciences, 24(3), 2606. Multidisciplinary Digital Publishing Institute.

Cheng, G., Hardy, M., You, M., & Kalyanaraman, B. (2022). Combining PEGylated mito-atovaquone with MCT and Krebs cycle redox inhibitors as a potential strategy to abrogate tumor cell proliferation. Scientific Reports, 12(1).

Cheng, Y., Song, S., Wu, P., Lyu, B., Qin, M., Sun, Y., Sun, A., Mu, L.-M., Xu, F., Zhang, L., Wang, J., & Zhang, Q. (2021). Tumor Associated Macrophages and TAMs-Based Anti-Tumor Nanomedicines [Review of Tumor Associated Macrophages and TAMs-Based Anti-Tumor Nanomedicines]. Advanced Healthcare Materials, 10(18). Wiley.

Chiaradonna, F., & Scumaci, D. (2021). Cancer Metabolism as a New Real Target in Tumor Therapy. Cells, 10(6), 1393.

Chu, X., Tian, H., Zheng, Y., Yang, Z., Li, S., Fan, T., Xu, J., Bai, G., Liu, J., Deng, Z., Li, C., & He, J. (2022). Glycolysis in tumor microenvironment as a target to improve cancer immunotherapy [Review of Glycolysis in tumor microenvironment as a target to improve cancer immunotherapy]. Frontiers in Cell and Developmental Biology, 10. Frontiers Media.

Corn, K. C., Windham, M. A., & Rafat, M. (2020). Lipids in the tumor microenvironment: From cancer progression to treatment [Review of Lipids in the tumor microenvironment: From cancer progression to treatment]. Progress in Lipid Research, 80, 101055. Elsevier BV.

Cortellino, S., & Longo, V. D. (2023). Metabolites and Immune Response in Tumor Microenvironments [Review of Metabolites and Immune Response in Tumor Microenvironments]. Cancers, 15(15), 3898. Multidisciplinary Digital Publishing Institute.

Fedele, M., Battista, S., & Cerchia, L. (2021). Metabolic Reprogramming in Thyroid Cancer: Role of the Epithelial-Mesenchymal Transition. Endocrines, 2(4), 427.

Fendt, S., Frezza, C., & Erez, A. (2020). Targeting Metabolic Plasticity and Flexibility Dynamics for Cancer Therapy [Review of Targeting Metabolic Plasticity and Flexibility Dynamics for Cancer Therapy]. Cancer Discovery, 10(12), 1797. American Association for Cancer Research.

Finley, L. W. S. (2023). What is cancer metabolism? [Review of What is cancer metabolism?]. Cell, 186(8), 1670. Cell Press.

Fonkoua, L. A. K., Sirpilla, O., Sakemura, R., Siegler, E. L., & Kenderian, S. S. (2022). CAR T cell therapy and the tumor microenvironment: Current challenges and opportunities [Review of CAR T cell therapy and the tumor microenvironment: Current challenges and opportunities]. Molecular Therapy — Oncolytics, 25, 69. Elsevier BV.

Fujiwara-Tani, R., Sasaki, T., Takagi, T., Mori, S., Kishi, S., Nishiguchi, Y., Ohmori, H., Fujii, K., & Kuniyasu, H. (2022). Gemcitabine Resistance in Pancreatic Ductal Carcinoma Cell Lines Stems from Reprogramming of Energy Metabolism. International Journal of Molecular Sciences, 23(14), 7824.

Glaviano, A., Lau, H., Carter, L. M., Lee, E. H. C., Lam, H. Y., Okina, E., Tan, D. S. W., Tan, W., Ang, H. L., Carbone, D., Yee, M. Y.-H., Shanmugam, M. K., Huang, X. Z., Sethi, G., Tan, T. Z., Lim, L. H. K., Huang, R. Y., Ungefroren, H., Giovannetti, E., … Kumar, A. P. (2025). Harnessing the tumor microenvironment: targeted cancer therapies

through modulation of epithelial-mesenchymal transition [Review of Harnessing the tumor microenvironment: targeted cancer therapies through modulation of epithelial-mesenchymal transition]. Journal of Hematology & Oncology, 18(1). BioMed Central.

Hasan, M. N., Capuk, O., Patel, S. M., & Sun, D. (2022). The Role of Metabolic Plasticity of Tumor-Associated Macrophages in Shaping the Tumor Microenvironment Immunity [Review of The Role of Metabolic Plasticity of Tumor-Associated Macrophages in Shaping the Tumor Microenvironment Immunity]. Cancers, 14(14), 3331. Multidisciplinary Digital Publishing Institute.

Hass, R., Ohe, J. von der, & Ungefroren, H. (2020). Impact of the Tumor Microenvironment on Tumor Heterogeneity and Consequences for Cancer Cell Plasticity and Stemness [Review of Impact of the Tumor Microenvironment on Tumor Heterogeneity and Consequences for Cancer Cell Plasticity and Stemness]. Cancers, 12(12), 3716. Multidisciplinary Digital Publishing Institute.

Huang, K., Han, Y., Chen, Y., Shen, H., Zeng, S., & Cai, C. (2025). Tumor metabolic regulators: key drivers of metabolic reprogramming and the promising targets in cancer therapy [Review of Tumor metabolic regulators: key drivers of metabolic reprogramming and the promising targets in cancer therapy]. Molecular Cancer, 24(1). BioMed Central.

Jaworska, M., Szczudło, J., Pietrzyk, A., Shah, J. B., Trojan, S., Ostrowska, B., & Kocemba-Pilarczyk, K. A. (2023). The Warburg effect: a score for many instruments in the concert of cancer and cancer niche cells [Review of The Warburg effect: a score for many instruments in the concert of cancer and cancer niche cells]. Pharmacological Reports, 75(4), 876. Elsevier BV.

Jin, H.-R., Wang, J., Wang, Z., Xi, M., Xia, B., Deng, K., & Yang, J. (2023). Lipid metabolic reprogramming in tumor microenvironment: from mechanisms to therapeutics [Review of Lipid metabolic reprogramming in tumor microenvironment: from mechanisms to therapeutics]. Journal of Hematology & Oncology, 16(1). BioMed Central.

Kaoutari, A. E., Fraunhoffer, N. A., Hoare, O., Teyssedou, C., Soubeyran, P., Gayet, O., Roques, J., Lomberk, G., Urrutia, R., Dusetti, N., & Iovanna, J. (2021). Metabolomic profiling of pancreatic adenocarcinoma reveals fundamental clinical features. bioRxiv (Cold Spring Harbor Laboratory).

Khalaf, K., Hana, D., Chou, J. T.-T., Singh, C., Maćkiewicz, A., & Kaczmarek, M. (2021). Aspects of the Tumor Microenvironment Involved in Immune Resistance and Drug Resistance [Review of Aspects of the Tumor Microenvironment Involved in Immune Resistance and Drug Resistance]. Frontiers in Immunology, 12. Frontiers Media.

Khosravi, G., Mostafavi, S., Bastan, S., Ebrahimi, N., Gharibvand, R. S., & Eskandari, N. (2024). Immunologic tumor microenvironment modulators for turning cold tumors hot. Cancer Communications, 44(5), 521.

Kim, S. K., & Cho, S. W. (2022). The Evasion Mechanisms of Cancer Immunity and Drug Intervention in the Tumor Microenvironment [Review of The Evasion Mechanisms of Cancer Immunity and Drug Intervention in the Tumor Microenvironment]. Frontiers in Pharmacology, 13. Frontiers Media.

Koltai, T., & Fliegel, L. (2023). Fructose, Another Sweet for Cancer: A Context Acting Nutrient Hypothesis. Gene Expression, 22(2), 141.

Krysztofiak, A., Szymonowicz, K., Hlouschek, J., Xiang, K., Waterkamp, C., Larafa, S., Goetting, I.,

Vega-Rubín-de-Celis, S., Theiß, C., Matschke, V., Hoffmann, D., Jendrossek, V., & Matschke, J. (2021). Metabolism of cancer cells commonly responds to irradiation by a transient early mitochondrial shutdown. iScience, 24(11), 103366.

Li, L. (2022). Tumor Microenvironment Characterization in Breast Cancer and an Immune Cell Infiltration Score Development, Validation, and Application. Frontiers in Oncology, 12.

Li, S., Jiang, B., Zhou, H., Yang, S., Liu, Y., & Hong, Y. (2025). Development of a prognostic immune cell-based model for ovarian cancer using multiplex immunofluorescence. Journal of Translational Medicine, 23(1).

Liu, S., Tian, B., Wang, N., Wang, Z., Zhang, W., Li, Q., Wang, J., Fan, G.-H., & Zhou, C. (2025). MARCO expression on myeloid-derived suppressor cells is essential for their differentiation and immunosuppression. Cell Death Discovery, 11(1).

Liu, X., Zhang, P., Xu, J., Lv, G., & Li, Y. (2022). Lipid metabolism in tumor microenvironment: novel therapeutic targets [Review of Lipid metabolism in tumor microenvironment: novel therapeutic targets]. Cancer Cell International, 22(1). BioMed Central.

Liu, X., Zhao, Y., Wu, X., Liu, Z., & Liu, X. (2022). A novel strategy to fuel cancer immunotherapy: targeting glucose metabolism to remodel the tumor microenvironment [Review of A novel strategy to fuel cancer immunotherapy: targeting glucose metabolism to remodel the tumor microenvironment]. Frontiers in Oncology, 12. Frontiers Media.

Ma, Q., Zhang, W., Wu, K., & Shi, L. (2025). The roles of KRAS in cancer metabolism, tumor microenvironment and clinical therapy [Review of The roles of KRAS in cancer metabolism, tumor microenvironment and clinical therapy]. Molecular Cancer, 24(1). BioMed Central.

Malfitano, A. M., Pisanti, S., Napolitano, F., Somma, S. D., Martinelli, R., & Portella, G. (2020). Tumor-Associated Macrophage Status in Cancer Treatment [Review of Tumor-Associated Macrophage Status in Cancer Treatment]. Cancers, 12(7), 1987. Multidisciplinary Digital Publishing Institute.

Mathew, M., Nguyen, N., Bhutia, Y. D., Sivaprakasam, S., & Ganapathy, V. (2024). Metabolic Signature of Warburg Effect in Cancer: An Effective and Obligatory Interplay between Nutrient Transporters and Catabolic/Anabolic Pathways to Promote Tumor Growth. Cancers, 16(3), 504.

Mukha, A., & Dubrovska, A. (2020). Metabolic Targeting of Cancer Stem Cells [Review of Metabolic Targeting of Cancer Stem Cells]. Frontiers in Oncology, 10. Frontiers Media.

Nair, V. S., Saleh, R., Toor, S. M., Cyprian, F., & Elkord, E. (2021). Metabolic reprogramming of T regulatory cells in the hypoxic tumor microenvironment [Review of Metabolic reprogramming of T regulatory cells in the hypoxic tumor microenvironment]. Cancer Immunology Immunotherapy, 70(8), 2103. Springer Science+Business Media.

Nong, S., Han, X., Yu, X., Qian, Y., Wei, Y., Zhang, T., Tian, K., Shen, K., Yang, J., & Ma, X. (2023). Metabolic reprogramming in cancer: Mechanisms and therapeutics [Review of Metabolic reprogramming in cancer: Mechanisms and therapeutics]. MedComm, 4(2). Wiley.

Nunnery, S., Mayer, I. A., & Balko, J. M. (2021). Triple-Negative Breast Cancer [Review of Triple-Negative Breast Cancer]. The Cancer Journal, 27(1), 2. Lippincott Williams & Wilkins.

Ohshima, K., & Morii, E. (2021). Metabolic Reprogramming of Cancer Cells during Tumor Progression and Metastasis [Review of Metabolic Reprogramming of Cancer Cells during Tumor Progression and Metastasis]. Metabolites, 11(1), 28. Multidisciplinary Digital Publishing Institute.

Otto, A. M. (2020). Metabolic Constants and Plasticity of Cancer Cells in a Limiting Glucose and Glutamine Microenvironment—A Pyruvate Perspective [Review of Metabolic Constants and Plasticity of Cancer Cells in a Limiting Glucose and Glutamine Microenvironment—A Pyruvate Perspective]. Frontiers in Oncology, 10. Frontiers Media.

Pandey, S., Singh, R., Habib, N., Tripathi, R. P., Kushwaha, R., & Mahdi, A. A. (2024). Regulation of Hypoxia Dependent Reprogramming of Cancer Metabolism: Role of HIF-1 and Its Potential Therapeutic Implications in Leukemia. Asian Pacific Journal of Cancer Prevention, 25(4), 1121.

Park, K., Veena, M. S., & Shin, D. S. (2022). Key Players of the Immunosuppressive Tumor Microenvironment and Emerging Therapeutic Strategies [Review of Key Players of the Immunosuppressive Tumor Microenvironment and Emerging Therapeutic Strategies]. Frontiers in Cell and Developmental Biology, 10. Frontiers Media.

Saeed, A. F. U. H. (2025). Tumor-Associated Macrophages: Polarization, Immunoregulation, and Immunotherapy [Review of Tumor-Associated Macrophages: Polarization, Immunoregulation, and Immunotherapy]. Cells, 14(10), 741. Multidisciplinary Digital Publishing Institute.

Schiliro, C., & Firestein, B. L. (2021). Mechanisms of Metabolic Reprogramming in Cancer Cells Supporting Enhanced Growth and Proliferation [Review of Mechanisms of Metabolic Reprogramming in Cancer Cells Supporting Enhanced Growth and Proliferation]. Cells, 10(5), 1056. Multidisciplinary Digital Publishing Institute.

Ting, K. (2024). Fructose-induced metabolic reprogramming of cancer cells [Review of Fructose-induced metabolic reprogramming of cancer cells]. Frontiers in Immunology, 15. Frontiers Media.

Vecchiotti, D., Clementi, L., Cornacchia, E., Nolfi, M. D. V., Verzella, D., Capece, D., Zazzeroni, F., & Angelucci, A. (2024). Evidence of the Link between Stroma Remodeling and Prostate Cancer Prognosis [Review of Evidence of the Link between Stroma Remodeling and Prostate Cancer Prognosis]. Cancers, 16(18), 3215. Multidisciplinary Digital Publishing Institute.

Veerasubramanian, P. K., Trinh, A., Akhtar, N., Liu, W. F., & Downing, T. L. (2020). Biophysical and Epigenetic Regulation of Cancer Stemness, Invasiveness, and Immune Action. Current Tissue Microenvironment Reports, 1(4), 277.

Wan, Y., Li, G., Cui, G., Duan, S.-L., & Chang, S. (2025). Reprogramming of Thyroid Cancer Metabolism: from Mechanism to Therapeutic Strategy [Review of Reprogramming of Thyroid Cancer Metabolism: from Mechanism to Therapeutic Strategy]. Molecular Cancer, 24(1). BioMed Central.

Wang, R., Zhuang, J., Zhang, Q., Wu, W., Yu, X., Zhang, H., & Xie, Z. (2025). Decoding the metabolic dialogue in the tumor microenvironment: from immune suppression to precision cancer therapies. Experimental Hematology and Oncology, 14(1).

Wu, P., Gao, W., Su, M., Nice, E. C., Zhang, W., Lin, J., & Xie, N. (2021). Adaptive Mechanisms of Tumor Therapy Resistance Driven by Tumor Microenvironment [Review of Adaptive Mechanisms of Tumor Therapy Resistance Driven

by Tumor Microenvironment]. Frontiers in Cell and Developmental Biology, 9. Frontiers Media.

Wu, T.-N., Chen, H.-M., & Shyur, L. (2021). Current Advancements of Plant-Derived Agents for Triple-Negative Breast Cancer Therapy through Deregulating Cancer Cell Functions and Reprogramming Tumor Microenvironment [Review of Current Advancements of Plant-Derived Agents for Triple-Negative Breast Cancer Therapy through Deregulating Cancer Cell Functions and Reprogramming Tumor Microenvironment]. International Journal of Molecular Sciences, 22(24), 13571. Multidisciplinary Digital Publishing Institute.

Xiao, L., Li, X., Fang, C., Yu, J., & Chen, T. (2023). Neurotransmitters: promising immune modulators in the tumor microenvironment [Review of Neurotransmitters: promising immune modulators in the tumor microenvironment]. Frontiers in Immunology, 14. Frontiers Media. https://doi.org/10.3389/fimmu.2023.1118637

Xing, Y., Ruan, G., Ni, H., Qin, H. H., Chen, S., Gu, X., Shang, J., Zhou, Y., Xi, T., & Zheng, L. (2021). Tumor Immune Microenvironment and Its Related miRNAs in Tumor Progression [Review of Tumor Immune Microenvironment and Its Related miRNAs in Tumor Progression]. Frontiers in Immunology, 12. Frontiers Media.

Xu, L., Yang, Q., & Zhou, J. (2024). Mechanisms of Abnormal Lipid Metabolism in the Pathogenesis of Disease [Review of Mechanisms of Abnormal Lipid Metabolism in the Pathogenesis of Disease]. International Journal of Molecular Sciences, 25(15), 8465. Multidisciplinary Digital Publishing Institute.

Xu, Y., Zhang, H., & Nie, D. (2025). Histone modifications and metabolic reprogramming in tumor-associated macrophages: a potential target of tumor immunotherapy [Review of Histone modifications and metabolic reprogramming in tumor-associated macrophages: a potential target of tumor immunotherapy]. Frontiers in Immunology, 16. Frontiers Media.

Xun, Z., Ding, X., Zhang, Y., Zhang, B., Lai, S., Zou, D., Zheng, J., Chen, G., Su, B., Han, L., & Ye, Y. (2023). Reconstruction of the tumor spatial microenvironment along the malignant-boundary-nonmalignant axis. Nature Communications, 14(1).

Yang, Y., Li, S., To, K. K. W., Zhu, S., Wang, F., & Fu, L. (2025). Tumor-associated macrophages remodel the suppressive tumor immune microenvironment and targeted therapy for immunotherapy [Review of Tumor-associated macrophages remodel the suppressive tumor immune microenvironment and targeted therapy for immunotherapy]. Journal of Experimental & Clinical Cancer Research, 44(1). BioMed Central.

Yu, Y., Gong, L., & Ye, J. (2020). The Role of Aberrant Metabolism in Cancer: Insights Into the Interplay Between Cell Metabolic Reprogramming, Metabolic Syndrome, and Cancer [Review of The Role of Aberrant Metabolism in Cancer: Insights Into the Interplay Between Cell Metabolic Reprogramming, Metabolic Syndrome, and Cancer]. Frontiers in Oncology, 10. Frontiers Media.

Zhang, C., Zhu, N., Li, H., Gong, Y.-Z., Gu, J., Shi, Y., Liao, D., Wang, W., Dai, A., & Li, Q. (2022). New dawn for cancer cell death: Emerging role of lipid metabolism [Review of New dawn for cancer cell death: Emerging role of lipid metabolism]. Molecular Metabolism, 63, 101529. Elsevier BV.

Zhang, J., Zou, S., & Fang, L. (2023). Metabolic reprogramming in colorectal cancer: regulatory networks and therapy [Review of Metabolic reprogramming in colorectal cancer: regulatory

networks and therapy]. Cell & Bioscience, 13(1). BioMed Central.

Zhang, Y., Li, Q., Huang, Z., Li, B., Nice, E. C., Huang, C., Wei, L., & Zou, B. (2022). Targeting Glucose Metabolism Enzymes in Cancer Treatment: Current and Emerging Strategies [Review of Targeting Glucose Metabolism Enzymes in Cancer Treatment: Current and Emerging Strategies]. Cancers, 14(19), 4568. Multidisciplinary Digital Publishing Institute.

Zhang, Y., Yang, Z., Liu, Y., Pei, J., Li, R.-J., & Yang, Y. (2025). Targeting lipid metabolism: novel insights and therapeutic advances in pancreatic cancer treatment [Review of Targeting lipid metabolism: novel insights and therapeutic advances in pancreatic cancer treatment]. Lipids in Health and Disease, 24(1). BioMed Central.

Zhao, H., & Li, Y. (2021). Cancer metabolism and intervention therapy [Review of Cancer metabolism and intervention therapy]. Molecular Biomedicine, 2(1). Springer Nature.

Zhao, J., Jin, D., Huang, M., Ji, J., Xu, X., Wang, F., Zhou, L., Bao, B., Jiang, F., Xu, W., Lu, X., & Xiao, M. (2024). Glycolysis in the tumor microenvironment: a driver of cancer progression and a promising therapeutic target. Frontiers in Cell and Developmental Biology, 12.

Zhao, Q., Han, B., Wang, L., Wu, J., Wang, S., Ren, Z., Wang, S., Yang, H., Carbone, M., Dong, C., Melino, G., Chen, W., & Jia, W. (2024). AKR1B1-dependent fructose metabolism enhances malignancy of cancer cells. Cell Death and Differentiation, 31(12), 1611.

Zhou, D., Duan, Z., Li, Z., Ge, F., Wei, R., & Kong, L. (2022). The significance of glycolysis in tumor progression and its relationship with the tumor microenvironment [Review of The significance of glycolysis in tumor progression and its relationship with the tumor microenvironment]. Frontiers in Pharmacology, 13. Frontiers Media.