

Table S11. Pathways associated with SEGS123 common to H1, and H2+H3 isochore classes.

Pathways	Accession ¹	References
ATP synthesis	P02721	(Wang et al., 2021) □
Axon guidance mediated by netrin	P00009	(Chédotal et al., 2005) □
Axon guidance mediated by semaphorins	P00007	(Chédotal et al., 2005) □
Axon guidance mediated by Slit/Robo	P00008	(Chédotal et al., 2005) □
Blood coagulation	P00011	(Hill et al., 2020) □
Cytoskeletal regulation by Rho GTPase	P00016	(Rodenburg and Van Buul, 2021) □
De novo pyrimidine ribonucleotides biosynthesis	P02740	(Wang et al., 2021) □
FAS ² signaling pathway	P00020	(Papadaki et al., 2024) □
Glycolysis	P00024	(Zhou et al., 2022) □
Gonadotropin-releasing hormone receptor pathway	P06664	(Gründker and Emons, 2017) □
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	P00026	(Chaudhary and Kim, 2021; Liu et al., 2022) □
Hypoxia response via HIF ³ activation	P00030	(Zhao et al., 2024) □
Muscarinic acetylcholine receptor 2 and 4 signaling pathway	P00043	(Friedman et al., 2019) □
Notch signaling pathway	P00045	(Shi et al., 2024) □
Oxidative stress response	P00046	(Ahmad et al., 2022) □
Proline biosynthesis	P02768	(Burke et al., 2020) □
Ras pathway	P04393	(Bahar et al., 2023) □
Vitamin D metabolism and pathway	P04396	(Jeon and Shin, 2018) □

¹ Pathway map accession number (replace X by the corresponding accession number in <https://www.pantherdb.org/pathway/pathwayDiagram.jsp?catAccession=X> to access the related pathway map). ² FAS, fetal alcohol syndrome. ³ HIF, hypoxia inducible factor.

Contextualization of Table S11 information

Table S11 lists the 18 pathways that we observed to be common to H1 and H2+H3 isochore families. To make this table more informative, we compiled and briefly summarized the quotations from its publication references as presented below.

Reprogramming of cellular metabolism is a hallmark of cancer. Mitochondrial ATP synthase (MAS) produces most of the ATP that drives the cell. High expression of the MAS-composing proteins is found during cancer and is linked to a poor prognosis (Wang et al., 2021). Slits, semaphorins and netrins are three families of proteins that can attract or repel growing axons and migrating neurons in the developing nervous system of vertebrates and invertebrates. Recent studies have shown that they are widely expressed outside the nervous system and that they may play important roles in cancers. Proteins in all these families and their receptors appear to control the vascularization of the tumors. Last, many axon guidance molecules also regulate cell

migration and apoptosis in normal and tumorigenic tissues (Chédotal et al., 2005)□. The signaling of the coagulation cascade occurs through the autophagic pathway within cancer cell. It has been suggested that coagulation factors can enhance metastasis through increased endothelial-cancer cell adhesion and enhanced endothelial cell activation (Hill et al., 2020)□. Rho GTPases are small signalling G-proteins that are central regulators of cytoskeleton dynamics, and thereby regulate many cellular processes, including the shape, adhesion and migration of cells. Rho GTPase signaling could therefore be therapeutically targeted in cancer treatment (Rodenburg et al., 2021). The salvage nucleotide synthesis pathway uses exogenous nucleic acid raw materials or endogenous nucleic acid degradation intermediates as substrates. It has been shown that the dysfunction of pyrimidine metabolism is closely related to cancer progression and numerous drugs targeting pyrimidine metabolism have been approved for multiple types of cancer (Wang et al., 2021)□. The Fas/Fas ligand (FasL) system is a major apoptosis-regulating pathway with a key role in tumor immune surveillance and metastasis that can provide valuable prognostic information for patients with metastatic breast cancer (Papadaki et al., 2024)□. Tumor cells rely mainly on aerobic glycolysis for energy production even in the presence of oxygen, and glycolysis is a modulator of tumorigenesis and tumor development. Glycolysis promotes tumor growth, metastasis, and chemoresistance, as well as inhibiting the apoptosis of tumor cells. In addition, lactic acid, a metabolite of glycolysis, can also accumulate in the tumor microenvironment, leading to reduced extracellular pH and immunosuppression (Zhou et al., 2022)□. Expression of gonadotropin-releasing hormone (GnRH) and its receptor is part of an autocrine system, which regulates cell proliferation. Dose- and time-dependent growth inhibitory effects of GnRH agonists were observed on cell lines (Gründker and Emons, 2017)□. Various molecules such as hormones, lipids, peptides, and neurotransmitters activate GPCRs that enable the coupling of these receptors to highly specialized transducer proteins, called G-proteins, and initiate multiple signaling pathways. Integration of these intricate networks of signaling cascades leads to numerous biochemical responses involved in controlling various aspects of cancer progression such as tumor growth, invasion, migration, survival, and metastasis through its aberrant overexpression and/or mutations (Chaudhary and Kim, 2021; Liu et al., 2022)□. The neurotransmitter acetylcholine (ACh) acts as an autocrine growth factor for human lung cancer. The released ACh binds back to nicotinic (nAChRs) and muscarinic receptors on lung cancer cells to accelerate their proliferation, migration and invasion (Friedman et al.,

2018)□. Oxygen availability modulates hypoxia-inducible factors which in turns affect malignant cell phenotypes in many ways (Bo et al., 2024)□. The Notch signaling pathway serves as both an oncogenic factor and a tumor suppressor in various cancer types. Dysregulation of this pathway promotes epithelial-mesenchymal transition and angiogenesis in malignancies, closely linked to cancer proliferation, invasion, and metastasis. Furthermore, the Notch signaling pathway contributes to maintaining stem-like properties in cancer cells, thereby enhancing cancer invasiveness. The regulatory role of the Notch signaling pathway in cancer metabolic reprogramming and the tumor microenvironment suggests its pivotal involvement in balancing oncogenic and tumor suppressive effects. Moreover, the Notch signaling pathway is implicated in conferring chemoresistance to tumor cells (Shi et al., 2024)□. Oxidative stress, characterized by the production of reactive oxygen species within cells, plays a critical role in the development of cancer by affecting genomic stability, signaling pathways within the cellular microenvironment, and contributing to the loss of normal cellular functions, which are associated with the initiation and progression of various types of cancer (Iqbal et al., 2024)□. The metabolism of the non-essential amino acid L-proline is emerging as a key pathway in the metabolic rewiring that sustains cancer cells proliferation, survival and metastatic spread and have been extensively associated with the progression of several malignancies (Burke et al., 2020)□. RAF kinase is a primary mediator of the MAPK pathway, responsible for the sequential activation of downstream targets, such as MEK and the transcription factor ERK, which control numerous cellular and physiological processes, including organism development, cell cycle control, cell proliferation and differentiation, cell survival, and death. Defects in this signaling cascade are associated with diseases such as cancer (Bahar et al., 2023)□. Vitamine D is a precursor of a potent steroid hormone that regulates a broad spectrum of physiological processes. Low levels of vitamin D correlate with a higher risk of cancer progression or poorer outcomes. Accumulating data suggest that the metabolism and functions of vitamin D are dysregulated in many types of cancer, conferring resistance to the antitumorigenic effects of vitamin D and thereby contributing to the development and progression of cancer (Jeon and Shin, 2018; Salman et al., 2023).□

References

Bahar, M.E.; Kim, H.J.; Kim, D.R. Targeting the RAS/RAF/MAPK Pathway for Cancer Therapy: From Mechanism to Clinical Studies. *Signal Transduct. Target. Ther.* **2023**, *81*, 1–38, doi:10.1038/s41392-023-01705-z.

Bo, T.; Van Wijk, K.; Nakajima, O. Heme Biosynthesis Is Crucial for Cell Survival and Mitochondrial OXPHOS after X Irradiation. *Radiat. Res.* **2024**, *201*, 48–54, doi:10.1667/RADE-23-00035.1.

Burke, L.; Guterman, I.; Palacios Gallego, R.; Britton, R.G.; Burschowsky, D.; Tufarelli, C.; Rufini, A. The Janus-like Role of Proline Metabolism in Cancer. *Cell Death Discov.* **2020**, *6*, 1–17, doi:10.1038/s41420-020-00341-8.

Chaudhary, P.K.; Kim, S. An Insight into GPCR and G-Proteins as Cancer Drivers. *Cells* **2021**, *10*, doi:10.3390/CELLS10123288.

Chédotal, A.; Kerjan, G.; Moreau-Fauvarque, C. The Brain within the Tumor: New Roles for Axon Guidance Molecules in Cancers. *Cell Death Differ.* **2005**, *12*, 1044–1056, doi:10.1038/SJ.CDD.4401707.

Friedman, J.R.; Richbart, S.D.; Merritt, J.C.; Brown, K.C.; Nolan, N.A.; Akers, A.T.; Lau, J.K.; Robateau, Z.R.; Miles, S.L.; Dasgupta, P. Acetylcholine Signaling System in Progression of Lung Cancers. *Pharmacol. Ther.* **2018**, *194*, 222, doi:10.1016/J.PHARMTHERA.2018.10.002.

Gründker, C.; Emons, G. The Role of Gonadotropin-Releasing Hormone in Cancer Cell Proliferation and Metastasis. *Front. Endocrinol. (Lausanne)*. **2017**, *8*, doi:10.3389/FENDO.2017.00187.

Hill, C.N.; Hernández-Cáceres, M.P.; Asencio, C.; Torres, B.; Solis, B.; Owen, G.I. Deciphering the Role of the Coagulation Cascade and Autophagy in Cancer-Related Thrombosis and Metastasis. *Front. Oncol.* **2020**, *10*, 605314, doi:10.3389/FONC.2020.605314.

Iqbal, M.J.; Kabeer, A.; Abbas, Z.; Siddiqui, H.A.; Calina, D.; Sharifi-Rad, J.; Cho, W.C. Interplay of Oxidative Stress, Cellular Communication and Signaling Pathways in Cancer. *Cell Commun. Signal.* **2024**, *22*, 1–16, doi:10.1186/S12964-023-01398-5/TABLES/3.

Jeon, S.M.; Shin, E.A. Exploring Vitamin D Metabolism and Function in Cancer. *Exp. Mol. Med.* **2018**, *50*, doi:10.1038/S12276-018-0038-9.

Liu, X.; Zhu, H.; Gao, H.; Tian, X.; Tan, B.; Su, R. Gs Signaling Pathway Distinguishes Hallucinogenic and Nonhallucinogenic 5-HT_{2A}R Agonists Induced Head Twitch Response in Mice. *Biochem. Biophys. Res. Commun.* **2022**, *598*, 20–25, doi:10.1016/J.BBRC.2022.01.113.

Papadaki, M.A.; Papadaki, E.; Chatziavraam, S.; Aggouraki, D.; Michaelidou, K.; Fotsitzoudis, C.; Vassilakopoulou, M.; Mavroudis, D.; Agelaki, S. Prognostic Value of Fas/Fas Ligand Expression on Circulating Tumor Cells (CTCs) and Immune Cells in the Peripheral Blood of

Patients with Metastatic Breast Cancer. *Cancers (Basel)*. **2024**, *16*, 2927, doi:10.3390/CANCERS16172927/S1.

Rodenburg, W.S.; van Buul, J.D. Rho GTPase Signalling Networks in Cancer Cell Transendothelial Migration. *Vasc. Biol. (Bristol, England)* **2021**, *3*, R77–R95, doi:10.1530/VB-21-0008.

Salman, P.; Oliveira-Cruz, L.; Soza-Ried, C. Unraveling the Complex Link between Vitamin D Levels and Cancer: A Crucial Understanding for Designing Future Supplementation Approaches. *Brazilian J. Pharm. Sci.* **2023**, *59*, e23319, doi:10.1590/S2175-97902023E23319.

Shi, Q.; Xue, C.; Zeng, Y.; Yuan, X.; Chu, Q.; Jiang, S.; Wang, J.; Zhang, Y.; Zhu, D.; Li, L. Notch Signaling Pathway in Cancer: From Mechanistic Insights to Targeted Therapies. *Signal Transduct. Target. Ther.* **2024**, *9*, 1–37, doi:10.1038/s41392-024-01828-x.

Wang, W.; Cui, J.; Ma, H.; Lu, W.; Huang, J. Targeting Pyrimidine Metabolism in the Era of Precision Cancer Medicine. *Front. Oncol.* **2021**, *11*, 684961, doi:10.3389/FONC.2021.684961/BIBTEX.

Wang, T.; Ma, F.; Qian, H. li Defueling the Cancer: ATP Synthase as an Emerging Target in Cancer Therapy. *Mol. Ther. Oncolytics* **2021**, *23*, 82, doi:10.1016/J.OMTO.2021.08.015.

Zhou, D.; Duan, Z.; Li, Z.; Ge, F.; Wei, R.; Kong, L. The Significance of Glycolysis in Tumor Progression and Its Relationship with the Tumor Microenvironment. *Front. Pharmacol.* **2022**, *13*, doi:10.3389/FPHAR.2022.1091779.