

Table S12. Pathways associated with SEGS123 and specific to H2+H3 isochore classes.

Pathways	Accession ¹	References ²
5HT1 ³ type receptor mediated signaling pathway	P04373	(Karmakar and Lal, 2021)
5HT2 ⁴ type receptor mediated signaling pathway	P04374	
Alpha adrenergic receptor signaling pathway	P00002	(Huang et al., 2018)
B cell activation	P00010	(Michaud et al., 2021)
Beta1 adrenergic receptor signaling pathway	P04377	(Kim et al., 2014)
Beta2 adrenergic receptor signaling pathway	P04378	(Kim et al., 2014)
Corticotropin releasing factor receptor signaling pathway	P04380	(Grammatopoulos, 2012)
Dopamine receptor mediated signaling pathway	P05912	(Grant et al., 2022)
Endothelin signaling pathway	P00019	(Bagnato et al., 2008; Tocci et al., 2019)
Enkephalin release	P05913	(Sánchez et al., 2023; García-Domínguez, 2024)
Flavin biosynthesis	P02741	(Ozsvari et al., 2017)
Fructose galactose metabolism	P02744	(Saito et al., 2021)
Hedgehog signaling pathway	P00025	(Kostenis et al., 2020; Jing et al., 2023)
Heme biosynthesis	P02746	(Fiorito et al., 2020)
Heterotrimeric G-protein, Gq and Go alpha mediated pathways	P00027	(Kostenis et al., 2020)
Histamine H1 receptor mediated signaling pathway	P04385	(Zhao et al., 2020)
Histamine H2 receptor mediated signaling pathway	P04386	(Zhao et al., 2020)
Huntingin protein	P00029	(Gibbins et al., 2012; Pircs et al., 2018)
Interferon-gamma signaling pathway	P00035	(Jorgovanovic et al., 2020)
Metabotropic glutamate receptor group I pathway	P00041	(Yu et al., 2017)
Metabotropic glutamate receptor group II pathway	P00040	(Yu et al., 2017)
Metabotropic glutamate receptor group III pathway	P00039	(Yu et al., 2017)
mRNA splicing	P00058	(Choi et al., 2023)
Nicotinic acetylcholine receptor signaling pathway	P00044	(Bele et al., 2024)
Opioid proopiomelanocortin pathway	P05917	(Millington, 2006)
Oxytocin receptor mediated signaling pathway	P04391	(Lerman et al., 2018)
p38 MAPK ⁵ pathway	P05918	(Phan et al., 2023)
P53 pathway feedback loops 1	P04392	(Chen et al., 2023; Harris and Levine, 2005)
Pentose phosphate pathway	P02762	(Ghanem et al., 2021)
Salvage pyrimidine deoxyribonucleotides	P02774	(Wang et al., 2021)
Salvage pyrimidine ribonucleotides	P02775	(Mollick and Laín, 2020)
TGF- β ⁶ signaling pathway	P00052	(Giarratana et al., 2024)
Thyrotropin-releasing hormone receptor signaling	P04394	(Chan et al., 2017; Krashin et al., 2019)
Toll receptor signaling pathway	P00054	(Chan et al., 2017)

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 A short summary of these pathways is given in File S6. ³ 5HT1, serotonin 1A receptor. ⁴ 5HT2, stands for serotonin 2A receptor. ⁵ MAPK, mitogen-activated protein kinase. ⁶ TGF- β , transforming growth factor- β .

Contextualization of Table S12 information

Table S12 shows the 34 pathways specific to the H2+H3 isochore class. To make this table more informative, we compiled and briefly summarized the quotations from its publication references as presented below.

5HT pathway encodes genes in the transmembrane transport of monoamines, such as dopamine, norepinephrine, serotonin, and histamine. The crosstalk between the immune cells and the nervous system through serotonin or 5-hydroxytryptamine (5-HT) in the tumor microenvironment affect cancer pathogenesis (Karmakar and Lal, 2021)□; the vesicular monoamine transporter-2 (VMAT-2) facilitates the sequestration of catecholamines and serotonin into synaptic vesicles, and is therefore an essential regulator of neuronal function. Increasing evidence suggests that the immune system can be affected by the nervous system and neurotransmitters, such as dopamine Feng (Kang et al., 2023)□. Activation of adrenergic receptors (ARs) signalling promotes the development and progression of lung cancer and that pharmacological interference by β -AR blockers could partially reverse lung cancer progression (Huang et al., 2018)□. Negative regulation of immune responses in cancer can be mediated by regulatory B cells and is often a result of increased production of cytokines that can directly and indirectly affect anti-tumor immune function and cancer cell growth (Michaud et al., 2020)□. Selective ligands for the β_1 AR modulate the metabolism of specific miRs. Consequently, the activation of β_1 AR-mediated β -arrestin1 signaling has been shown to be involved in miR biogenesis, which may be linked to cell survival (Kim et al., 2014)□. Corticotropin-releasing hormones are neuropeptides ('stress'-peptides), which the integration of an intricate series of physiological responses involving the autonomic, endocrine, immune, cardiovascular, and reproductive systems. Their ability to couple to multiple G-proteins and regulate diverse intracellular networks that involve intracellular effectors such as cAMP and an array of PKs in an agonist and tissue-specific manner, a property that allows them to exert unique roles in the integration of homeostatic mechanisms. Interestingly, in cancer, corticotropin-releasing hormones appear to employ the cAMP/PKA cascade to inhibit the ERK1/2 activation affecting cell proliferation or differentiation (Grammatopoulos, 2012)□. Despite mechanistic data supporting the direct involvement of dopamine in cancer is still challenging, the dopamine pathway is emerging as a potential target in antitumor therapies (Grant et al., 2022)□. The endothelin pathway includes two G protein-coupled receptor subtypes and promotes growth and progression of a variety of tumors including pulmonary (Bagnato et al., 2008; Thompson et al., 2019). Enkephalins includes a subclass of endogenous opioid peptides that play a key role in pain modulation through opioid receptors located widely throughout both the central and peripheral nervous systems (García-Domínguez, 2024)□. These peptides mediate cancer progression favoring the mitogenesis, migration, and invasion of tumor cells, promoting metastasis and anti-apoptotic mechanisms, and facilitating angiogenesis/lymphangiogenesis (Sánchez et al., 2023)□. Flavin is essential for mitochondrial respiration. Targeting flavin-containing enzymes eliminates cancer stem cells (Ozsvari et al., 2017)□. Fructose metabolism

can be driven under low oxygen; it promotes the Warburg effect to preferentially downregulate mitochondrial respiration and increases aerobic glycolysis that may aid metastases that initially have low oxygen supply. Uric acid may facilitate carcinogenesis by inhibiting the TCA cycle, stimulating cell proliferation by mitochondrial ROS, and blocking fatty acid oxidation. Lactate may also contribute to cancer growth by suppressing fat oxidation and inducing oncogene expression. Fructose intake was associated with cancer growth and that fructose transporters are upregulated in various malignant tumors (Nakagawa et al., 2020)□. Aberrant activation of Hedgehog pathway is associated with neoplastic transformations, malignant tumors, and drug resistance of a multitude of cancers. It drives the progression of cancers by regulating cancer cell proliferation, malignancy, metastasis, and the expansion of cancer stem cells (Sari et al., 2018; Jing et al., 2023). The heme biosynthesis is essential to regulate the tumor suppressor P53, a transcription factor that controls a large network of biological processes (Fiorito et al., 2020) including oxygen transport. To date, no single therapeutic agent exerts its effects via perturbing heterotrimeric G protein function, despite a plethora of evidence linking G protein malfunction to human disease. Several recent studies have brought to light that the Gq family-specific inhibitor FR900359 (FR) is unexpectedly efficacious in silencing the signaling of Gq oncoproteins, mutant Gq variants that mostly exist in the active state (Kostenis et al., 2020). H1 histamine receptors belong to the family of rhodopsin-like G-protein-coupled receptors. It has been shown that their expression is increased in several types of cancer. However, its functional roles in tumor progression remain largely unknown (Zhao et al., 2019)□. Due to impaired autophagy, Argonaute-2 (AGO2) accumulates in the presence of neuronal protein aggregates. Accumulation of AGO2, a key factor of the RNA-induced silencing complex that executes microRNA functions, results in global alterations of microRNA levels and activity. Together, these results demonstrate that impaired autophagy found in neurodegenerative diseases not only influences protein aggregation but also directly contributes to global alterations of intracellular post-transcriptional networks (Pircs et al., 2018)□. Each miRNA may target tens-to-hundreds of transcripts to control key biological processes. Autophagy, a degradative process in which cytoplasmic material is targeted into double-membrane vacuoles, is recognized to critically contribute to cellular homeostasis. Autophagy establishes a checkpoint required for continued loading of miRNA into AGO2. Consequently, cell homeostasis disrupted by autophagy impairment may lead to cancer (Gibbins et al., 2012)□. Interferon- γ (IFN- γ) has cytostatic, pro-apoptotic and antiproliferative functions, IFN- γ and is, therefore, considered potentially useful for adjuvant immunotherapy for different types of cancer. However, it has been shown that the concentration of IFN- γ in the tumor microenvironment determines its function, which may also contribute to tumor growth and progression (Jorgovanovic et al., 2020)□. In addition to its function in synaptic signaling, Metabotropic glutamate receptors (mGluRs) have been shown to participate in the transformation and maintenance of various cancer types indicating that genes encoding mGluRs, GRMs, can function as oncogenes (Yu et al., 2016)□. Specific splicing isoforms are critical in certain cellular processes, particularly in regulating cell numbers. These isoforms have been found to intricately control signaling pathways crucial for cell cycle

progression, proliferation, and apoptosis. Disruptions in splicing caused by genetic mutations, have been implicated in the development and progression of tumors (Choi et al., 2023)□. The expression of nicotinic acetylcholine receptors is increased in certain cancers, such as lung cancer, and has been associated with cell proliferation, epithelial-to-mesenchymal cell transition, angiogenesis and apoptosis prevention (Bele et al., 2024)□. The precursor protein proopiomelanocortin (POMC) produces many biologically active peptides via a series of enzymatic steps in a tissue-specific manner, yielding the melanocyte-stimulating hormones (MSHs), corticotrophin (ACTH) and beta-endorphin. Expression mutant receptor may correlate with an increased incidence of skin cancer, for instance (Millington et al., 2006)□. The neuropeptide hormone oxytocin, which is released from the posterior pituitary gland, is involved in a number of physiological processes and may promote cell proliferation (Lerman et al., 2018)□. p38 Mitogen Activated Protein Kinases (p38 MAPKs) was first identified as a stress response protein kinase that phosphorylates different transcriptional factors. Dysregulation of p38 pathways, in particular p38 γ , are associated with cancer development, metastasis, autophagy and tumor microenvironment (Phan et al., 2023)□. Feedback Loops 1 primarily involves negative feedback loops that tightly regulate p53 levels and activity to prevent uncontrolled cell death or tumor suppression and whose key components are MDM2, MDM4, WIP1, and miR-34 (Harris and Levine, 2005)□. The pentose phosphate pathway (PPP) is a major glucose metabolic shunt that is upregulated in cancer cells. The PPP comprises an oxidative and a nonoxidative phase and is essential for nucleotide synthesis of rapidly dividing cells. The PPP also generates nicotinamide adenine dinucleotide phosphate, which is required for reductive metabolism and to counteract oxidative stress in tumor cells (Ghanem 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 pyrimidine ribonucleotides pathway provides the necessary building blocks for nucleic acids and precursors for cell membrane synthesis, which makes it essential for cell growth and proliferation (Mollick and Laín, 2020)□. Increased TGF- β signaling can lead to both cell cycle arrest and apoptosis, or paradoxically, to proliferation and differentiation (Giarratana et al., 2024)□. In normal condition, hypothalamus releases thyrotropin-releasing hormone triggering the pituitary gland to release thyroid-stimulating hormone, which stimulates thyroid to release T3 and T4. In vitro studies as well as research in animal models demonstrated an effect of the thyroid hormones T3 and T4 on cancer proliferation, apoptosis, invasiveness and angiogenesis (Krashin et al., 2019)□. Moreover, high thyrotropin concentrations are associated with increased incidence of colorectal cancer in older men (Chan et al., 2017)□. Toll receptors play a dual regulatory role in the tumor microenvironment. The inflammatory response induced by Toll receptors contributes to the immune escape of tumor cells (Chen et al., 2022)□.

References

- Bagnato, A.; Spinella, F.; Rosanò, L. The Endothelin Axis in Cancer: The Promise and the Challenges of Molecularly Targeted Therapy. *Can. J. Physiol. Pharmacol.* **2008**, *86*, 473–484, doi:10.1139/Y08-058.
- Bele, T.; Turk, T.; Križaj, I. Nicotinic Acetylcholine Receptors in Cancer: Limitations and Prospects. *Biochim. Biophys. acta. Mol. basis Dis.* **2024**, *1870*, doi:10.1016/J.BBADIS.2023.166875.
- Chan, Y.X.; Alfonso, H.; Chubb, S.A.P.; Fegan, P.G.; Hankey, G.J.; Golledge, J.; Flicker, L.; Yeap, B.B. Higher Thyrotropin Concentration Is Associated with Increased Incidence of Colorectal Cancer in Older Men. *Clin. Endocrinol. (Oxf).* **2017**, *86*, 278–285, doi:10.1111/CEN.13271.
- Chen, X.; Zhang, Y.; Fu, Y. The Critical Role of Toll-like Receptor-Mediated Signaling in Cancer Immunotherapy. *Med. Drug Discov.* **2022**, *14*, 100122, doi:10.1016/J.MEDIDD.2022.100122.
- Choi, S.; Cho, N.; Kim, E.M.; Kim, K.K. The Role of Alternative Pre-mRNA Splicing in Cancer Progression. *Cancer Cell Int. 2023 231* **2023**, *23*, 1–18, doi:10.1186/S12935-023-03094-3.
- Fiorito, V.; Chiabrando, D.; Petrillo, S.; Bertino, F.; Tolosano, E. The Multifaceted Role of Heme in Cancer. *Front. Oncol.* **2020**, *9*, doi:10.3389/FONC.2019.01540.
- García-Domínguez, M. Enkephalins and Pain Modulation: Mechanisms of Action and Therapeutic Perspectives. *Biomolecules* **2024**, *14*, doi:10.3390/BIOM14080926.
- Ghanem, N.; El-Baba, C.; Araji, K.; El-Khoury, R.; Usta, J.; Darwiche, N. The Pentose Phosphate Pathway in Cancer: Regulation and Therapeutic Opportunities. *Chemotherapy* **2021**, *66*, 179–191, doi:10.1159/000519784.
- Giarratana, A.O.; Prendergast, C.M.; Salvatore, M.M.; Capaccione, K.M. TGF- β Signaling: Critical Nexus of Fibrogenesis and Cancer. *J. Transl. Med. 2024 221* **2024**, *22*, 1–16, doi:10.1186/S12967-024-05411-4.
- Gibbins, D.; Mostowy, S.; Jay, F.; Schwab, Y.; Cossart, P.; Voinnet, O. Selective Autophagy Degrades DICER and AGO2 and Regulates MiRNA Activity. *Nat. Cell Biol. 2012 1412* **2012**, *14*, 1314–1321, doi:10.1038/ncb2611.
- Grammatopoulos, D.K. Insights into Mechanisms of Corticotropin-Releasing Hormone Receptor Signal Transduction. *Br. J. Pharmacol.* **2012**, *166*, 85, doi:10.1111/J.1476-5381.2011.01631.X.
- Grant, C.E.; Flis, A.L.; Ryan, B.M. Understanding the Role of Dopamine in Cancer: Past, Present and Future. *Carcinogenesis* **2022**, *43*, 517–527, doi:10.1093/CARCIN/BGAC045.

Harris, S.L.; Levine, A.J. The P53 Pathway: Positive and Negative Feedback Loops. **2005**, *24*, 2899–2908.

Huang, Q.; Tan, Q.; Mao, K.; Yang, G.; Ma, G.; Luo, P.; Wang, S.; Mei, P.; Wu, F.; Xu, J.; et al. The Role of Adrenergic Receptors in Lung Cancer. *Am. J. Cancer Res.* **2018**, *8*, 2227.

Jing, J.; Wu, Z.; Wang, J.; Luo, G.; Lin, H.; Fan, Y.; Zhou, C. Hedgehog Signaling in Tissue Homeostasis, Cancers and Targeted Therapies. *Signal Transduct. Target. Ther.* **2023**, *8*, 1–33, doi:10.1038/s41392-023-01559-5.

Jorgovanovic, D.; Song, M.; Wang, L.; Zhang, Y. Roles of IFN- γ in Tumor Progression and Regression: A Review. *Biomark. Res.* **2020**, *8*, 1–16, doi:10.1186/S40364-020-00228-X.

Kang, Z.; Fu, P.; Ma, H.; Li, T.; Lu, K.; Liu, J.; Ginja, V.; Romanienko, P.; Feng, Z.; Guan, M.; et al. Distinct Functions of EHMT1 and EHMT2 in Cancer Chemotherapy and Immunotherapy. *bioRxiv Prepr. Serv. Biol.* **2023**, doi:10.1101/2023.10.03.560719.

Karmakar, S.; Lal, G. Role of Serotonin Receptor Signaling in Cancer Cells and Anti-Tumor Immunity. *Theranostics* **2021**, *11*, 5296, doi:10.7150/THNO.55986.

Kim, I.M.; Wang, Y.; Park, K.M.; Tang, Y.; Teoh, J.P.; Vinson, J.; Traynham, C.J.; Pironti, G.; Mao, L.; Su, H.; et al. β -Arrestin1-Biased B1-Adrenergic Receptor Signaling Regulates MicroRNA Processing. *Circ. Res.* **2014**, *114*, 833–844, doi:10.1161/CIRCRESAHA.114.302766.

Kostenis, E.; Pfeil, E.M.; Annala, S. Heterotrimeric Gq Proteins as Therapeutic Targets? *J. Biol. Chem.* **2020**, *295*, 5206–5215, doi:10.1074/JBC.REV119.007061.

Krashin, E.; Piekietko-Witkowska, A.; Ellis, M.; Ashur-Fabian, O. Thyroid Hormones and Cancer: A Comprehensive Review of Preclinical and Clinical Studies. *Front. Endocrinol. (Lausanne)*. **2019**, *10*, doi:10.3389/FENDO.2019.00059.

Lerman, B.; Harricharran, T.; Ogunwobi, O.O. Oxytocin and Cancer: An Emerging Link. *World J. Clin. Oncol.* **2018**, *9*, 74, doi:10.5306/WJCO.V9.I5.74.

Michaud, D.; Steward, C.R.; Mirlekar, B.; Pylayeva-Gupta, Y. Regulatory B Cells in Cancer. *Immunol. Rev.* **2020**, *299*, 74, doi:10.1111/IMR.12939.

Millington, G.W.M. Proopiomelanocortin (POMC): The Cutaneous Roles of Its Melanocortin Products and Receptors. *Clin. Exp. Dermatol.* **2006**, *31*, 407–412, doi:10.1111/J.1365-2230.2006.02128.X.

Mollick, T.; Laín, S. Modulating Pyrimidine Ribonucleotide Levels for the Treatment of Cancer. *Cancer Metab.* **2020**, *8*, 1–11, doi:10.1186/S40170-020-00218-5.

Nakagawa, T.; Lanaspá, M.A.; Millan, I.S.; Fini, M.; Rivard, C.J.; Sanchez-Lozada, L.G.; Andres-Hernando, A.; Tolan, D.R.; Johnson, R.J. Fructose Contributes to the Warburg Effect for Cancer Growth. *Cancer Metab.* **2020**, *81*, 1–12, doi:10.1186/S40170-020-00222-9.

Ozsvari, B.; Bonuccelli, G.; Sanchez-Alvarez, R.; Foster, R.; Sotgia, F.; Lisanti, M.P. Targeting Flavin-Containing Enzymes Eliminates Cancer Stem Cells (CSCs), by Inhibiting Mitochondrial Respiration: Vitamin B2 (Riboflavin) in Cancer Therapy. *Aging (Albany NY)* **2017**, *9*, 2610, doi:10.18632/AGING.101351.

Phan, T.; Zhang, X.H.; Rosen, S.; Melstrom, L.G. P38 Kinase in Gastrointestinal Cancers. *Cancer Gene Ther.* **2023**, *30*, 1181–1189, doi:10.1038/S41417-023-00622-1.

Pircs, K.; Petri, R.; Madsen, S.; Brattås, P.L.; Vuono, R.; Ottosson, D.R.; St-Amour, I.; Hersbach, B.A.; Matusiak-Brückner, M.; Lundh, S.H.; et al. Huntingtin Aggregation Impairs Autophagy, Leading to Argonaute-2 Accumulation and Global MicroRNA Dysregulation. *Cell Rep.* **2018**, *24*, 1397–1406, doi:10.1016/J.CELREP.2018.07.017.

Sánchez, M.L.; Rodríguez, F.D.; Coveñas, R. *Involvement of the Opioid Peptide Family in Cancer Progression*; Multidisciplinary Digital Publishing Institute, 2023; Vol. 11, p. 1993.

Sari, I.N.; Phi, L.T.H.; Jun, N.; Wijaya, Y.T.; Lee, S.; Kwon, H.Y. Hedgehog Signaling in Cancer: A Prospective Therapeutic Target for Eradicating Cancer Stem Cells. *Cells* **2018**, *7*, 208, doi:10.3390/CELLS7110208.

Thompson, M.D.; Combarnous, Y.; Bagnato, A.; Tocci, P.; Rosanò, L. Targeting Endothelin-1 Receptor/ β -Arrestin-1 Axis in Ovarian Cancer: From Basic Research to a Therapeutic Approach. *Front. Endocrinol. (Lausanne)*. **2019**, *10*, 609, doi:10.3389/FENDO.2019.00609.

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.

Yu, L.J.; Wall, B.A.; Wangari-Talbot, J.; Chen, S. Metabotropic Glutamate Receptors in Cancer. *Neuropharmacology* **2016**, *115*, 193, doi:10.1016/J.NEUROPHARM.2016.02.011.

Zhao, J.; Hou, Y.; Yin, C.; Hu, J.; Gao, T.; Huang, X.; Zhang, X.; Xing, J.; An, J.; Wan, S.; et al. Upregulation of Histamine Receptor H1 Promotes Tumor Progression and Contributes to Poor Prognosis in Hepatocellular Carcinoma. *Oncogene* **2019**, *39*, 1724–1738, doi:10.1038/s41388-019-1093-y.