

Table S7. Pathways associated with SEGS123 common to L, H1, and H2+H3 isochore classes.

Athway	Accession ¹	References
Adenine and hypoxanthine salvage pathway	P02723	(Tran et al., 2024)
Amyloid secretase pathway	P00003	(Pine, 2018)
Angiogenesis	P00005	(Ngaha et al., 2023)
Apoptosis signaling pathway	P00006	(Tian et al., 2024)
Cadherin signaling pathway	P00012	(Kourtidis et al., 2017)
CCKR ² signaling	P06959	(Smith et al., 2016)
Cell cycle	P00013	(Eymin and Gazzeri, 2010)
Cytoskeletal regulation by Rho GTPase	P00016	(Haga and Ridley, 2016)
De novo purine biosynthesis	P02738	(Tran et al., 2024)
De novo pyrimidine deoxyribonucleotide biosynthesis	P02739	(Wang et al., 2021)
De novo pyrimidine ribonucleotides biosynthesis	P02740	(Chen et al., 2023)
DNA replication	P00017	(Primo and Teixeira, 2020)
Inflammation mediated by chemokine and cytokine signaling pathway	P00031	(Ramachandran et al., 2021)
Integrin signalling pathway	P00034	(Caccavari et al., 2010)
Muscarinic acetylcholine receptor 2 and 4 signaling pathway	P00043	(Friedman et al., 2019)
p53 pathway	P00059	(Marei et al., 2021)
p53 pathway feedback loops 2	P04398	(Harris and Levine, 2005; Hage-Sleiman et al., 2017)
Parkin protein	P00049	(Li et al., 2021)
PDGF ³ signaling pathway	P00047	(Pandey et al., 2023)
PI3K pathway	P00048	(Rascio et al., 2021)
Presenilin pathway	P00004	(Li et al., 2016)
Serine glycine biosynthesis	P02776	(Pan et al., 2020)
Transcription regulation by bZIP transcription factor	P00055	(Deng et al., 2023)
Ubiquitin proteasome pathway	P00060	(Soave et al., 2017)
Wnt signaling pathway	P00057	(Zhang et al., 2024)

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 CCKR, cholecystokinin receptors. ³ PDGF, *platelet-derived growth factor*.

Contextualization of Table S7 information

Table S7 shows that 25 pathways were found to be common across all the three isochore classes. To make this table more informative, we compiled and briefly summarized the quotations from its publication references as presented below.

Quantitative metabolic analysis demonstrates comparative contribution from *de novo* synthesis and salvage (recycling) pathways in maintaining purine nucleotide pools in tumors. Inhibiting purine salvage slows down tumor progression, revealing a crucial role of the salvage pathway in tumor metabolism (Tran et al., 2024). Within the amyloid secretase pathway, the γ -secretase has

over 100 known γ -secretase cleavage substrates. Many of the γ -secretase substrates are directly involved in carcinogenesis or tumor progression (including NSCLCs), and are ideal candidates to be the "on-target" biomarkers for γ -secretase inhibitors (Pine, 2018). Angiogenesis is essential in the development of lung cancer because it allows oxygen and nutrients to flow to rapidly developing tumor cells, contributing to tumor invasion and dissemination (Ngaha et al., 2023). Apoptosis acts in the elimination of potentially malignant cells, hyperplasia and against tumour progression. Hence, reduced apoptosis promotes carcinogenesis (Tian et al., 2024). Cadherins are adhesion molecules with important functions in cell-cell adhesion. The fact that the majority of human solid tumors are epithelial in origin has focused attention to these molecules. Receptor tyrosine kinase, PI3K/AKT, Rho GTPase, and HIPPO signaling, are all regulated by cadherin. Nuclear signaling mediated by the cadherin associated proteins promote growth, migration and pluripotency (Kourtidis et al., 2017). Cholecystokinins (CCK) are neuropeptides and gut hormones. CCKR refers to its receptors. CCK is also significantly involved with growth of various malignancies through activation of the cholecystokin-B (CCK-B) receptor (Smith et al., 2016). The cell cycle checkpoints are designed to preserve genome integrity. Therefore, abnormalities of components of these networks induce tumors development (Eymin and Gazzeri, 2010). A highly conserved function of Rho GTPases is the control of the actin cytoskeleton. Several cellular processes including cell migration, cell division, endocytosis and chemotaxis depend on the actin cytoskeleton, and it plays a central role in cancer cell migration and invasion (Haga and Ridley, 2016). Purine nucleotides are vital for RNA and DNA synthesis, signaling, metabolism, and energy homeostasis. To synthesize purines, cells use two principal routes: the *de novo* and salvage pathways. Quantitative metabolic analysis demonstrates comparative contribution from *de novo* synthesis and salvage in maintaining purine nucleotide pools in tumors (Tran et al., 2024). Metabolic rewiring is considered as a primary feature of cancer. Malignant cells reprogram metabolism pathway in response to various intrinsic and extrinsic drawback to fuel cell survival and growth. Among the complex metabolic pathways, pyrimidine biosynthesis is conserved in all living organism and is necessary to maintain cellular fundamental function (i.e. DNA and RNA biosynthesis). A wealth of evidence has demonstrated that dysfunction of pyrimidine metabolism is closely related to cancer progression (Wang et al., 2021). Both purine nucleotides and pyrimidine nucleotides are necessary for cell metabolism and proliferation. Thus, the dysregulation of the *de novo* nucleotide biosynthetic pathway contributes

to the development of many human diseases, such as cancer. It has been shown that many enzymes in this pathway are overactivated in different cancers (Chen et al., 2023). DNA replication is a tightly regulated process that ensures faithful copies of DNA molecules to daughter cells during each cell cycle. Oncogene-induced replication stress is an important source of genomic instability in human carcinogenesis (Primo and Teixeira, 2019). Inflammation promotes tumor growth and subsequent metastasis through different cytokines (ILs, TGF- β , and TNF- α) and chemokine (CC, CXC, C, and CX3C) families in the microenvironment of lung tumors (Ramachandran et al., 2021). The poor prognosis of most NSCLC cells is due to their ability to efficiently invade surrounding tissues and blood vessels as well as metastasizing to distant organs. Adhesive interactions mediated by integrin with the surrounding extracellular matrix are a key limiting step in the regulation of the invasive properties of several cancer cell types (Caccavari et al., 2010). 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). The p53 protein is a transcription factor whose critical function is preserving genomic integrity. The *TP53* gene is mutated in approximately half of all human malignancies, including those of lung. When DNA damage occurs, the p53 stops the cell cycle. If p53 protein is mutated, the cell cycle is unrestricted and the damaged DNA is replicated, resulting in uncontrolled cell proliferation and cancer tumors (Marei et al., 2021). The transcriptional network of p53-responsive genes produces proteins that interact with a large number of other signal transduction pathways in the cell and a number of positive and negative autoregulatory feedback loops act upon the p53 response (Harris and Levine, 2005; Hage-Sleiman et al., 2017). The combination of seven Parkinson family genes may help predict LUAD prognosis as well as the treatment outcome for high-risk patients (Li et al., 2021). Numerous cancers express platelet-derived growth factors (PDGFs) and PDGF receptors (PDGFRs). By directly stimulating tumor cells in an autocrine manner or by stimulating tumor stromal cells in a paracrine manner, the platelet-derived growth factor (PDGF)/platelet-derived growth factor receptor (PDGFR) pathway is crucial in the growth and spread of several cancers (Pandey et al., 2023). The PI3K/AKT pathway is one of the most frequently over-activated intracellular pathways in several human cancers, which may explain why genes of H2+H3 isochore classes are shared with the H1 and L1 ones. This pathway, acting on different downstream target

proteins, contributes to the carcinogenesis, proliferation, invasion, and metastasis of tumour cells (Rascio et al., 2021). Presenilin enhances cell invasion and migration (metastasis) without altering cell proliferation, both *in vitro* and *vivo* following either up- or down-regulation. It is associated with the disassembly of cadherin-based adherens junctions. Presenilin enzymatic role contributes to the relocalization of β -catenin from the cell membrane to the nucleus and drives cancer progression by triggering TCF/LEF-1 activation (Li et al., 2016). Serine/glycine biosynthesis and one-carbon metabolism are crucial in sustaining cancer cell survival and rapid proliferation, and of high clinical relevance. Excessive activation of serine/glycine biosynthesis drives tumorigenesis and provides a single carbon unit for one-carbon metabolism, which is a complex cyclic metabolic network based on the chemical reaction of folate compounds that provides the necessary proteins, nucleic acids, lipids and other biological macromolecules to support tumor growth (Pan et al., 2020). The Maf proteins (Mafs) belong to basic leucine zipper (bZIP) transcription factors and are members of the activator protein-1 (AP-1) superfamily, which are involved in a wide range of biological processes, such as the cell cycle, proliferation, oxidative stress, and inflammation (Deng et al., 2023). The Ubiquitin proteasome pathway is a protein-based cascade that is responsible for degrading proteins that are involved in many cellular events, including cell cycle progression, apoptosis, DNA damage/repair, endocytosis, drug resistance, angiogenesis and cell differentiation (Soave et al., 2017). The Wnt signaling pathway is an important pathway that transmits cell growth-stimulating signals, and its abnormal activation is closely related to tumor growth and metastasis (Zhang et al., 2021).

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