

Table S10. Pathways associated with SEGS123 and specific to the H1 isochore class.

Pathways	Accession ¹	References
Adrenaline and noradrenaline biosynthesis	P00001	(Zhang et al., 2024)
Insulin/IGF ³ pathway-protein kinase B signaling cascade	P00033	(Ghosal et al., 2022)
Mannose metabolism	P02752	(Saito et al., 2021; Gomes et al., 2022)
Methylcitrate cycle	P02754	(Ando et al., 1972; McCammon et al., 2003)
Methylmalonyl pathway	P02755	(Ilter and Gomes, 2021)
Pyridoxal-5-phosphate biosynthesis	P02759	(Banerjee et al., 2024)
Succinate to propionate conversion	P02777	(Head et al., 2023; Wei et al., 2023)
Vitamin B6 metabolism	P02787	(Ueland et al., 2015)

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 S4. ³ IGF, insulin-like growth factor.

Contextualization of Table S10 information

Table S10 shows the eight pathways specific to the L isochore class. To make this table more informative, we compiled and briefly summarized the quotations from its publication references as presented below.

Chronic stress reduces the tissue infiltration of immune cells in the tumor microenvironment (TME) by continuously activating the adrenergic signaling, inhibits antitumor immune response and tumor cell apoptosis while also inducing epithelial-mesenchymal transition (EMT) and tumor angiogenesis, promoting tumor invasion and metastasis (Zhang et al., 2024)□. Insulin/IGF pathway-protein kinase B signaling cascade and interleukin signaling pathways are part of inflammation signaling (Ghosal et al., 2022)□. By up-regulating glycolysis, cancer cells access energy source alternative to glucose for the maintenance of cell growth. Mannose is an alternative energy source that may serve to feed glycolysis, the tricarboxylic acid (TCA) cycle, and the pentose phosphate pathway (Djureinovic et al., 2016)□. Another source of energy occurs through succinate to propionate conversion (Gomes et al., 2022)□. The function of the methylcitrate cycle is intimately linked to the TCA cycle. The three distinct enzymes of this mitochondrial pathway: methylcitrate synthase, methylaconitate dehydratase, and methylisocitrate lyase, appear to be encoded by the *CIT3*, *PDH1*, and *ICL2* genes, respectively (McCammon et al., 2003), and are involved in energy production from alternative source as well (Ando et al., 1972)□. The methylmalonic acid drives the production of transforming growth factor beta (TGFβ) ligand, which acts as an inducer of tumor progression (Ilter and Gomes,

2021). Pyridoxal phosphate phosphatase, a negative regulator of intracellular vitamin B6 levels, is under the control of the hypoxia-inducible transcription factor (HIF1) and is considered as a relevant target for therapeutic intervention (Banerjee et al., 2024)□. The succinate-to-propionate conversion pathway is primarily associated with anaerobic metabolism in certain bacteria. Most intestinal microorganisms metabolize indigestible dietary carbohydrates into propionate through the succinate pathway (Wei et al., 2023)□. Cancer cells may rewire their metabolism, when succinate accumulates into mitochondria, reroute succinate through propionyl-CoA via methylmalonyl-CoA intermediates (Head et al., 2023)□. The B vitamins act as cofactors, precursors, and substrates for numerous biological processes. Vitamin B6 (pyridoxine) is a cofactor for over 150 enzymes involved mainly in amino acid synthesis and degradation (Ueland et al., 2015).

References

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