

**Table S8.** Pathways associated with SEGS123 and specific to the L isochore class.

| Pathways                 | Accession <sup>1</sup> | References                     |
|--------------------------|------------------------|--------------------------------|
| Cholesterol biosynthesis | P00014                 | (Xiao et al., 2023)            |
| Coenzyme A biosynthesis  | P02736                 | (Guertin and Wellen, 2023)     |
| Threonine biosynthesis   | P02781                 | (Zhang et al., 2022)           |
| Vasopressin synthesis    | P04395                 | (Villalobos and Wistuba, 2017) |

<sup>1</sup> 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).

### *Contextualization of Table S8 information*

Table S8 shows the four 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.

Cholesterol is an essential structural component of membranes that plays a critical role in the maintenance of cellular activities. Scientific reports demonstrated the functional significance of cholesterol metabolism in tumorigenesis, cancer progression and metastasis through its regulatory effects on the immune response, ferroptosis, autophagy, cell stemness, and the DNA damage response (Xiao et al., 2023)□. Coenzyme A (CoA) is an importance carrier of acyl residues in cell metabolism that participates in many different catabolic and anabolic reactions, including the metabolism of lipids, carbohydrates, proteins, ethanol, bile acids, and xenobiotics. In the hypoxic tumoral conditions, various enzymes in the CoA are up-regulated due to oncogenic signaling to sustain the growth of hypoxic tumor cells via recapturing acetate to produce acetyl-CoA and promote FAS (Guertin and Wellen, 2023). It has been shown that amino acids contribute to tumorigenesis and tumor immunity by acting as nutrients, signaling molecules, and could also regulate gene transcription and epigenetic modification (Chen et al., 2024)□. Amino acids such as threonine were shown to be effective as diagnostic biomarkers for NSCLC (Zhang et al., 2022). Vasopressin is a hormonal component in the regulation of blood pressure. Its gene expression has been demonstrated to be a common feature of all small-cell lung cancer and to be a reliable plasma marker for determining the presence of small-cell lung cancer (SCLC) and monitoring response to treatment (North, 2023)□.

## References

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