δ1-pyrroline-5-carboxylate reductase (PYCR1), a new target for anticancer therapeutics

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δ1-Pyrroline-5-carboxylate reductase (PYCR1) is crucial in proline biosynthesis because it catalyzes the last step, which is the conversion of δ1-pyrroline-5-carboxylate (P5C) to proline using NADH as a cofactor. The rewiring of proline metabolism to enable cancer progression is well-established, whereby one of the hallmarks is the upregulated expression of PYCR1. These observations sparked research on the role of PYCR1 in cancer, which likely involves the production of both proline and NAD+. Proline is required to remodel the extracellular matrix, whereas NAD+ produced by PYCR1 can be utilized by the TCA cycle in hypoxia when the electron transport chain is inactive. Consistently, not only PYCR1 overexpression is correlated with advanced stages in highly aggressive types of cancer (breast cancer, gastric cancer, heptacellular carcinoma), but also pycr1 knockdown inhibits proliferation. Therefore, PYCR1 has emerged as a potential target for anticancer therapeutics; however, no suitable candidate has been identified yet. So far, the most potent PYCR1 inhibitor (3,5-Br2-PAMBPA) features IC50 of > 500 nM. To develop more potent inhibitors, we implemented two strategies, high-throughput screening (HTS), and crystallographic fragment screening (XFS). Both represent important steps in rational drug design. For HTS, we utilized the European Chemical Biology Library (ECBL) comprising ~100 000 compounds and a focused library of kinase inhibitors (~2600 compounds). We identified 132 compounds from ECBL and 42 from kinase inhibitors library that are significantly more potent than 3,5-Br2-PAMBPA. In XFS, we tested 96 diverse small organic compounds and identified two promising hits.
The combination of data from XFS and HTS will provide valuable starting points for the design of highly selective inhibitors targeting PYCR1, which can be further developed into anticancer therapeutics. This research is funded by Polish National Centre (grant number 2021/43/B/NZ7/01611).