Editorial

James M. Phang¹

Published online: 29 November 2021

© The Author(s), under exclusive licence to Springer-Verlag GmbH Austria, part of Springer Nature 2021

In 2007, the Second International Symposium on “Proline Metabolism in Health and Disease” was held at the National Cancer Institute at Frederick organized by yours truly of the NCI, Dr. David Valle of Johns Hopkins School of Medicine and Dr. Chien-an A. Hu of the New Mexico School of Medicine. Dr. Andy Hu initiated contact with Gert Lubec, then Editor-in-Chief of the journal, *Amino Acids*, who agreed on a Special Issue of peer-reviewed articles from the symposium. Twelve articles were published in 2008 as the 4th number, volume 35 of *Amino Acids* and were well received with the articles achieving a mean citation rate of 135 per article.

This Special Issue focused on linkages between proline metabolism and oncologic regulatory pathways. The finding that proline dehydrogenase (PRODH) showed a rapid and robust transcriptional response to P53, (Polyak et al. 1997) a known cancer suppressor gene, provided a strong suggestion that the proline metabolic pathway functioned as a regulatory axis in cancer (Phang and Liu 2012). The seminal issue of *Amino Acids* was followed by the finding that the biosynthetic enzymes for proline were induced by c-MYC and they played a key role in the proliferation of cancer cells (Liu et al. 2012). A flurry of papers showed that these findings were relevant to a variety of human cancers. In the period 2015–2020, over a thousand articles on “proline metabolism and cancer” appeared in the scientific literature.

This historical record and the recent spike in findings which have extended proline metabolism into the effects of prolyl, hydroxyprolyl peptides, and collagen (D'Aniello et al. 2020) matched well with the journalistic brand for *Amino Acids* as “the forum for amino acid, peptide and protein research.” It was an ideal time for another Special Issue on proline.

In the intervening 12 years, the cancer metabolism landscape has undergone considerable change. Formerly, the focus was on the glucose and glutamine addiction of cancer

cells. Although important, the central role assigned these two nutrients may have been influenced by conditions where cancer cells were cultured in monolayers with supranormal levels of glucose and glutamine. Also, proline was omitted from many media which selected for cells with high capacity for endogenous proline synthesis. The pioneering work of Dr. Herbert Windmueller in animals in vivo showed that glutamine is the major carrier of carbons and nitrogen between organs (Windmueller and Spaeth 1974). It is synthesized in muscle and carried to the liver, kidney, and GI tract. In the latter, the major site for tissue turnover in adult animals, glutamine is metabolized to citrulline and proline. Additionally, the finding that oncogene c-MYC markedly increased the transcription of pyrroline-5-carboxylate synthase (P5CS) and the three isozymes of pyrroline-5-carboxylate reductases designated PYCR1, PYCR2, and PYCR3 (aka PYCRL) make them attractive targets for inhibiting cancer proliferation (Tanner et al. 2018). Inhibitors of glutaminolysis have exhibited varying efficacy in clinical trials (Grinde et al. 2019). One may speculate that their ability to suppress tumor growth may depend on whether glutamine in a specific cancer is a source of proline.

Although a number of nonessential amino acids may play important roles in carcinogenesis, the metabolic properties of proline allow it to provide special features, i.e., to connect a number of important pathways in energy generation, redox balance, de novo synthesis and salvage of nucleotides, mechanoregulation, sensor for mTOR, and mechanism for epigenetics. As an imino acid, proline is unique among proteinogenic amino acids, and the characteristic of its peptide-bond is an important basis for protein structure. The proline precursor/product, glutamic- γ -semialdehyde, is in tautomeric equilibrium with pyrroline-5-carboxylate, an unusual but not unique feature in amino acid metabolism. The differential characteristics of the PYCR isozymes may be important in their physical interaction with proteins from other metabolic systems (Bogner et al. 2021; Hu 2021), allowing for channeling of metabolites in specific pathways.

It was recognized by Adams and colleagues that P5C is an obligate metabolite in the transfer of carbons between

✉ James M. Phang
phangj@mail.nih.gov

¹ National Cancer Institute at Frederick, Frederick, MD, USA

the tricarboxylic and urea cycles (Adams 1970). Thus, the direction of the flux through P5C could serve as an indicator of the cellular repletion or depletion for these cycles. P5CS, the principal enzyme mediating entry into the proline/P5C cycle, has an obligate requirement for NADPH, but the 3 PYCRs with their differential redox preferences (PYCR 1,2 preferring NADH whereas PYCR 3, NADPH), subcellular localization (PYCR 1,2 in mitochondria and PYCR 3 in cytosol), and regulation of catalytic activity by feedback inhibition (PYCR 1,2 sensitive to proline with PYCR2 with greater sensitivity, whereas PYCR 3 is inhibited by NADP⁺) (Bogner et al. 2021) suggest that each isozyme has special functions. Furthermore, the routing of biosynthesized proline to collagen and the competition for co-substrates in analogous reactions for hydroxylation of collagen proline, regulation of the level of HIF as the oxygen sensor, and modulation of enzyme activities for epigenetic remodeling (Tets, JmjC) provide a master communication system for the reprogramming necessary for survival, growth, and transformation of cancer cells.

We realize now that amino acids, especially proline, play a central role in cancer metabolism. Although we were drawn to the system by the symmetry of the proline-P5C cycle, its regulatory properties and ubiquity have transcended our wildest imagination. I thank Dr. Closs as Editor-in-Chief and Dr. Bloom, and her managerial staff for making this special issue possible and I hope that it will stimulate readership to work on the regulatory functions of amino acids in the context of state-of-the-art cell and molecular oncobiology, and to submit their discoveries to future issues of *Amino Acids*.

Declarations

Conflict of interest The author has no competing interests to declare.

References

- Adams E (1970) Metabolism of proline and of hydroxyproline. *Int Rev Connect Tissue Res* 5:1–91
- Bogner AN, Stiers KM, Tanner JJ (2021) Structure, biochemistry, and gene expression patterns of the proline biosynthetic enzyme pyrroline-5-carboxylate reductase (PYCR), an emerging cancer therapy target. *Amino Acids*. <https://doi.org/10.1007/s00726-021-02999-5>
- D’Aniello C, Patriarca EJ, Phang JM, Minchiotti G (2020) Proline metabolism in tumor growth and metastatic progression. *Front Oncol* 10:776. <https://doi.org/10.3389/fonc.2020.00776>
- Grinde MT, Hilmarsson B, Tunset HM, Henriksen IM, Kim J, Haugen MH, Rye MB, Maelandsmo GM, Moestue SA (2019) Glutamine to proline conversion is associated with response to glutaminase inhibition in breast cancer. *Breast Cancer Res* 21(1):61. <https://doi.org/10.1186/s13058-019-1141-0>
- Hu CA (2021) Isozymes of P5C reductase (PYCR) in human diseases: focus on cancer. *Amino Acids*. <https://doi.org/10.1007/s00726-021-03048-x>
- Liu W, Le A, Hancock C, Lane AN, Dang CV, Fan TW, Phang JM (2012) Reprogramming of proline and glutamine metabolism contributes to the proliferative and metabolic responses regulated by oncogenic transcription factor c-MYC. *Proc Natl Acad Sci USA* 109(23):8983–8988. <https://doi.org/10.1073/pnas.1203244109>
- Phang JM, Liu W (2012) Proline metabolism and cancer. *Front Biosci* 17:1835–1845. <https://doi.org/10.2741/4022>
- Polyak K, Xia Y, Zweier JL, Kinzler KW, Vogelstein B (1997) A model for p53-induced apoptosis. *Nature* 389(6648):300–305. <https://doi.org/10.1038/38525>
- Tanner JJ, Fendt SM, Becker DF (2018) The proline cycle as a potential cancer therapy target. *Biochemistry* 57(25):3433–3444. <https://doi.org/10.1021/acs.biochem.8b00215>
- Windmueller HG, Spaeth AE (1974) Uptake and metabolism of plasma glutamine by the small intestine. *J Biol Chem* 249(16):5070–5079

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.