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INTRODUCTION

Introduction to second proline symposium

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The idea that proline, the only proteogenic secondary amino acid, has special metabolic and regulatory features has increasingly found adherents. Because its alpha-nitrogen is within the pyrrolidine ring, proline cannot be substrate for generic amino acid-metabolizing enzymes. Instead, a paradigm of enzymes with their special tissue and subcellular localizations and regulatory mechanisms participates in a metabolically exceptional system. Increasingly, the regulatory functions of this system are being discovered.

However, as recently as the early 1980s, the proposal that metabolism of proline could serve as a regulatory system, even under special conditions, met with considerable resistance. In fact, to paraphrase critics, "if there are unusual features to proline metabolism lending to its regulatory function, certainly they would have been discovered by now (i.e. pre-1980)."

That such was not the case was affirmed recently. Special features of proline metabolism lending to its role in regulating general metabolism and cell behavior were explored at the first International Symposium on Proline Metabolism held October 2004 at Frederick, Maryland. That meeting focused on findings in two specific areas. First, genetic epidemiology linked schizophrenia with mutations in proline oxidase/proline dehydrogenase (POX/PRODH). The neurophysiologic function of proline as a neurotransmitter suppressing glutamergic neurons was presented as a potential pathophysiologic link between proline and neuropsychiatric disorders in humans. The finding that proline oxidase/proline dehydrogenase is a p53-induced gene (PIG6) led to the documentation of POX/PRODH as a ROS generating enzyme capable of inducing apoptosis independent of p53, thereby establishing the importance of POX/PRODH in carcinogenesis.. Seminal advances had been made in the structural biology of PRODH from *E. coli*. The response of the participants at this meeting was enthusiastic, and the concensus was to have a meeting on proline metabolism triennially.

We thank the Center for Cancer Research, NCI, the Office of Dietary Supplements, NIH and the Office of Rare Diseases, NIH for sponsoring this second International Symposium on Proline Metabolism and Human Disease. In planning this meeting, the organizers responded to comments made by the attendants at the last meeting and included several areas in addition to those focusing on human disease. The new invitees and their subject area are as follows: (1) functions in prokaryotic regulation of proline including proline transporters (Janet Wood, Donald Becker); (2) plant biochemistry especially proline as an osmoprotectant (Nathalie Verbruggen) and the role of proline in regulating plant biochemistry and metabolism (Kalidas Shetty); (3) collagen metabolism (Steve Krane) and the role of prolidase in collagen metabolism (Jerzy Palka); (4) the importance of metabolism in cancer (Chi Dang), and (5) the role of TOR in the response to nutrient stress (Alan Kimmel). As a basis for understanding the role of proline in neurophysiologic function, the function of glutamate as a neurotransmitter was reviewed (Joseph Cable).

Significant advances have been made in the areas previously explored in 2004. In the area of neuropsychiatric disorders, David Valle reviewed the work characterizing biochemical phenotypes expressed by specific mutations identified in patients with early schizophrenia. In the

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cancer area, Yongmin Liu presented his work on POX induction of apoptosis by both intrinsic and extrinsic pathways and Jim Phang presented the work on responses of POX/PRODH to stress signaling. Guoyao Wu presented his work on proline as a source of arginine for in utero development of pigs. Especially revealing was the new structural biological findings that substantiates PRODH as a source of superoxide (Jack Tanner) and the possibility that the electrons from proline transferred by PRODH can be used either for electron transport (ATP generation) or for reducing oxygen (production of superoxide). Dave Valle summarized insights gained from characterization of the inborn errors of proline and ornithine metabolism, Antonella Forlino presented the clinical and genetic characterization of prolidase deficiency.

C. Andy Hu, the Editor-in-Chief of this volume, reviewed the knowledge of pyrroline-5-carboxylate synthase.

It is encouraging to find advances in the understanding of proline metabolism on a broad front. The impact of these discoveries is beginning to be felt. In fact, if you googled either "proline oxidase" or "proline dehydrogenase" AND cancer, you would get more than 5,000 sites. Interestingly, the antibody for POX/PRODH is now commercially available from at least two sources, and perhaps more importantly, siRNA for studying the effects of POX/PRODH knockdown has recently become available. It is evident that momentum has been generated to establish this symposium as a continuing event. The organizing committee will be expanded, and an enlarged steering committee will be responsible for future meetings.