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THE SPECIAL ISSUE "PROLINE METABOLISM IN HEALTH AND DISEASE"

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PREFACE

Traditionally, proline is categorized as one of the nonessential amino acids in mammals, however, proline is indispensable in the neonatal small intestine. In addition, proline has features of an inhibitory neuromodulator and a metabolic precursor for glutamate in glutamatergic synapses in the central nervous system. Importantly, recent studies have shown that the gene PRODH, which encodes POX the first enzyme in the proline catabolic pathway, is one of a handful of genes whose expression is induced by p53, a pivotal tumor suppressor. Subsequent work has demonstrated that the increased amounts of POX together with availability of proline results in increased reactive oxygen production that can lead to mitochondria- and caspase 8-mediated apoptosis. These perturbations may play a key role in oncogenesis in certain types of cell and tissue. In bacteria and plants, proline serves as an osmoprotectant to assist in maintaining appropriate osmotic pressure and participates in balancing redox potential and the pH. Proline metabolism in mammals involves two other amino acids, glutamate and ornithine, and five enzymatic activities, Δ^1-pyrroline-5-carboxylate (P5C) reductase (P5CR), proline oxidase (POX), P5C dehydrogenase (P5CDH), P5C synthase (P5CS) and ornithine-δ-aminotransferase (OAT). With the exception of OAT, which catalyzes a reversible reaction, the other 4 enzymes are unidirectional, suggesting that proline metabolism is purpose-driven, tightly regulated, and compartmentalized. This tri-amino-acid system also links with three other essential metabolic systems, namely TCA cycle, urea cycle, and pentose phosphate pathway. Abnormalities in proline metabolism are relevant in several diseases: six monogenic inborn errors of metabolism and/or transport involving proline and its immediate metabolites have been described and mouse models are available for some of these. In addition, impaired proline metabolism has been implicated as a susceptibility factor for schizophrenia, a complex neuropsychiatric disorder with a frequency of ~1% around the world.

The International Symposium on "Proline Metabolism in Health and Disease" has been held twice (in 2004 and 2007) in the past 4 years. Both meetings brought together leaders in research involving all aspects of proline metabolism and its relationship to human disease. After the second Symposium, the meeting participants reasoned that after some 40 years of research on proline metabolism in different organisms and in humans in health and disease, a publication summarizing the area is needed. We feel grateful that the journal Amino Acids agreed to publish our peer-reviewed manuscripts and abstracts in this special issue. The contents of this issue have been grouped into four main sections:

- Proline Metabolism in Animals, Plants and Bacteria
- Endogenous Source of Proline
- Proline Metabolism in Health and Disease
- Selected Abstracts from Speakers and Posters

The collected papers and abstracts provide an important summary of recent advances in understanding the metabolic inter-relationships, protein structure, functional genomics and genetics related to proline metabolism and its associated enzymes as well as the consequences of disruption of these pathways in inborn errors, cancer and neuropsychiatric disorders. Some aspects of proline metabolism in bacteria, yeast and plants are also reviewed. We hope that this review of proline metabolism in health and disease will stimulate new lines of investigation increasing our understanding of the role of proline metabolism in these complex and important problems.