Serum alkaline phosphatase (AP) is perhaps the most widely used biomarker since it was discovered in bone tissue by Robison (Biochem. J. 17: 286, 1923). The work by Kay (Brit. J. exp. Path. 10: 253, 1929) and Roberts (Brit. J. exp. Path. 11: 90, 1930) demonstrating elevation of this enzyme in bone and hepatobiliary diseases helped establish the usefulness of this simple enzymatic assay for clinical chemistry. However, most of what we know about the function(s) of this enzyme comes not from the study of clinical conditions displaying increased levels of the enzyme but rather from studying hypophosphatasia (HPP), a life-threatening inborn-error-of-metabolism described by Rathbun (Am J Dis Child 75:822–831, 1943) caused by a deficiency in the expression of the tissue-nonspecific AP (TNAP, a.k.a liver-bone-kidney type AP) isozyme. Fast forward to 2015, we now understand that TNAP plays a fundamental role in establishing the phosphate/pyrophosphate ratio conducive to proper skeletal and dental mineralization, and that increasing concentration of pyrophosphate alters this ratio causing the rickets (in children) or osteomalacia (in adults) characteristic of HPP as well as the lack of acellular cementum, dentin and tooth enamel mineralization in patients and mouse models of this disease. Enzyme replacement has proven efficacious in correcting these mineralization defects in HPP mice and clinical trials are now underway in infants and children with severe disease where it appears to preserve life and provide benefit to their skeletal condition. Little is known about the role(s) of TNAP in the kidney and even less on its function(s) in the liver, the brain and other soft tissues. Now that HPP patients under treatment are expected to survive their skeletal disease we must fill this void in knowledge to help us understand other manifestations of HPP, not associated with the skeleton or teeth.

This book by Caroline Fonta and László Négyessy is a timely contribution to the literature focusing on what we know and do not know about TNAP in the nervous system that will undoubtedly help focus more research on this important area. The book is organized into four parts. The first part predictably starts with a recapitulation of what we have learned about TNAP function through the study of hypophosphatasia patients. Dr. Salles (Chap. 1) provides a comprehensive review of the pathophysiology and symptomatology of the various forms of HPP, while
Dr. Mornet (Chap. 2) summarizes the structure of the ALPL gene and mutation analyses that have led to our current knowledge regarding genotype–phenotype correlations. Much of this important work has been driven by Dr. Mornet and his group who also maintain a publicly available database of all known HPP mutations (http://www.sesep.uvsq.fr/03_hypo_mutations.php). This first part ends with a chapter by Dr. Narisawa (Chap. 3) who has contributed to the generation and characterization of many of the currently available animal models examining TNAP function, including transgenic models that overexpress TNAP, global and conditional ablation models of Alpl function and knockin models of dominant HPP-causing Alpl mutations. These models are very important research tools to probe the metabolic pathways affected in HPP and also for the pre-clinical evaluation of possible treatments for HPP and other diseases of TNAP dysfunction.

The second part of the book (Chaps. 4–7) summarizes what is known about TNAP expression in the central nervous system (CNS). Chapter 4, by Drs. Zimmermann and Langer, reviews the patterns of expression of TNAP during embryonic and post-natal neurogenesis and summarizes in vitro experiments that point to a role of TNAP in axonal growth and neuronal cell differentiation. Chapter 5, by Drs. Fonta, Négüssy and collaborators delve into the methods that have been used to document expression of TNAP in a cell-specific manner in CNS, and describe this group’s extensive comparative studies of TNAP expression in the rodent and primate cerebral cortex. Dr. Kantor and collaborators continue in Chap. 6 with comparative studies throughout speciation, including zebrafish, frogs, rats, mice, squirrel monkeys, ferrets, chickens, golden hamsters, cats, rabbits, guinea pigs and humans, but focusing on the pattern of expression of TNAP in the retina of the eye, a subject where little prior information existed and to which this group has recently contributed. In Chap. 7, Dr. Deracinois and collaborators review published data as well as their own results using a proteomics approach, demonstrating the expression of TNAP in brain capillary endothelial cells and discussing the possible implication of this expression for the function of the blood–brain barrier.

The third part of the book, Chaps. 8–13, presents some of the new active areas of research regarding TNAP function in the brain. Some are tentative explorations of hypothetical new ideas while some document well established lines of investigation. My own chapter (Chap. 8) summarizes what we know about TNAP function mainly using mouse models and how that information can help us design further studies to understand the role(s) of TNAP in the brain. In Chap. 9, Dr. Ermonval and collaborators point to the possibility that TNAP may exert pathophysiological roles as part of a dynamic versatile lipid rafts population present in neuronal cells. Dr. Négüssy and collaborators (Chap. 10) build on this theme but using bioinformatic tools to come to the conclusion that TNAP is at the crossroad of numerous biochemical pathways. Not unexpectedly, many of those connectivity diagrams support a role for TNAP in neurotransmission and purinergic signaling in good agreement with currently available data. In fact, in Chap. 11, Dr. Coburn, a world-renowned investigator in the vitamin B6 field, summarizes the vast amount of data linking TNAP function with the metabolism of pyridoxal-5’phosphate, the major chemical form of the vitamin, and its essential role in the synthesis of
neurotransmitters such as gamma-aminobutyric acid (GABA). Indeed, GABA insufficiency appears to largely explain the seizures experienced by infants as well as mice with life-threatening HPP. In Chap. 12, Dr. Nowak and collaborators share a cautionary note on the widespread use of levamisole and tetramisole as inhibitors of TNAP. These compounds are known to cause many off-target effects and are therefore not an optimal choice for in vivo studies, especially now that better pharmacological inhibitors have been developed. Chapter 13, by Drs. Street and Sowa, present truly exciting new information regarding the role of TNAP in the production of the anti-nociceptive adenosine in dorsal root ganglia neurons, at synapses that transmit pain signals. These studies not only point to TNAP as a possible new target for pain management but also may help explain the mechanism of alleviation of pain in HPP patients undergoing enzyme replacement therapy.

The fourth and last part of the book (Chaps. 14–18) takes us back to the clinical issues that these new directions of research should help us understand. Thus, in Chap. 14, Dr. Taketani, points us beyond the seizures, whose pathophysiology are better understood, towards encephalopathy, intracranial hypertension, mental retardation, deafness and growth hormone deficiency as conditions associated with HPP that we do not yet understand. Dr. Hofmann and collaborators review the clinical experience with the use of enzyme replacement therapy with asfotase alfa, what works well and what is yet unknown regarding efficacy with this therapeutic approach. Drs Cole and Thompson (Chap. 15) summarize current information on Marbry Syndrome, a condition with hyperphosphatasemia caused by defective synthesis of the glycosyl phosphatidylinositol (GPI) anchor needed for TNAP to be tethered to the membrane of cells and vesicles. It is unclear if the neurological deficits in Marbry patients are caused by the persistent hyperphosphatasemia or by another pathway that depends on GPI anchoring for its function. In Chap. 17, Drs Kellett and Hooper discuss clinical data related to elevated plasma and brain TNAP level in Alzheimer’s Disease patients and the possibility that neuronal toxicity and cell death might be associated with ability of unregulated TNAP to dephosphorylate Tau protein. To conclude this volume, Dr. Diaz-Hernandez and collaborators (Chap. 18) recount their studies that demonstrate that dephosphorylated tau protein behaves as an agonist of muscarinic M1 and M3 receptors, provoking a robust and sustained intracellular calcium increase that triggers neuronal death while also increasing TNAP expression. These authors have demonstrated that the promoting effect of TNAP on axonal growth is due to its ability to hydrolyze extracellular ATP thus preventing P2X7 receptor activation.

To close on these introductory remarks, I think that after finishing this book the readers will be left with the impression that while much needs to be learned about the role of TNAP in the CNS, there are some good solid leads that researchers have started to pursue and that much progress and new understanding of the pathophysiology of HPP and other diseases associated with TNAP dysfunction is to be expected in the not-too-distant future.

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