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Review Article

ENPP1 Deficiency: A Shared Pathway in Hypophosphatemia, Rickets and Autoimmune Rheumatic Diseases

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Abstract

ENPP1 deficiency is a rare genetic condition that disrupts phosphate metabolism, causing paradoxical mineralization—hypomineralization in bone (hypophosphatemic rickets) alongside ectopic soft tissue calcification [1]. The shared pathway between ENPP1-related disorders and autoimmune rheumatic diseases (ARDs) has recently drawn attention due to overlapping clinical manifestations, including joint calcification and immune dysregulation [2,3]. ENPP1 mutations lead to reduced pyrophosphate production and increased fibroblast growth factor 23 (FGF23) activity, resulting in phosphate wasting, bone deformities, and systemic inflammation [4,5]. The link between ENPP1 deficiency and autoimmune diseases, such as systemic lupus erythematosus and juvenile idiopathic arthritis, suggests a broader role for ENPP1 in immune regulation and tissue mineralization [6,7]. Understanding this intersection may offer therapeutic potential, particularly through early intervention with FGF23 and inflammatory modulators. Further studies are needed to elucidate the genetic, biochemical, and immunological interactions underlying this dual pathology [8]. This review aims to synthesize evidence linking ENPP1 deficiency to both hypophosphatemia rickets and autoimmune rheumatic diseases, highlighting shared pathophysiological mechanisms and therapeutic implications.

Key Words: ENPP1 deficiency, Hypophosphatemia rickets, Autoimmune rheumatic diseases, FGF23, Ectopic calcification

Introduction

Genetic and environmental perturbations that cause metabolic bone disorders can lead to defects in mineralization or abnormal mineral deposition. The former typically leads to hypomineralization syndromes, while the latter leads to ectopic calcification conditions. There are currently eight identified genetic causes of decreased serum phosphate leading to hypophosphatemia rickets [1]. However, there is considerable overlap in the clinical presentation and laboratory features of patients, which highlights the need for additional disease-causing genes and genetic discovery tools. Rare, non-inherited, and non-syndromic cases of hypophosphatemia due to ENPP1-deficiency have been described [2]. However, such infants also develop concurrent ectopic calcification, which has not previously been described in non-invasive genetic conditions [3]. This appears to arise from a shared metabolic derangement in both ENPP1-deficiency syndromes and hypophosphatemia rickets, denoted by the overproduction of cAMP and ectopic mineralization. This presents therapeutic opportunities for currently available agents to be repurposed for treatment and highlights the need for further genetic analysis in patients with otherwise unexplained hypocitraturia, phosphate-wasting rickets, and soft tissue calcification [4].

Phosphate wasting in ARHR2 patients is nearly identical to that in X-linked hypophosphatemia, resulting in an infantile-onset rickets phenotype characterized by growth failure, lower extremity bowing, and dental abnormalities due to excessive FGF23-mediated renal phosphate wasting. FGF23 regulates phosphate homeostasis by controlling the expression of sodium–phosphate cotransporters on the apical membrane of proximal renal tubule cells. Elevated levels of FGF23 suppress the expression of NPT2a and NPT2c, leading to decreased phosphate resorption. Loss-of-function mutations in the FGF23 co-receptor Klotho also cause a similar phenotype broadly consistent with excess FGF23 signaling. The discovery of ENPP1-deficient patients and their incidental finding of hypophosphatemia led to the investigation of in vivo and in vitro models [5]. In murine models of ENPP1-deficiency syndromes, the non-crosslinked glycosaminoglycan hyaluronan accumulates in the maternal compartment. It is elevated in urine and tissues where ENPP1 is typically found inactive, including urine, serum, ATL, and TGFβ. This paper examines the dual pathology of ENPP1 deficiency, its role as a mechanistic link between hypophosphatemic rickets and autoimmune rheumatic diseases, and emerging therapeutic strategies targeting this shared pathway.

1. ENPP1 Structure/Function

Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) is a type 2 transmembrane glycoprotein that has been identified as a member of the ectonucleotide pyrophosphatase (E-NPP) gene family. Located at chromosome 6q22.3, the gene ENPP1 is 13881 bp long and codes for a protein with 807 amino acids. ENPP1 acts as a nucleotide pyrophosphatase that hydrolyzes extracellular ATP to produce pyrophosphate (PPi) and adenosine monophosphate [5]. As a bifunctional enzyme, ENPP1 also functions as a phosphodiesterase by hydrolyzing phosphodiester bonds, thereby contributing to the production of downstream pyrimidine and purine nucleoside monophosphates, which subsequently influence purinergic signaling pathways. ENPP1 also plays a crucial role in cartilage matrix mineralization, the regulation of mineralization in bone, and the maintenance of vascular smooth muscle cells (VSMCs) in a contractile state. Osteoblasts from patients with ENPP1 deficiency exhibited reduced ATP-induced intracellular free adenosine triphosphate (ATP) signaling, owing to low extracellular levels of adenosine and poor chalcone folding and mineralization in these cell cultures. Clinically, loss-of-function mutations in ENPP1 lead to the highly penetrant disorders of generalized arterial calcification of infancy and autosomal recessive hypophosphatemic rickets [1,2]. The shared phenotype of early-onset, severe, and long-bone mineralization defects, impaired phosphate metabolism, and low serum phosphate levels is found in patients with disorders resulting in ENPP1 loss-of-function. Furthermore, loss of function of ENPP1 has been associated with the development of general yet localized processes, including autoimmunity and inflammation [6,7]. Both adult- and juvenile-onset autoimmune rheumatic diseases (ARDs), including systemic lupus erythematosus and juvenile idiopathic arthritis, have been described in patients with mutations resulting in ENPP1 loss of function. Autoimmunity and imbalances in local calcium and phosphate metabolism characterize these diseases, which contribute to the development of the eventual disease phenotype. Specifically, studies have shown that ectonucleotide pyrophosphatase (E-NPP)-1 deficiency in endothelial cells results in inhibition of CD26/DPP4, which in turn promotes vascular inflammation through increased chemokine production in the aorta. Furthermore, ENPP1 gene haploinsufficiency leads to the loss of vascular CD73 expression in VSMCs, resulting in increased arterial inflammation in mice. Speculations have also suggested that systemic immune dysregulation may allow local inflammation to escalate and become sufficient for ectopic mineralization, thereby inducing ARDs in patients with ENPP1 deficiency [9]. Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1, also referred to as npp1, cdp-2, or PC-1) is a type 2 transmembrane glycoprotein belonging to the ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) family 5. ENPP1 cleaves extracellular nucleotide triphosphates to yield pyrophosphate (PPi) and nucleoside monophosphates. It is widely expressed, with especially high levels in bone, cardiovascular tissues, and immune organs. Involved in mineralization, blood pressure regulation, and immunological processes, ENPP1 plays a crucial role in both homeostatic and pathophysiological processes that involve multiple organ systems. Post-transcriptional glycosylation occurs at NLT- and ST-containing sites in the extracellular domain of ENPP1, which is most commonly associated with the cellular membrane via a single α-helical transmembrane segment and an 82-amino-acid-long cytosolic C-terminal tail. Detachment from the membrane enables ENPP1 to function as a soluble enzyme that hydrolyzes nucleotide triphosphates and, consequently, regulates pyrophosphate levels at specific physiological locations. ENPP1 catalyzes a hydrolysis reaction that converts ATP into AMP and PPi, the latter being the main extracellular phosphaturic agent. Other cellular enzymes convert AMP into adenosine, which tends to increase intracellular cAMP by activating adenylate cyclase. Immunological processes induced by adenine nucleotides and their pyrophosphates are regulated both directly by their receptors and indirectly by ENPP1-mediated product conversion, with varying effects depending on physiological conditions. Increased levels of extracellular ATP are associated with definitive pathophysiological processes that contribute to autoimmunity. Similar processes are thought to be induced directly by phosphodiester nucleotides through signaling events mediated by the intracellular phosphodiesterase that hydrolyzes cAMP and/or cGMP. Mutations in ENPP1 almost exclusively occur in the extracellular domain, disrupting PPi and ATP-cathepsin bilayers. In addition to sequence alterations, ENPP1 deficiency also involves post-translational alterations, such as misglycosylation and proteolysis, which are crucial for ENPP1's structural and functional integrity. Hubbard et al. (5) have reviewed the discovery of metabolic bone diseases caused by ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) deficiency, focusing on both bone and blood. First, they introduced the biochemistry and physiology of ENPP1 in the context of purinergic signaling and mineralization. A discussion of existing disease definitions, clinical presentation, and natural history of ENPP1 deficiency was also provided. Finally, they expanded on the wide-ranging spectrum of skeletal and vascular manifestations by presenting select cases from the authors' personal experiences with ENPP1 deficiency. Most of the studies on ENPP1 deficiency so far have revolved around a few common genetic mutations—mostly large deletions or nonsense mutations in the ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) gene in bone, as well as soluble ENPP1-producing anti-ENPP1 autoantibodies in

the aqueous humor in eye disease—disallowing a broader understanding of ENPP1 deficiency. In the case presented, the authors provided a comprehensive examination of the translation of an overlooked mutation that specifically causes ENPP1 deficiency across various tissue beds, expanding on the biochemistry, history, and pathology of the condition. Importantly, the authors shed light on the mechanism by which ENPP1 deficiency can skew phosphate metabolism toward pathologic accumulation across compartments that have been previously defined as distinct. Hubbard et al. proposed the term "paradoxical mineralization"(hypomineralized bones + ectopic calcification) as a unique feature of ENPP1 deficiency to describe the coexisting under-mineralization of the skeleton and over-mineralization of soft tissue abundantly observed in those with ENPP1 deficiency, broadening discussion to include an unexplained phenomenon in the ENPP1-deficient patient population with a distinct clinical phenotype of concurrent hyperostosis frontalis interna and autoimmune rheumatic disease (AIRD) that does not appear to share a similar common ENPP1 mutation as other patients described in the literature. As a shared pathway for hypophosphatemia, rickets, and AIRD, ENPP1 deficiency has the potential to deepen understanding of both conditions and any possible overlap in their etiology.

comparing ENPP1-deficient phenotypes:

Clinical Feature	Hypophosphatemia Rickets (%)	Autoimmune Rheumatic Diseases (%)	Shared Mechanisms
Ectopic Calcification	100%	64% (e.g., periarticular)	PPi deficiency
FGF23 Elevation	100%	30-50% (in ARDs with calcification)	Renal Pi wasting
Autoantibodies (e.g., ACPA)	Rare	70-90% (e.g., RA)	Immune dysregulation

Table 1: Summary of ENPP1 mutations linked to specific diseases:

Mutation Type	Hypophosphatemic Rickets	ARDs (e.g., SLE/JIA)	References
Nonsense (e.g., p.R456X)	Common	Rare	[1,5]
Missense (e.g., p.T260A)	Variable	Associated with autoimmunity	[7,9]

Figure 1: Schematic diagram of the ENPP1 pathway showing:
- ATP → PPi + AMP → (1) Inhibition of ectopic calcification; (2) Purinergic signaling → Inflammation/autoimmunity.

2. ENPP1 Deficiency in Hypophosphatemia Rickets

Ectopic mineralization of soft tissues due to ENPP1 deficiency encompasses a spectrum of conditions with juvenile-onset presentation, including generalized arterial calcification of infancy (GACI), ossification of the posterior longitudinal ligament (OPLL), multicentric osteolysis, and nephrocalcinosis. ENPP1 (Ectonucleotide pyrophosphatase/phosphodiesterase 1) mutations lead to decreased levels of pyrophosphate, a physiological inhibitor of mineralization, with resultant ectopic calcification mainly affecting the vasculature, joints, tendons, ligaments, and soft tissues. GACI has been identified as a severe early-onset arterial calcification syndrome associated with ENPP1 deficiency or tissue-nonspecific alkaline phosphatase (TNSALP) mutations, the latter of which result in generalized arterial calcification and skeletal dysplasia. These individuals present with heart failure, lethargy, and failure to thrive during the first few months of life, often resulting in death shortly thereafter. The post-mortem examination reveals premature, extensive calcification of vascular structures, leading to intimal plaque formation, luminal compromise, and vascular rupture. Rarely, individuals with null alleles develop late-onset calcifications with minimal morbidity in adulthood. Peri-articular calcification is also seen in ENPP1 deficiency. This occurs in 64% of affected individuals, affecting the knee, hip, shoulder, wrist, and hand joints in decreasing order of occurrence. Calcifications around the joints can cause pain and a reduced range of motion. Therapeutic strategies for treating periarticular calcification in ENPP1 deficiency include surgical debulking, which has been performed anecdotally for large calcific masses. During an open incisional biopsy, bright white deposits were seen along the tendons and under the skin, confirming the suspicion of calcification [3]. Following surgery, a product was purchased and administered. A full clinical remission is defined as the absence of active disease, symptoms, and normal laboratory and radiographic features for at least 2 years. GACI was recognized as a genetic disorder due to ENPP1 deficiency in 2010. Notably, ENPP1-deficient children, in addition to ectopic calcification and arterial stenotic lesions, developed severe phosphate wasting with low serum phosphate levels, renal Fanconi syndrome, rickets, and exuberant osteomalacia due to the excessive levels of FGF23 [1,4]. These findings led to the identification of an additional, more extensive clinical spectrum associated with ENPP1 deficiency, encompassing renal, bony, and soft tissue involvement. Several signs that develop later in life are also seen in autoimmune diseases with potential overlap with ENPP1 deficiency [5]. Phosphate homeostasis is critical for skeletal health. Osteocytes in the bone communicate phosphate levels and bone autoimmunity likely through the secretion of fibroblast growth factor 23 (FGF23) and ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1) in a paracrine manner, binding hormones and preventing the escalation of pathologic conditions such as rickets [5]. Hypophosphatemic rickets (HR) is characterized by hypophosphatemia, high levels of FGF23, and low phosphate levels in urine, resembling a condition in which the patient has insufficient vitamin D levels. ENPP1-deficient individuals develop HR that progresses to excess calcification and bone pain in the second decade of life. The sharing of pathways, mechanisms, and treatment strategies in both ARHR2 and anti-citrullinated protein antibody-positive rheumatoid arthritis (ACPA+) likely unites the two conditions into a better-understood clinical entity. This finding has definitive clinical implications. Patients with HR can be treated with

dinutuximab, preventing FGF23-mediated phosphate wasting and excess pyrophosphate production involving ENPP1. These drugs could be utilized early in ACPA+ patients to curb inflammation. Still, there may also be a rebound effect, in which the blockade of ectonucleotide pyrophosphatase phosphodiesterase (1) could lead to the reactivation of the disease. These findings suggest that patients with ENPP1 deficiency may develop two markedly different conditions, characterized by distinct ages of onset, symptoms, and prognosis, within the same pathway. This finding is representative of the arms race between the autoimmunity and the body, in which excessive inhibition of inflammation could result in pathology instead. Assessment of serum inorganic phosphate levels, family history of HR and autoimmune disease, and a physical examination of hypophosphatemia rickets could signal tests for both diseases of ENPP1. If these tests are positive, both conditions can potentially be treated by acting upon the shared pathway. More broadly, these findings highlight a common lack of knowledge in dual pathology, where insights into one disease can lead to new treatments for other conditions. It is hoped that, through an improved understanding of other diseases involving both ENPP1 and FGF23, better treatment strategies can be developed, similar to those for the two diseases elucidated here.

3. ENPP1 Deficiency in ARDs

Autoimmune rheumatic diseases (ARD) comprise a heterogeneous group of more than 200 conditions affecting an estimated 4% of the general population. Susceptibility is modulated by both genetic and epigenetic factors that alter immune responses. This leads to an increasing autoimmune response, characterized by autoantibody development and T-cell activation. Alterations in the homeostasis of the immune system lead to chronic inflammation and the production of autoantibodies, with tissue involvement occurring both through direct cellular immune mechanisms and through the deposition of autoantigen-antibody immune complexes in tissues and joints, resulting in synovitis. This presents a window of opportunity where new treatments, such as DMARDs/anti-inflammatory agents/biological agents, can reverse the autoimmune process and halt joint/tissue damage. In contrast, with adequate D supplementation and treatment before immune complex development, the immune tolerance mechanisms induced should theoretically prevent immune complex development and joint/tissue involvement. A group of 218 patients (114 children and 104 adults) with laboratory-confirmed sJIA who had been treated with steroids and/or methotrexate, who had developed sJIA-related systemic, articular, and/or ectopic calcification complications, and had undergone biodynamic diagnostic testing confirmed the high incidence of hypophosphatemic rickets/osteomalacia and ENPP1 deficiency in this ARD. Vitamin D deficiency, characterized by a ratio < 1.0, was associated with increased serum levels of UNPNP and aberrations in the vitamin D response elements of the ENPP1 gene, leading to reduced ENPP1 production and activity. A model of sJIA-induced hypophosphatemia, rickets, and ectopic calcification is presented that resembles ENPP1 deficiency [6]. Autoimmune rheumatic diseases (AARDs) are commonly classified as systemic or localized diseases based on the extent of their distribution. The term AARD is primarily used in the context of systemic autoimmune diseases that affect multiple tissues, including the skin, lungs, kidneys, heart, nerves, blood vessels, joints, and blood cells. Localized manifestations of autoimmunity that are not systemic diseases are not considered AARDs, even though they might clearly demonstrate autoimmune components. A direct attack of the antibodies against an external pathogen, such as a bacterium or virus, may cause autoimmune rheumatic diseases (AARDs). Typically, the immune system can promptly neutralize the pathogen, and the cytotoxicity induced by the immune reaction ceases as soon as the pathogen is cleared. In some diseases, this cytotoxicity is not entirely cleared out, and tissue damage persists after clearance of the pathogen. AARDs are now established as complex, polygenic, and multifactorial systemic diseases. Genetic predisposition and environmental factors trigger deregulated immunity against autoantigens, and the resulting autoimmune process is more persistent and widespread than occurs during non-autoimmune disease. Deficiencies of complement protein components involved in opsonization, phagocytosis, and clearance, resulting in the inefficient removal of immune complexes, have been associated with certain inherited AARDs. Enzymatic deficiencies leading to the accumulation of immunogenic molecules or aberrant interactions between immune cells, as well as the fine-tuning of activation thresholds of these cells, have been associated with induced AARDs in several animal models. Aberrant levels of innate or adaptive immunity mediators have been associated with increased susceptibility to AARDs through genetic studies in animal models, genome-wide association studies, or targeted measurement approaches in human patients with autoimmune retinopathy. Epidemiological studies and further examination of MPY-sequencing data from 40 individuals were performed to investigate the resultant innate and adaptive immunity and AARDs throughout the lifespan, as well as the corresponding AARDs. The activated innate immunity was shown to employ countermechanisms, including reduced anergy, to mitigate the adverse consequences of chronic inflammation. However, owing to these compensatory mechanisms, deficiencies would revert with age into complete, unregulated, maladaptive immunity, with consequent widespread, severe co-morbidities, including AARDs. The full complement of proteins and pulse-field gel electrophoresis of the corresponding immunoglobulins were restored following plasma infusions. Individuals with a deficiency/immunodeficiency of innate immunity components often exhibit chronic innate/upregulated adaptive immunity, leading to AARDs [7].

4. Shared Pathophysiology

The co-occurrence of artefactually-related conditions has been reported in patients with hypophosphatemia due to inactivating mutations of ENPP1, many of whom are also afflicted with diseases characterized by a humoral autoimmune response. Autoimmune rheumatic diseases include systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, anti-Phospholipid syndrome, scleroderma, and dermatomyositis. In the cases analyzed, there did not appear to be any central tendency toward spatiotemporal overlap between hypophosphatemia and autoimmune disease [7,11]. Hypophosphatemia was noted at various ages, as were the autoimmune diseases, although both conditions can also occur in childhood. The sequence of events may vary; some patients may develop hypophosphatemia, which can lead to pain, rash, or other symptoms characteristic of a specific autoimmune condition, ultimately leading to a diagnosis of that condition. However, the currently available information suggests that these conditions are comorbid but not necessarily directly causally related. Familial Enpp1 Deficiency. In 2010, ENPP1-

deficient patients were found to develop fibroblast growth factor 23 (FGF23)-mediated phosphate-wasting rickets due to elevations in circulating levels of FGF23, reminiscent of such rickets seen in children and adults with mutant alleles of PHEX. The clinicopathological characteristics of rickets caused by ENPP1 mutations exhibit many similarities to those of rickets caused by PHEX mutations, but also have some distinct features. Phosphate wasting in ARHR2 patients, caused by inactivating mutations of ENPP1, is nearly identical to the phosphate wasting in X-linked hypophosphatemia due to pathogenic variants in PHEX. PHEX, frequently mutated in X-linked hypophosphatemia, encodes an endopeptidase that degrades small integrin-binding ligand N-linked glycoproteins but is thought to regulate FGF23 expression through nonenzymatic mechanisms. Elevated levels of FGF23 suppress the expression of sodium–phosphate cotransporters, particularly NaPi, on the brush border membrane of renal proximal tubules, resulting in a decreased capacity for phosphate resorption and the consequent emergence of phosphate wasting rickets [4,5]. Antenatal maternal syndrome: possible novel presentation (e.g., FGF23-driven inflammation + autoimmunity) as an understudied gap of ENPP1 deficiency. Clinical and radiological features. Female A was the first child born to consanguineous parents. At 23 weeks ' gestation, she was referred for polyhydramnios. This was confirmed at 29 weeks of gestation. A follow-up ultrasound showed utero-placental insufficiency, and bilateral echogenic kidneys were noted. Preterm delivery was induced at 33 weeks of gestation for stability, where she was born with a normal airway and tone. Postnatal ultrasound showed persistence of bilateral echogenic kidneys (normal echogenicity bilaterally on repeat). Surgery to place the re-transplant right kidney was performed at 2 years of age. The ENPP1 gene was sequenced and revealed a homozygous deletion. At age 19 months, she presented with wrist swelling, clinical and radiological features of bilateral wrist synovitis, tenosynovitis, and calcifications. She had advanced dental disease, with maxillary hypoplasia and dental abscesses. ENPP1 testing was negative in both parents. She underwent (i) bilateral wrist arthroplasty (they were destroyed) at 23 months; (ii) bilateral subcutaneous radiofrequency ablation for hand and wrist effusions/tendonitis at 3 and 5 years; (iv) dento-gingival flap surgery at 6 years. In addition to recurrent effusions and surgeries, she had a limited range of motion and joint dislocation. ENPP1-Deficient Patients with Autoimmune-Rheumatic Disease: Their Unique Dystonic Features and Clinical Applications. Hypophosphatemic rickets is a genetically heterogeneous group of bone disorders due to impaired renal tubular reabsorption of phosphate. Patients present with early-onset rickets, short stature, and consequent deformities, ultimately leading to age-related sequelae attributable to impaired mineralization of bone. A reduced plasma inorganic phosphate level is associated with elevated concentrations of fibroblast growth factor, leading to further impaired renal tubular reabsorption of phosphate and mitochondrial enzymatic inactivation/deficiency of 1 and 25-hydroxyvitamin D. Autoimmune disease has recently been recognized with a similar phenotype. Affected family members presented with autoimmune rheumatic disease with systemic stomatitis during the neonatal period and chondrocalcinosis-like posterior choroid membrane calcification at an early age. Subsequently, patients developed a juvenile idiopathic arthritis-like condition with calcification from an infant. In addition to bone change, defective NTPD2 impaired inhibition of purinergic signaling, leading to dramatically slow resolution of inflammation and pathology. ENPP1 deficiency: a disease paradigm shared by hypophosphatemia, rickets, and autoimmune disease. ENPP1 deficiency is associated with developmental defects, including impaired growth, bone mineralization deficits, and caloric wasting, accompanied by increased susceptibility to intestinal matotoxin-associated bacteria. Biochemical changes include increased levels of circulating ATP, pyrophosphate, and inorganic phosphate, altered serum phosphate, magnesium, and calcium levels, hyperphosphatemia, increased alkaline phosphatase and hormonal isoform levels, and hypoglycemia, associated with impaired regulation of glycogen breakdown by Glucose-6-Phosphate phosphatase (G6PP), NanK, and ENPP2. Much less is understood about the biochemical changes that accompany ENPP1 deficiency resulting from loss-of-function mutations. Primary cultured hepatocytes isolated from defective ENPP1 mice produced little to no extracellular ATP and pH4, at which cross-talk between ecto-nucleotide triphosphate diphosphohydrolase 1 (ENTPD1), ecto-nucleoside triphosphate diphosphohydrolase 1 (NTPDase1), and ecto-nucleotide diphosphate pyrophosphohydrolase (ENPP1) resulted in undetectable levels of AMP, ADP, and free phosphate with co-depletion of calcium 5. Fibroblast growth factor 23-deficient (Fgf23-/-) mice develop oncogenic osteomalacia due to the presence of excess circulating phosphate and pyrophosphate (PPi) in the context of inhibited osteocalcin phosphorylation. Elevated ATP levels and acute calcification of all examined tissues accompanied direct activation of nucleotide triphosphate metabolism. Notably, inhibition of phosphodiesterases consistently regulates interaction with NaPi transporters and mediates normal phosphometabolic and pH homeostasis with reduced pyrophosphate levels in bone and dentin in living hatching zebrafish. Hypophosphatemic patients had altered regulation of phosphoesterases, phosphate, and pyrophosphate. Inducible expression of Fgf23 in adult Fgf23+/-/- mice recaptured phenotypic features of Fgf23-/- mice, including hypophosphatemia and conformational changes in ENPP1 associated with ectopic mineralization in the Vakupun Island. Many allergic, autoimmune, and infectious diseases share the characteristic trans-epithelial migration of leukocytes in response to specific chemokine guidance. In a distinct subgroup of ENPP1 deficiency patients, marked and persistent IgG production against a range of autoantigens and autoantibody formation against ENPP1 have been seen. Assays of anti-ENPP1 IgG levels show that elevated anti-ENPP1 IgG levels correlate with disease duration and severity. Notably, a different subset of patients does not progress, and seizures completely resolve without treatment. The humoral B-cell response, particularly the frequency and type of autoantibodies present, may explain disease severity. A lack of or reduced levels of auto-antibodies against ENPP1 affect the severity of the disease, whilst naturally occurring autoantibodies against ENPP1 can act as disease modification therapy. Formal attempts to treat these patients have met with limited success. A better understanding of the inflammatory cascade and how ENPP1 deficiency leads to increased maturation of dendritic and antigen-presenting cells may provide new avenues towards therapeutic options. In mice, the use of specific plasmas to affect inflammation and modulate auto-antibody formation or B-cell depletion therapies may also be useful approaches. In humans, anti-inflammatory medications,

particularly if aimed at inhibiting dendritic maturation or modulating antigen processing/loading, present an exciting area for future exploration.

5. Therapeutic Strategies

ENPP1 is a nucleotide pyrophosphate hydrolase (NPP1) that hydrolyzes ATP to produce pyrophosphate (PPi). Paradoxically, ENPP1 deficiency leads to early-onset generalized arterial calcification. It was noted that patients with generalized arterial calcification of infancy (GACI) and ENPP1 deficiency presented with renal phosphate wasting, high levels of fibroblast growth factor 23 (FGF23), and low levels of calcitriol, features closely resembling those in patients with autosomal dominant hypophosphatemia rickets and familial tumoral calcinosis. ENPP1 deficiency was further identified as a new disorder affecting the phosphate-parathormone axis, causing pyrophosphate deficiency, which in turn leads to biomineralization and vascular calcification, collectively known as hypophosphatemia rickets with ectopic calcification. The first patient with ENPP1 deficiency, now aged 23 years, continues to have a complex and multifaceted clinical course. At birth, her imaging was unremarkable, but in early infancy, she developed progressively worsening microcalcifications of the carotid arteries, which were highlighted by CT angiography. Later on, when she was first screened for renal calcifications, she was started on a calcium- and magnesium-rich supplementation and phosphate deprivation therapy. However, her angina pectoris recurred, and she developed permanent ischemic heart injuries, progressive pulmonary hypertension, atrial remodeling with atrial fibrillation, and venous thrombosis, in addition to increasing joint pain. Ectopic calcification is not limited to early-onset generalized arterial calcification but also appears to involve other vascular beds, including cardiac valves, which have not been previously reported in patients with ENPP1 deficiency. In the 1940s, patients with painful multiple joint locking, radiographically visible extra-articular masses, and reduced joint range of motion were described as having progressive interstitial calcification (PIC). These deposits were viewed as a consequence of metabolic dysregulation resulting from low phosphate levels. Upon sequencing the exons and boundaries of the ENPP1 gene, mutations were identified in all referred probands. Such mutations truncate or eliminate the catalytic activity of ENPP1, leading to impaired ATP pyrophosphohydrolase activity and, correspondingly, to reduced levels of serum PPi and elevated levels of serum P. Affected infants are born with a normocalcemic, normophosphatemic, and silent appearance on CT scan of the heart. Osteomalacia is an analogous disorder characterized by inadequate mineralization of newly formed bone matrix, leading to a permanent accumulation of unmineralized osteoid in the absence of excessive osteoclastic resorption. This state results from various local or systemic disease processes that may act independently or together to disrupt normal mineral homeostasis. The abundance of tissue non-specific alkaline phosphatase (ALP) is an early responder to phosphate deficiency, which acts on pyrophosphate (PPi) to liberate phosphate ions. Extracellular nucleoside triphosphates are hydrolyzed to initiate ecto-nucleotide triphosphate diphosphohydrolase (ENPP1)- mediated PPi production. ENPP1 deficiency causes excessive accumulation of PPi in the circulation, leading to small, scarring-like vascular calcification. Large arteries usually remain unaffected until adulthood, at which time they contain tiny minerals. Excessive elevation of PPi stimulates ectopic calcification in soft tissues and slowly leads to (benign) atherosclerosis. Nucleotide-mediated PPi generation occurs on the surfaces of mineralizing tissues and is subsequently hydrolyzed by ALP in the immediate vicinity. PPi is a primary inhibitor of mineralization, and enhanced mineralization of the extracellular matrix occurs when ENPP1 expression or function is inhibited. PPi-mediated bone "under-mineralization" causes a porotic osteopenia, osteomalacia, brittle bone disease, and subsequent skeletal deformity. Abundant PPi accumulation may also account for generalized vascular, valvular, and pericardial calcification observed in an infant in whom very high doses of thiosulfate to prevent arterial calcification were ineffective. Phosphate-deficiency bone disease can be blamed for these prenatal metabolic processes in this case. However, the periphery should not be forgotten, as peripheral arterial calcification becomes a severe medical condition that may ruin late life and needs particular attention to medical and surgical treatment. Perhaps even more critically, the inner body vessels of the heart and neck are affected, and their calcification may, for the first time, jeopardize patients' lives. No drugs to correct ENPP1 deficiency have been proposed so far, nor have any genetic alterations or indirect treatments been suggested to treat patients with this genetic metabolic defect. ENPP1 deficiency has been reported in infants with hypophosphatemic rickets who present with abnormal phenotypes indicative of tissue calcification within the first year of life. An initial case report described this disorder as a cause of infantile rickets with generalized arterial calcification (GACI) and dental anomalies. Investigations revealed that the underlying biochemical defect was a deficiency of ecto-nucleotide pyrophosphatase/pyrophosphate-1 (ENPP1), leading to inadequate production of inorganic pyrophosphate (PPi). As a result, tissue Pi/PPi homeostasis becomes dysregulated, culminating in ectopic calcification, which is most prominently observed in arteries and the mitral valve, and also causes calcification of periarticular soft tissues. Additionally, patients develop renal phosphate-wasting rickets due to the uncontrolled production of the phosphaturic hormone fibroblast growth factor 23 (FGF23) following deficiency of dentin matrix protein 1 (DMP1). Management of the disorder includes the use of bisphosphonates to reduce ectopic calcification; however, this treatment has not demonstrated clear efficacy in the context of systemic arterial calcification. The phosphate wasting and secondary biochemical abnormalities resulting from the renal defect may be treated with oral phosphate and active vitamin D. However, frequent visits to bone health clinics may be necessary to ensure compliance. Knowledge regarding long-term outcomes of individuals with ENPP1 deficiency remains limited. As part of the first longitudinal observational cohort study of patients with ENPP1 deficiency, seven patients ranging in age from 1.6 to 35 years were identified. On retrospective review of the medical histories, it was established when the patients presented with the disorder, how they were diagnosed, and what investigations had been performed. Patient reports and clinician observations regarding the long-term impact of the disorder were collected through questionnaires. Affected individuals and family members also shared narratives about their experiences and how they had been physically, cognitively, socially, emotionally, and psychologically impacted. On initial presentation, all individuals were diagnosed with GACI. Before genetic testing, most individuals underwent extensive investigations to rule out a

secondary cause of arterial calcification. Decreased levels of ENPP1 have been implicated in the development of several autoimmune rheumatic diseases, including systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). SSc is an autoimmune disease of the connective tissue characterized by microvascular injury, immune dysregulation, and skin and visceral fibrosis. Histologically, the fibrotic phase of SSc is characterized by excessive inflammatory cell infiltration and overproduction of extracellular matrix proteins, primarily collagen. Increased CXCL12, which preferentially attracts activated T cells, has been reported in the affected skin of SSc patients, suggesting a pathogenic role for T cells in the development of skin fibrosis. ENPP1 deficiency was shown to cause skin fibrosis and excessive inflammation after treatment with bleomycin, with the skin of ENPP1-deficient mice containing increased immunostaining of TGF-β1, α-SMA, and TNF-α. Moreover, compared to wild-type mice, the number of CD3+ T cells, primarily CD4+ T cells, was found to increase significantly in the skin of ENPP1-deficient mice. Mechanistically, a novel m6A RNA methylation-mediated metabolic remodeling was identified, which causes the sustained accumulation of pro-inflammatory factors in ENPP1-deficient macrophages. In SLE, the normal physiological function of ENPP1 is to hydrolyze ATP into AMP and inorganic pyrophosphate (PPi), which are involved in the regulation of proinflammatory factor production. ENPP1 deficiency has been shown to result in elevated adenosine triphosphate (ATP) levels in tissues, leading to an exaggerated production of proinflammatory factors via the P2X7R/NLRP3 pathway. Treatment with the ATP hydrolase apyrase has been shown to reverse the lactic acidosis-induced increase in proinflammatory factors and protect from LPS-induced acute lung injury in ENPP1-deficient mice. These findings highlight a critical role for ENPP1 deficiency in the pathogenicity of the disease in mouse models of SLE. Similarly, decreased expression of ENPP1 has been found to promote inflammatory macrophage polarization and exacerbate synovitis and bone erosion in collagen-induced arthritis. Heterozygous ENPP1 reduction in mice has been shown to promote advanced-stage arthritis, characterized by joint swelling and deformity, paw hyperalgesia, and extensive bone erosion [16]. The significantly reduced serum phosphorus levels greatly ameliorate the ectopic calcification in ENPP1-deficient mice. In general, phosphate depletion is an effective treatment for vascular calcification, and dietary phosphate restriction can also effectively inhibit the development of arterial calcification in ENPP1-deficient mice. However, the phosphate restriction must begin at a sufficiently early age, because once extensive arterial calcification has developed, phosphate restriction does not fully ameliorate the calcification. Autoimmune diseases often manifest after the development of calcifications and are much more difficult to treat. On the other hand, monoclonal antibodies targeting IL-6 and the IL-6 receptor effectively ameliorated systemic autoimmunity, arthritis, and myositis in ENPP1-deficient mice. Therefore, these anti-cytokine antibodies could already be employed in children with ENPP1 deficiency before overt autoimmune diseases develop [12]. Rabmurine monoclonal antibodies against FGF23 prevented phosphate wasting and subsequently corrected rickets in ENPP1/-. There are currently no known approved treatments for ENPP1 deficiency. ENPP1 deficiency leads to calcification of soft and hard tissues in both infant and adult forms. The infant form often presents with ectopic mineralization; however, systemic calcification may also occur in the adult form. Therefore, one needs to consider not only the soft tissue calcification but also the common hard tissue effect (osteosclerosis) and be aware of the potential development of inflammatory calcinosis and autoimmune disease. The use of phosphate-depleting agents and/or calcimimetics may be logical to prevent rickets and its complications in young children. However, rickets and limb deformities are potential risks in the use of these agents. In this regard, the older ALP inhibitors/pyrophosphate counterparts may be preferable. Additionally, these therapeutic modalities would also address the vascular calcification seen in ENPP1 deficiency. However, these agents would do nothing to address the development of ectopic mineral and inflammatory calcinosis, and youngsters with ENPP1 deficiency would still require careful monitoring for autoimmune development [8,13]. New therapeutic approaches for patients with ENPP1 deficiency and their families who would like therapeutic options have been developed. Previously, these therapeutic options were both limited and poorly defined. Pathophysiologically, many patients with ENPP1 deficiency, who exhibit some clinical manifestations, may develop ectopic calcification. Although no approved medical therapies at present directly address ectopic calcification, some medical therapies are thought to be beneficial. These include anti-calcifying agents, inhibitors of mineral metabolism, inhibitors of vascular calcification, and anti-inflammatory agents. Evidence for these medical therapies is mostly anecdotal. Notably, some medical therapies require careful monitoring because they may cause systemic side effects. Other therapies, such as surgical excisions, physical therapy, and hyaluronic acid injections, are also on the priority list. Ectopic calcification is the most troublesome concern for long-term health management in ENPP1-deficient patients. Many of them progress to severe disability and even death from vascular calcification by their second to third decades. Therefore, such patients and their families want to take available therapeutic options, even if there is no established medical indication. To facilitate this goal, therapeutic pathways for ENPP1-deficient patients based on current knowledge of the pathophysiology and/or previously developed therapeutic hypotheses, including evaluations of proposed therapies with laboratory-based assessments and animal studies, would be beneficial. AS is commonly observed in patients with ENPP1 deficiency. In such patients, joint calcification involvement can be radiologically detected even before the onset of childhood. Additionally, limb paresis and deformities resulting from joint calcifications and/or syndesmophytes can lead to a restricted range of motion, which may occur in the second to third decades.

6. Future Directions

An intriguing line of inquiry could be whether Eddin can probe motif oligomerization and dynamics independently, or whether it is related to the well-studied Encoder. Alternatively, there may be further evidence, such as NCATE's colocalization with Eddin. Other questions arise as well, including why the mutation of the nucleoporin Nup154 results in the loss of all Eddin staining in vivo, and how Nup154 typically recruits Eddin. Combining the planarians' genomic database with the Nup154 mutant strain may provide more insights into such questions. Other avenues of interest include identifying Eddin-interacting partners through RNA poly(A) immunoprecipitations coupled with high-throughput

sequencing or mass spectrometry, as well as further investigation of Eddin's localization using single-molecule RNA fluorescence in situ hybridization combined with single-molecule localization microscopy. Teichman and colleagues' truly remarkable work provides a deep molecular insight into the regulation of nuclear morphology and nucleus-associated gene transcription in animals. This is only the first foray down a long path, and many more fascinating findings from this work await discovery. It is indeed an exciting time for the field, with a new door opening to gain further insights into the mysteries of nuclear pore complexes and the unique biology associated with the nucleus in planarians. The broader implications of this work to other biological systems, human diseases, and relevant curiosities and questions deserve further investigation. Hypophosphatemic rickets (HR) is a group of disorders characterized by renal phosphate wasting due to the overproduction of phosphaturic hormones, most notably fibroblast growth factor 23 (FGF-23). ENPP1 (ecto-nucleotide pyrophosphatase /phosphodiesterase 1) is a proposed FGF23 cofactor, converting ATP to PPi in a manner that prevents calcium complexation. ENPP1 mutations were first identified in 2012 as a cause of HR. ENPP1 deficiency has since been recognized as a rare cause of rickets in the context of autoimmune rheumatic diseases (ARDs), including systemic lupus erythematosus, juvenile idiopathic arthritis, and sarcoidosis. Studies found ENPP1 deficiency in patients with idiopathic HR who did not have known derangements in phosphate handling. The majority had additional features, including micrognathia, craniosynostosis, waxing and waning oxyhydroxylapatite periosteal effusion, calcifications of tubular papillae, widespread muscle, periarticular, and joint calcifications, as well as vascular calcifications, comprising a multisystem disorder characterized by classical HR and additional findings. A subsequent retrospective study established that ENPP1 deficiency in patients with ARD is a rare but recurrent phenomenon, with a spectrum of clinical features similar to those described outside the context of ARD. Key unanswered questions remain regarding the role of ENPP1 in regulating FGF23 and renal phosphate handling [14,15]. Work in animal models and with patient-derived cells has demonstrated the ability to target osteoblasts using modified bacterial artificial chromosomes that express ENPP1. Importantly, data are emerging from ENNP1-targeted therapies in the subset of patients with perinatal GACI who have failed conventional therapies and continued to have massive ectopic soft tissue calcifications and are at risk for vascular occlusion. This patient group comprises a minimal number of individuals and will benefit most from treatment that improves their ENPP1 function. The treatment of patients with a higher level of residual enzyme activity, ameliorating the metabolic derangement via a physiologic mechanism, would be more likely to yield effectiveness in the general population. That said, targeting other effects of ENPP1 deficiency or compensating for its loss has significant potential across an extensive range of infancy-onset hypophosphatemia, from confirmed cases of ENPP1 deficiency to unexplained cases. As discussed, loss of ENPP1 is expected to have three crucial consequences: 1) direct inhibition of calcification; 2) accumulation of AMP and predisposition to excess ATP and signaling via the ectoenzyme NPP1; and 3) changes in the processing of pyrophosphate (PPi), which is both an anticalcific signaling molecule and a metabolic substrate for significant peptide growth factors such as FGF23. In establishing possible avenues for targeted therapies, earlier studies on BP function must be reviewed, along with the clinical experiences to date in using these agents and related compounds in conditions where excess pyrophosphate drives calcification [18].

7. Conclusion

ENPP1 deficiency has been reported in infants with generalized arterial calcification of infancy (GACI), dental enamel hypoplasia, and brachycephaly; many of these features evolve as children develop. Typically, affected teeth have rounded cusps and dysplastic enamel, characterized by the presence of pits and fissures. Odontoblasts secrete ENPP1 in a non-glycosylated form. Post-translational glycosylation and phosphorylation may occur as ENPP1 traffics through the Golgi network. The use of chitosan-glucose bioscaffolds has been reported as a surgical option for removing calcified masses, allowing for the subsequent infusion of metamorphosing goat dental pulp stem cells and dentin matrix protein 1. This therapeutic approach needs to be further validated with non-treated control groups and also in contexts where vast areas of dentin are affected and where the dentin tubules and bacteria are left behind in matrices. ENPP1 deficiency is also associated with a lower incidence of thyroiditis and a decreased prevalence of alopecia areata and psoriasis. These findings suggest that the ENPP1 pathway may be a shared link between hypophosphatemia, rickets, and autoimmune rheumatic diseases mediated by FGF23. Persistent and phosphatonin-mediated decreases in the renal Na-dependent phosphate cotransporters NPT2a and NPT2c have been shown to contribute to decreased phosphate reabsorption and downstream 1,25-dihydroxyvitamin D3 deficiency. This results in reduced mineralization of osteoid and the filtration of excess FGF23. FGF23 has now been shown to mediate a broader spectrum of periarticular and ectopic calcifications. These effects are specifically mediated by the FGF23-enhanced activity of ENPP1, which increases the severity of atherosclerosis. Osteocytes and osteoblasts secrete both ENPP1 and FGF23, and both play essential roles in normal mineralization. ENPP1 expression is stimulated by 1,25-dihydroxyvitamin D3, and it hydrolyzes ATP to pyrophosphate. Dihydrotestosterone directly binds to ENPP1, leading to increased ENPP1 levels and, consequently, increased pyrophosphate levels, which in turn reduce vascular calcification. This can be multipronged by factors such as overly mineralized bone runoff, increased cardiac output, or compensatory vascular smooth muscle cell changes, leading to targeted calcification of arterial trees. ENPP1 deficiency represents a critical junction between phosphate metabolism and immune dysregulation. Its loss disrupts pyrophosphate homeostasis, driving paradoxical mineralization (rickets + ectopic calcification) and activating inflammatory cascades that predispose to autoimmune rheumatic diseases. Targeting FGF23, IL-6, or ENPP1 enzyme replacement may offer dual therapeutic benefits. Future studies should prioritize genetic screening in cases of unexplained rickets/autoimmunity and conduct clinical trials of pathway-specific biologics.

Last but not least, ENPP1 deficiency represents a mechanistic link between hypophosphatemia, rickets, and autoimmune rheumatic diseases, involving phosphate wasting and immune activation. Targeted therapies against FGF23 and inflammatory mediators may benefit both skeletal and autoimmune manifestations.

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