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Laurent Beck

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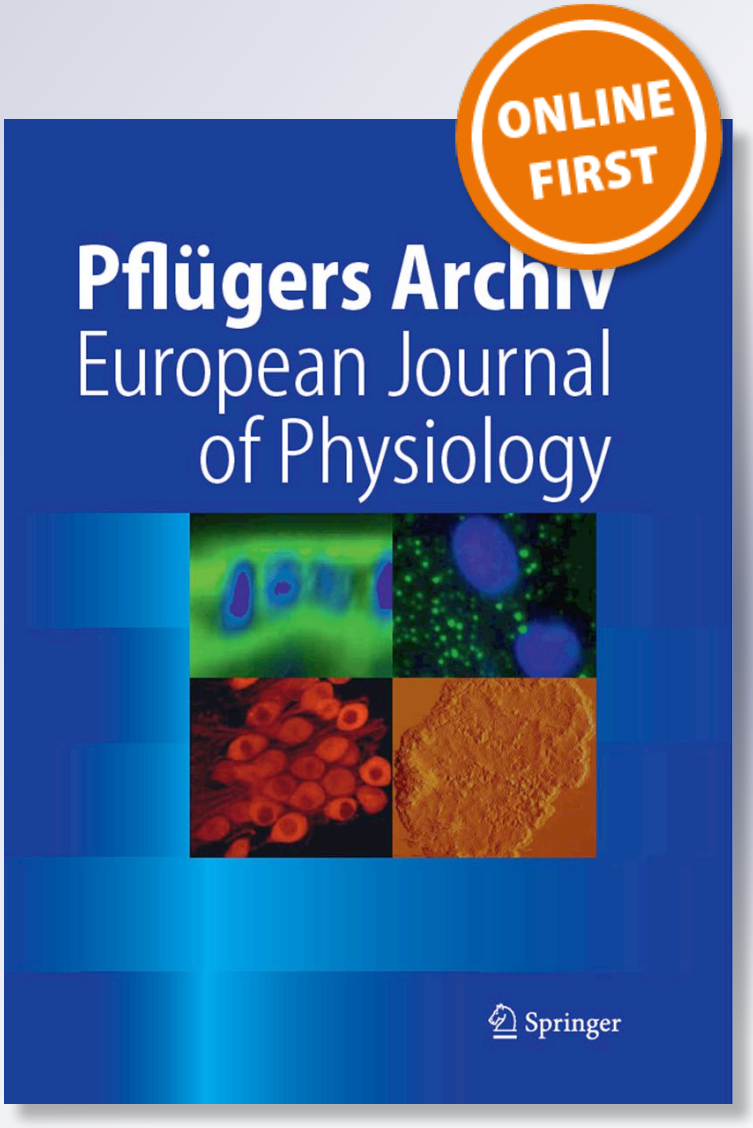

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INVITED REVIEW

Expression and function of Slc34 sodium–phosphate co-transporters in skeleton and teeth

Laurent Beck[1,2]

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Abstract

Under normal physiological condition, the biomineralization process is limited to skeletal tissues and teeth and occurs throughout the individual's life. Biomineralization is an actively regulated process involving the progressive mineralization of the extracellular matrix secreted by osteoblasts in bone or odontoblasts and ameloblasts in tooth. Although the detailed molecular mechanisms underlying the formation of calcium–phosphate apatite crystals are still debated, it is suggested that calcium and phosphate may need to be transported across the membrane of the mineralizing cell, suggesting a pivotal role of phosphate transporters in bone and tooth mineralization. In this context, this short review describes the current knowledge on the role of Slc34 Na^+–phosphate transporters in skeletal and tooth mineralization.

Keywords NaPi-II · Biomineralization · Bone · Cartilage · Tooth · Matrix vesicles

Biomineralization processes

Mineral nucleation

In vertebrates, biomineralization is the active process used by the organism to spatially and timely control the spontaneous crystallization of Ca^{2+} and inorganic phosphate (Pi) from saturated body fluids [12, 39]. Since extracellular concentrations of Ca^{2+} and Pi are higher than their solubilization products, soft tissues have developed complex regulatory systems that prevent crystal formation, while mineralizing tissues have acquired the ability to overcome mineralization inhibitory systems and activate mineralization initiation processes [81, 86]. The mineral phase of the skeleton and teeth is composed of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] crystals that settle in the extracellular matrix of mineralized tissues. For a human being weighing 70 kg, this corresponds to about 700 g of phosphorus or 85% of the body's total phosphorus [9].

A challenging question regarding biomineralization is to uncover the mechanisms by which hydroxyapatite crystal is initially formed, as well as the subsequent regulatory processes that control crystal growth [12, 39]. These aspects are actively debated by investigators in the field of mineralized tissues [14, 39]. Although the detailed process of apatite crystal formation in vivo still remains unclear, researchers have proposed that at least three majors mechanisms be involved (Fig. 1). The first and most studied process of initiation and regulation of biomineralization involves the formation and release from mineralizing cells of membrane-enclosed Ca–P particles named matrix vesicles (MVs) [15, 89]. These vesicles provide a microenvironment enabling to locally concentrate Ca^{2+} and Pi ions and generate hydroxyapatite crystals that will be deposited onto the extracellular matrix molecules. A second cell-dependent mechanism involves the intracellular transport of calcium and phosphate into vesicles that will transport Ca–P particles to the collagen fibers [14]. The third process has described either the direct nucleation of apatite crystals on the collagen gap zones of the extracellular matrix [28] and a transient formation of amorphous mineral precursors before deposition within collagen fibrils macromolecules [53, 54] (Fig. 1). Although more work is necessary to study the relative contribution of these mechanisms, a substantial body of evidence supports both cell-dependent and cell-independent theories. Indeed, crystal nucleation in cartilage

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✉ Laurent Beck
laurent.beck@inserm.fr

[1] INSERM, UMR 1229, RMeS, Regenerative Medicine and Skeleton, Faculté de Chirurgie Dentaire, Université de Nantes, ONIRIS, 1 place Alexis Ricordeau, 44042 Nantes, France

[2] Université de Nantes, UFR Odontologie, 44042 Nantes, France

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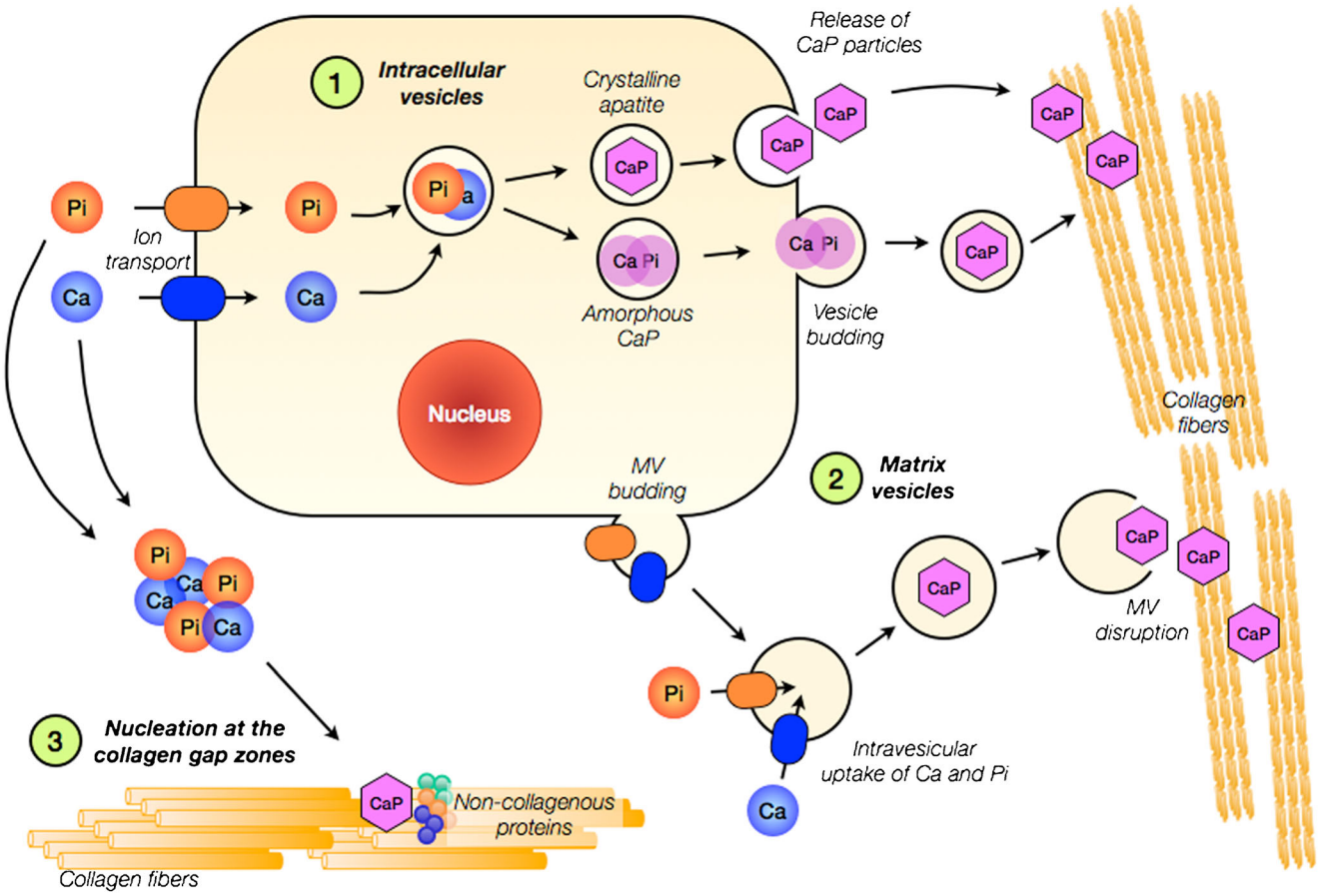

Fig. 1 Schematic view of ongoing biomineralization mechanisms hypotheses. (1) Phosphate and calcium ions are transported into the mineralizing cell and can be concentrated in intracellular vesicles where they will form amorphous calcium–phosphate particles that will be transported to the collagen fibers after vesicle budding. Crystalline apatite may also form and is released from the cell and deposited directly on collagen fibers. (2) Cell-dependent mechanism also rely on the plasma membrane budding that will form so-called matrix vesicles (MV) that will transport and concentrate calcium and phosphate ions extracellularly. Following their disruption, the MVs will deposit CaP apatite crystals onto collagen fibers. (3) Cell-independent mechanisms involves the direct nucleation of mineral in the collagen gap zones, which is mediated by non-collagenous proteins including osteopontin (OPN), dentin sialophosphoprotein (DSPP), and dentin matrix protein 1 (DMP1)

is often described as requiring MVs, as the formation of the first crystal phase depends upon a protected microenvironment, which the extracellular matrix of the cartilage, composed mainly of dispersed type II collagen fibrils, cannot provide. In contrast, the matrix synthesized by bone (osteoblasts), dentine (odontoblasts), or enamel (ameloblasts) contains large amounts of tightly packed type I collagen or non-collagenous proteins, which are believed to provide the microenvironment necessary for crystal nucleation without necessarily requiring MVs. Therefore, the different theories of mineral nucleation may not be mutually exclusive but may occur simultaneously, at different stages of development or in different tissues [39].

Requirement for phosphate transporters

Regardless of the nucleation mechanisms involved, the biochemical composition of hydroxyapatite crystals suggests that Pi availability could be a critical factor for the adequate formation of these crystals and, therefore, mineralization. In addition to locally deposited Pi, circulating Pi is a key determinant of skeletal and dental mineralization [7, 66, 87]. As a result, serum phosphate deficiency is the common characteristic of all rickets, and clinical evidence of the role of Pi in bone formation was highlighted more than 60 years ago [79]. Despite this, the mechanisms by which Pi is translocated from serum to mineralizing cells or mineralization sites are still poorly understood, while this knowledge is essential for understanding the biomineralization mechanisms at a molecular level. In contrast to the well described role of annexins allowing Ca^{2+} to enter MVs [5, 40, 41], the formal description of the Pi transport system allowing Pi entry into MVs is still lacking. The Na^{+}–Pi cotransporters Slc20a1 (PiT1) and Slc20a2 (PiT2) have been proposed to mediate Pi loading into the MVs [12, 58, 91]. Their role in the transport of Pi within MVs has been inferred from their expression in the mineralizing cells from which MVs are generated and from the

numerous publications describing the regulation of PiT1 (and PiT2 to a lesser extent) in bone and cartilage cells in vitro by osteogenic factors. However, no published experiment to date has formally demonstrated the presence of these transporters at the MVs surface, as this has been done for annexins. Moreover, early in vivo experiments using transgenic mice over-expressing PiT1 [75] or genetically modified mouse models under-expressing PiT1 [17] failed to demonstrate a major contribution of this transporter to mineralization processes. Recently, PiT2 KO mice have been described as having decreased bone mineralization, but the underlying mechanism has not been studied [92] and since the observed phenotype may result from an indirect effect of the ubiquitous deletion of PiT2, tissue-specific deletion of this transporter is necessary to confirm its direct role in mineralization. Finally, it is also important to note that apart from the mineralization process driven by MVs, which necessarily requires the transport of Pi through a phospholipid membrane, the involvement of Pi transporters for direct nucleation of apatite crystals on the extracellular matrix of bone or teeth remains an open question.

The lack of definite demonstration of a role of Slc20 transporters in biomineralization calls for alternative possibilities. While the Slc34 transporters were described as being essentially expressed in the kidney, liver or lung, detailed analysis of their expression pattern reveal that this is not the case [83] and that these transporters may be expressed in mineralizing organs. In addition, the availability of Slc34-deficient animal models allows for the investigation of bone and teeth phenotype in the absence of Slc34 transporters. In this brief review, we will gather available information on the expression of Slc34 transporters in mineralizing organs and their putative role in biomineralization mechanisms.

Expression and regulation of Slc34 Pi transporters in the skeleton and teeth (Table 1)

Studying the expression of multi-spanning transmembrane proteins in mineralized tissues has often been regarded as a laborious and troublesome task [4]. The first technical difficulty is the need to decalcify the bone samples before processing to the slide preparation. This step requires several days to several weeks depending on the tissue and its size and often increases technical issues for obtaining nice immunohistochemistry or in situ hybridization [4]. In addition, working with uncalcified cartilage can be still a challenge for the collection of clean and abundant mRNA due to the important amount of glycosaminoglycans preventing easy isolation of RNAs [68]. For these reasons, high-throughput analyses of proteins and/or mRNA expressed in the skeleton and the teeth are not often performed, and public databases that are available on the web (RNAseq, microarrays, SAGE) rarely include the bone, cartilage, or tooth.

Among the public databases reporting gene expression in the skeleton, the Eurexpress atlas (http://www.eurexpress.org), a genome-wide transcriptome atlas of RNA in situ hybridization of a developing mouse at embryonic day 14.5 [23], identified the expression of Slc34a1 in only two developing organs: the kidney and bone. Strong renal expression was illustrated in the metanephros, while strong expression was also found in the axial (ribs), appendicular (femur and clavicle), oral (mandible and maxilla), and cranial (basioccipital and orbito-sphenoid bones) skeletons. Moderate expression was also found in the humerus, scapula, and pelvis. The expression of Slc34a1 has not been reported in any other tissue in this model. As for the expression of Slc34a2 and Slc34a3, in situ hybridization was negative for Slc34a3, whereas data analysis for Slc34a2 is still pending [23]. A search for the expression of Slc34 transporters in mineralized tissues in other available databases led to negative results. Importantly, it should be noted that the reported expression of Slc34a1 in the Eurexpress database may be more likely to relate to a developmental role of Slc34a1 in the skeleton than a role in bone mineralization since no mineralized tissue is present at E14.5 in the mouse embryo.

In vitro, expression of Slc34a1 has been reported in osteoblastic cell lines (MC3T3 and UMR106 cells) during in vitro mineralization [49] by non-quantitative PCR and Western blots. In this report, Slc34a1 was upregulated by Pi supplementation and culture stage, suggesting a possible role during mineralization. In the bone resorbing cells osteoclasts, the expression of Slc34a1 was reported in vivo in bones (using western-blots and immunohistochemistry) more than 20 years ago [29, 30]. Slc34a1 was also expressed in vitro in murine osteoclast-like cells generated from RAW264.7 cells by treatment with receptor activator of NF-kB (RANKL) [31] and was shown to be located at the basolateral membrane of osteoclasts, opposite to the ruffled border [38]. In cartilage, a faint expression of Slc34a1 has been reported in the hypertrophic chondrocytes from the chick growth plate by immunohistochemistry [55]. That being said, it is important to realize that these results describing the expression of Slc34a1 in a number of skeletal cells must be taken with caution because, to our knowledge, the expression of Slc34a1 has not been confirmed in chondrocytes and osteoblasts (especially primary osteoblasts) and led to contradictory results in osteoclasts. Indeed, Ito et al. could not detect the expression of Slc34a1 protein by western-blot or immunofluorescence in the latter cells [35]. In dental cells, Slc34a1 was reported to be expressed (using non-quantitative PCR) in the rat odontoblast-like mineralizing pulpal cell line (MRPC-1), although protein expression was not studied [48]. In contrast, no Slc34a1 expression was detected in mouse germ cells by RT-PCR and northern blots [60] or ameloblasts [44]. Similarly, we were unable to detect Slc34a1 in teeth using PCR

Table 1 Summary of studies demonstrating the expression or the non-expression of Slc34 and Slc20 transporters in skeleton and tooth

Cell type	Slc34a1	Slc34a2	Slc34a3	Slc20a1	Slc20a2
Osteoblasts	(+) MC3T3 (PCR, WB) [49]	(+) MC3T3, UMR106, (PCR, WB) [49]		(+) MC3T3 (PCR) [49]	(+) MC3T3 (PCR) [49]
Osteoclasts	(+) Osteoclasts in vivo (WB, IHC) [29, 30] (+) RAW264.7 [31, 38] (−) Osteoclasts [35]				
Chondrocytes	(±) Hypertrophic chondrocytes (IHC) [55]			(+) Hypertrophic chondrocytes (ISH) [61]	
				(+) Growth plate chondrocytes [21]	(+) Growth plate chondrocytes [21]
Ameloblasts	(−) Ameloblasts [44]	(+) Ameloblasts in maturation stage [19, 44, 57, 93]	(−) Ameloblasts [44, 56, 57]	(+) Ameloblasts [56, 57]	(−) Ameloblasts [57]; (+) M2H4, ALC [56]
Odontoblasts		(+) Odontoblasts [57]	(−) Odontoblasts [44, 56, 57]	(+) Odontoblasts [56, 57]	(−) Odontoblasts in vivo [57]; (+) M2H4, ALC [56]
				(+) MO6-G3 odontoblasts [16, 88]	(+) MO6-G3 odontoblasts [16, 88]
Pulp cells	(+) MRPC1 [48]				
	(−) Human primary pulp cells differentiated into odontoblasts [76]	(−) Human primary pulp cells differentiated into odontoblasts [76]	(−) Human primary pulp cells differentiated into odontoblasts [76]	(+) Human primary pulp cells differentiated into odontoblasts [76]	(+) Human primary pulp cells differentiated into odontoblasts [76]
	(−) Mouse germ cells [60]				
	(−) Whole teeth, M2H4, ALC [56]				

(+) positive expression, *(−) negative expression*, *(±)* non-consolidated result

and in situ hybridization in mouse germ cells and human dental samples [57], as well as in the rat odontoblastic (M2H4) and mouse ameloblastic-like (ALC) cell lines [56]. In humans, Tada et al. reported negative expression of Slc34a1 in primary pulp cells differentiated into odontoblasts [76].

Similarly to Slc34a1, Slc34a2 expression was also reported in MC3T3 and UMR106 cell lines in vitro [49] using RT-PCR and western blots, although, unlike Slc34a1, no regulation of Slc34a2 was shown by Pi supplementation and culture stage. To our knowledge, no expression of Slc34a2 was demonstrated in osteoclasts or cartilage. While evidence of expression of Slc34a2 in the skeleton appears weak, expression of Slc34a2 has been found and confirmed in the tooth by several independent groups. We and others have shown that the expression of Slc34a2 mRNA in enamel is negligible during the secretory stage and significantly upregulated during the maturation-stage [44, 57, 93]. Using a murine anti-Slc34a2 antibody, we could detect the late expression of Slc34a2 in ameloblasts of the incisors and molars at P6 and P10 [57], consistent with the study of Bronckers and colleagues who showed that this expression was limited to the apical pole of mature ameloblasts [19]. While the significance of Slc34a2 expression at the apical pole of ameloblast during this differentiation stage remains to be explained, it is important to stress that this pattern of expression was rather specific and that no expression of Slc34a2 could be found elsewhere in the tooth, including in odontoblasts [57].

Since Slc34a3 has been discovered later than the other type II Na^+–Pi co-transporters, even less data are available on its specific profile of expression in the skeleton and teeth. To our knowledge, there no published data illustrating an expression of Slc34a3 in cells from the skeleton (either chondrocyte, osteoblast, or osteoclast). In addition, we and others have reported negligible expression in ameloblasts and odontoblasts [44, 56, 57], whereas expression in human primary pulp cells differentiated into odontoblasts was negative [76].

Lessons from Slc34-deficient mouse models and patients carrying Slc34 mutations

Slc34a1

The major physiological manifestation of Slc34a1 deletion in mice is the apparition of a renal Pi reabsorption defect [6, 72], accounting for the observed hypophosphatemia,

hyperphosphaturia, and appropriate increase in vitamin D serum levels. Bone histology analysis of Slc34a1 knockout mice revealed poorly developed metaphyseal trabeculae and retarded secondary ossification at 4 weeks of age [6]. However, this phenotype was reversed by 16 weeks of age, revealing an age-dependent adaptation upon loss of Slc34a1 in mice [6]. Interestingly, despite the low phosphate serum levels, no signs of persistent rickets could be seen in this mouse model [6, 38], consistent with the appropriate rise in vitamin D serum levels [11]. Moreover, an adequate phosphate supply was shown to ameliorate the bone mineralization defects [46], a finding that argued against a local role of Slc34a1 in bone in the observed skeletal phenotype and is consistent with the absence of published report describing Slc34a1 expression in osteoblasts and chondrocytes in vivo. It remained possible however that the observed bone phenotype in the Slc34a1 knockout mouse could originate from an osteoclast malfunction due to Slc34a1 deletion in these cells [29, 30, 38]. To clarify this possibility, Albano et al. investigated the expression of Slc34a1 during osteoclast differentiation, assessed the impact of Slc34a1 deletion on osteoclast differentiation and resorption in vitro, and studied the structural bone parameters in Slc34a1 KO mice [2]. Their functional study concluded that the Slc34a1 Pi transporter has no role in the differentiation and function of osteoclasts, a result consistent with the very low expression of Slc34a1 in osteoclasts compared to the Pi transporters of the Slc20a family [2].

In humans, the first reported mutation of SLC34A1 gene was observed in a cohort of patients with urolithiasis or bone demineralization and persistent idiopathic hypophosphatemia [62]. Although this first observation was subsequently controversial [45, 52, 82], many other mutations of SLC34A1 have now been discovered by independent laboratories [84] and linked to autosomal recessive hypophosphatemic rickets with renal Fanconi's syndrome [51], idiopathic infantile hypercalcemia and nephrocalcinosis [67], nephrocalcinosis and kidney stones [22, 24, 52], or mixed syndromes [25]. Sotos syndrome, characterized by learning disorders, facial dysmorphia, overgrowth, hypercalcemia, and nephrocalcinosis, was associated with increased deletions of the SLC34A1 gene [37]. Although in most cases patients have skeletal abnormalities, it is difficult to attribute the origin of these defects either to low levels of circulating Pi or to a lack of expression of SLC34A1 specifically in bone. In addition, skeletal abnormalities found in patients with Fanconi syndrome are persistent and severe, while they are transient in the Slc34a1 knockout mice, suggesting differences between humans and mice in the maintenance of bone homeostasis [7].

Slc34a3

Slc34a3 knockout mice exhibit hypercalcemia, hypercalciuria, and increased serum 1,25-dihydroxyvitamin D levels, together with no hypophosphatemia, hyperphosphaturia, or renal calcification. Accordingly, they have so sign of rickets or osteomalacia [71]. In contrast to the relative benign effects of Slc34a3 disruption in mice, mutation of the Slc34a3 gene in humans causes hereditary hypophosphatemic rickets with hypercalciuria (HHRH) [8, 34, 47]. This autosomal recessive disorder is characterized by hypophosphatemia, hyperphosphaturia, increased serum 1,25-dihydroxyvitamin D levels, hypercalciuria, rickets, and osteomalacia. These observations suggest that Slc34a3 has an important role in renal Pi reabsorption and bone mineralization in humans. Segawa et al. compared the biochemical findings in Slc34a1, Slc34a3, and double Slc34a1/Slc34a2 null mutant animals to assess the relative importance of each transporter to the phenotype [70]. Interestingly, mice that were deleted from both Slc34a1 and Slc34a3 exhibited severe hypophosphatemia, hypercalciuria, and rickets, similar to that seen in HHRH in humans. Altogether, this suggested that in mice, Slc34a1 and Slc34a3 have different roles in the regulation of serum Pi levels and bone mineralization, while they may functionally interfere in humans. Finally, it is important to note that a high Pi diet reversed the bone abnormalities found in the double null animals [70], as it is the case in HHRH patients, arguing against a local role of the Slc34a1 and Slc34a3 transporters in the skeletal phenotype.

Slc34a2

The wide range of tissue expression of Slc34a2 [26, 27, 32, 80, 90] probably explains that its deletion in mice leads to embryonic lethality at mid-gestation [73]. Conditional invalidation of Slc34a2 confirmed its role in the intestine [65], while homozygous Slc34a2 loss-of-function mutations in humans led to pulmonary alveolar microlithiasis, without effect on Pi homeostasis [20, 33]. This contrasts sharply with the effect of Slc34a2 disruption in mice and suggests that, similarly to Slc34a1 and Slc34a3, divergent functions for Slc34a2 probably exist in humans and mice. To date, no report has illustrated a role of this transporter in the development or mineralization of teeth or skeleton in vivo. In particular, given the strong and specific expression of Slc34a2 in the tooth, this transporter could play a pivotal role in this tissue and it would therefore be relevant to study its functionality in future studies using appropriate tissue-specific knockout animal models.

Discussion and future directions

Local phosphate versus circulating phosphate: what role for Slc34 Pi transporters?

Most of the skeleton develops through a process called endochondral ossification during which proliferative chondrocytes

of the growth plate differentiate into hypertrophic chondrocytes, which subsequently undergo apoptosis and are replaced by mineralized bone [50, 59]. It is known that a decrease in circulating Pi leads to defects in apoptosis of hypertrophic chondrocytes, resulting in enlargement of the late hypertrophic chondrocyte layer and, consequently, defective bone mineralization [1, 42, 55, 64]. This is a major and common feature of hypophosphatemic disorders such as hereditary vitamin D-resistant rickets, X-linked hypophosphatemia, or HHRH [79] but is also seen in wild-type mice fed with low Pi diets [42, 64].

While controlled circulating Pi levels are essential to proper bone mineralization, it remains to be shown whether bone mineralization depends upon the expression of identified Pi transporters in skeletal tissues. Indeed, as discussed above, the expression of Slc34 transporters is very low, or even not shown, in skeletal tissues. Experiments have also shown that feeding Slc34a1 knockout or Slc34a1/Slc34a3 double knockout mice with appropriate Pi diets rescued their bone phenotype [46, 69, 70], consistent with the absence of role of these transporters in providing Pi locally for mineralization purposes. It is therefore plausible that Pi requirements for bone mineralization are determined both by Slc34 Pi transporters expressed in renal and intestinal tissues (therefore controlling serum Pi availability) and by Pi transporters locally expressed in skeletal tissues (controlling Pi entry into mineralizing cells). In this context, it should be recalled that the identified Pi transporters belonging to the type I, II, or III families are low-capacity transporters, with a Km for Pi close to 0.1 mM. This contrasts with the high local concentrations of Pi at the vicinity of mineralizing cells, which can be estimated to represent four to five times the concentration of Pi found in serum (i.e., 6–8 mM) [3, 18, 36]. Under these conditions, Pi transporters from the type I, II, or III families would be maximally active at Pi values well below those found extracellularly in mineralizing bone, without however being able to transport the significant quantities of Pi required for mineralization. High-capacity Pi transporters with a Km for Pi closer to the extracellular Pi concentrations found in the skeleton would indeed be more relevant for this task. Interestingly, the existence and activity of such transporters have been widely described in early studies in kidney samples [10, 63, 77, 78, 85]. The question therefore remains whether such high-capacity component of Pi transport could exist in bone or teeth and mediate the bulk of Pi transport needed during mineralization processes. Alternatively, a role for locally expressed Pi transporters in bone may not be mandatory, since cell-independent biomineralization mechanisms have been described [12, 86], as discussed above.

While current knowledge does not provide strong evidence for a significant role of Slc34 Pi transporters in bone mineralization mechanisms, the marked and specific expression of Slc34a2 in early and late maturation-stage ameloblasts does suggest a role for this transporter in this tissue [19]. While the authors of this study suggest that the localization of Slc34a2 may indicate that Pi and sodium are excreted in the enamel space rather than transported in the ameloblast, this hypothesis requires that the orientation of the Slc34a2 protein in the membrane be inverted [19, 43]. In any case, the intriguing putative role of Slc34a2 in tooth is worth exploring and may help to understand how enamel is formed in vivo [74].

Final words

The technical investigation of skeletal and dental physiology is complex for a number of reasons. The cells of these two mineralized tissues are difficult to access, while the availability of relevant cell lines is very limited, especially for osteoclasts and osteocytes, the mature form of osteoblasts [13]. Therefore, although many major advances have been made recently in the understanding of biomineralization mechanisms, knowledge of Pi transport entities, especially Slc34 transporters, in mineralized tissues has been primarily descriptive rather than experimental-based. Yet, this knowledge would offer important opportunities to better understand biomineralization mechanisms and perhaps propose alternative therapeutic strategies to treat devastating consequences of poor regulation of mineralization mechanisms, leading for instance to kidney stones, osteoarthritis or vascular calcification [39]. However, it should be kept in mind that since there is significant species variability in physiological Pi transport functions, as summarized above, human studies are mandatory for the application of knowledge from animal models to human physiology and pathophysiology. And since several different mechanisms are involved in biomineralization, the respective role of each of the Pi transporter should be clarified in establishing their functions in a certain tissue or at a certain stage of the mineralization process before considering therapeutic applications. This would require, at a minimum, to generate appropriate animals models of the currently known Pi transporters, explore the possibility that other components of Pi transport may exist and have important local roles in biomineralization, and assess their roles in biomineralization in humans.

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