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Chapter 2

Vitamin K, SXR, and GGCX

Kotaro Azuma and Satoshi Inoue

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Abstract

Vitamin K was discovered in 1929 as a substance essential for blood coagulation and had been clinically utilized before the precise mechanism of action became aware in 1970s. The function as a cofactor of γ-glutamyl carboxylase (GGCX) was the mechanism firstly discovered with the identification of several substrate proteins including blood coagulation factors and osteocalcin. Recently, we and others have shown that vitamin K has other modes of function, such as ligand of nuclear receptor SXR (steroid and xenobiotic receptor) and its murine ortholog PXR (pregnane X receptor) and modulator of protein kinase A (PKA) activity. Besides its importance in blood coagulation, involvement of vitamin K has been shown in two major aging-related diseases, osteoporosis and osteoarthritis. Based on clinical and epidemiological studies, vitamin K is shown to have protective roles for both of them. Interestingly, clinical studies concerning single nucleotide polymorphisms (SNPs) of GGCX and γ-carboxylated status of osteocalcin suggested relationship between GGCX activity and bone-protective effect, while recent findings from basic research indicated that vitamin K functions mediated by SXR/PXR as well as GGCX are important in the bone metabolism. We also suggested that cartilage-protective effect is mediated by SXR/PXR signaling by animal experiments using *Pxr* knockout mice.

Keywords: γ-glutamyl carboxylase (GGCX), steroid and xenobiotic receptor (SXR), pregnane X receptor (PXR), protein kinase A (PKA), osteocalcin, osteoporosis, osteoarthritis

1. Introduction

In 1929, a Danish biochemist, Dr. Henrik Dam predicted a fat-soluble diet substance which is essential for blood coagulation. The substance was referred as "Koagulationsvitamin" in

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German; thus it is called vitamin K in English named after the initial letter of its German word. He shared the Nobel Prize in Physiology or Medicine in 1943 with an American biochemist Dr. Edward A. Doisy who later identified the structure of vitamin K. During the 1970s, the mechanism of vitamin K began to be revealed with the discovery, namely, vitamin K was necessary for γ-carboxylation of some coagulation factors which is catalyzed by an enzyme called γ-glutamyl carboxylase (GGCX) [1, 2]. Interestingly, warfarin, which inhibits vitamin K function, was in medical use since 1954, and vitamin K administration to newborn babies for preventing intracranial hemorrhage started in many countries in the 1960s before the enzymatic mechanisms of vitamin K function had been clarified.

Recently, epidemiological and clinical studies suggested that vitamin K is related to various physiological and pathological processes besides coagulation. Based on these studies, vitamin K was approved to be used as a drug preventing osteoporotic fracture in several Asian countries. Moreover, for these two decades, another mode of vitamin K action has been elucidated. We discovered vitamin K functions as a ligand for a nuclear receptor, SXR (steroid and xenobiotic receptor), and its murine ortholog, PXR (pregnane X receptor) [3], which have physiological or pathological significance. Summing up, vitamin K plays important roles in wide variety of biological process in various modes of actions.

In this chapter we are going to introduce novel mechanism of vitamin K action mediated by SXR/PXR as well as recent findings concerning classical vitamin K action mediated by GGCX. Then we would like to discuss the functions of vitamin K in some aging-related diseases based on recent discoveries.

2. Multiple mechanisms of vitamin K function

The classical function of vitamin K is a cofactor of GGCX which was clarified in the 1970s [1, 2]. GGCX catalyzes the addition of a carboxyl group to glutamate residues in the substrate proteins, which is coupled by oxidization of vitamin K hydroquinone to vitamin K epoxide. Vitamin K-dependent coagulation factors (II, VII, IX, and X) are well known substrates for GGCX. They become active when several glutamate residues are γ-carboxylated. So far, 18 human proteins are reported to be γ-carboxylated and their functions are regulated by γ-carboxylation status in most of them. It is known that cyclic use of vitamin K is necessary for its function as a cofactor for GGCX [4]. To be recycled, vitamin K epoxide should be reduced by an enzyme called vitamin K epoxide reductase (VKOR). Warfarin, which has an anticoagulant activity, inhibits VKOR, causing a subsequent decrease in GGCX activity (**Figure 1**).

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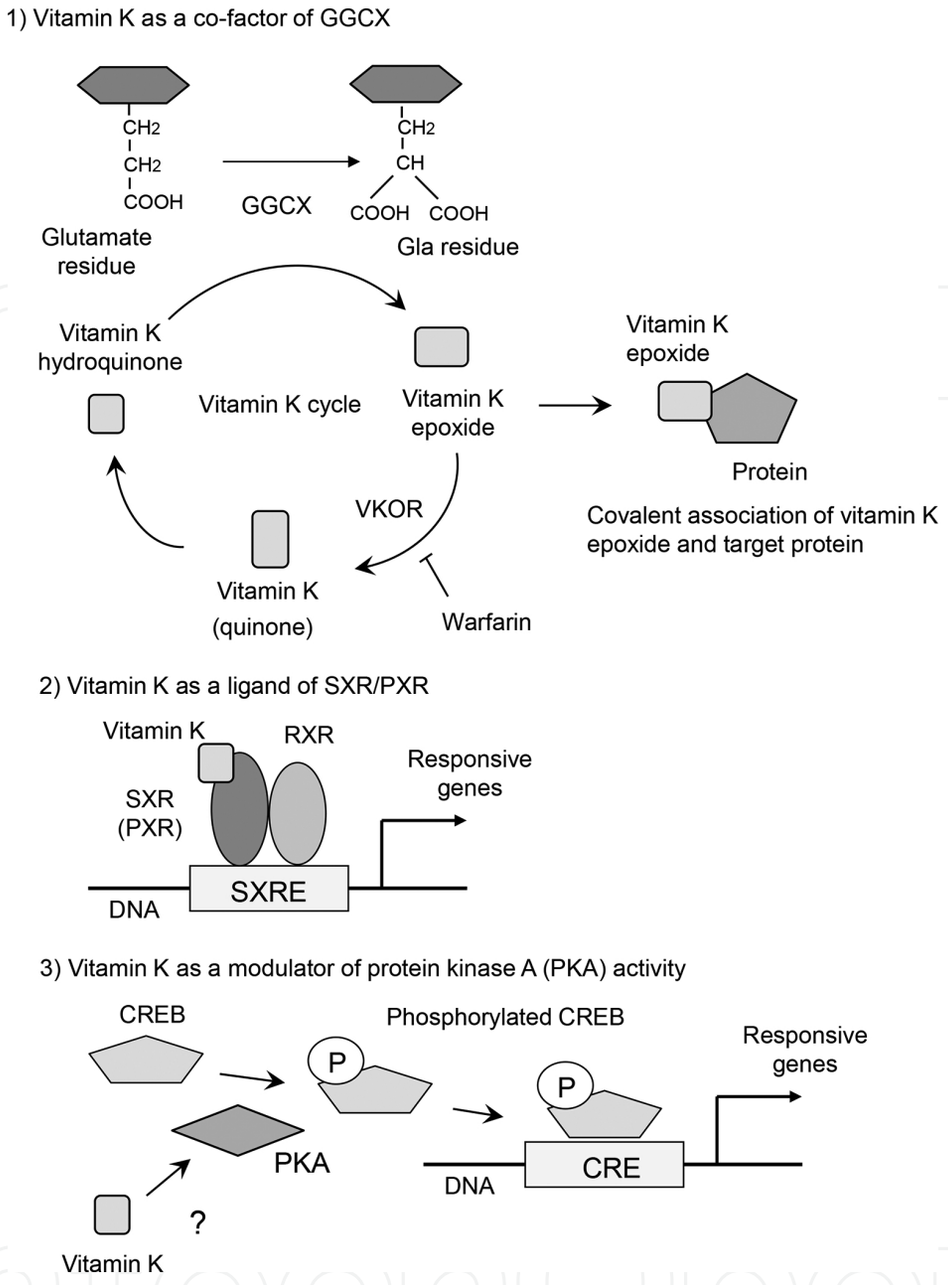


Figure 1. Multiple mechanisms of vitamin K actions. (1) GGCX catalyzes conversion of glutamate residues into Gla residues by incorporating an additional carboxyl group to glutamate. This reaction requires cyclic use of vitamin K. Vitamin K epoxide reductase (VKOR) is required for recycling vitamin K which is oxidized during γ-glutamyl carboxylation. Warfarin inhibits VKOR and vitamin K recycling, thereby suppressing GGCX activity. Covalent binding of vitamin K epoxide and a target protein is also proposed as a novel mode of vitamin K action which is dependent on GGCX activity. (2) Vitamin K also functions as a ligand of steroid and xenobiotic receptor (SXR) and its murine homolog, pregnane X receptor (PXR). On vitamin K binding, SXR/PXR forms heterodimers with 9-cis-retinoid acid receptor (RXR), and this complex binds to SXR-responsive elements (SXRE) within the promoter or enhancer regions of target genes. (3) Vitamin K also activates protein kinase A (PKA) with unknown mechanism. This action was suppressed by PKA inhibitor but not affected by stimulation with SXR agonist or knocking down of GGCX. Typical substrate of PKA is CREB (cyclic AMP-responsive element binding protein) and it binds to CRE (cyclic AMP-responsive element) within the promoter or enhancer regions of target genes when CREB is phosphorylated.

Recently, another mode of GGCX-dependent vitamin K function was reported in the study of proapoptotic effect of vitamin K. Handa et al. found proapoptotic protein Bak was covalently modified by vitamin K epoxide and regulated by its modification [5]. This function is dependent on GGCX-mediated vitamin K function since GGCX activity is required to generate vitamin K epoxide (**Figure 1**).

On the other hand, we discovered GGCX-independent mode of vitamin K function mediated by transcriptional regulation [3] as compared to posttranscriptional modifications explained above. Vitamin K was found to be one of the ligands of the nuclear receptor, SXR, and its murine ortholog, PXR. This receptor is also called NR1I2 according to standardized nomenclature designated by the nuclear receptor committee. In 1998, SXR/PXR was cloned as a novel nuclear receptor that is mainly expressed in the liver and intestine [6]. At first, its functions were characterized as a ligand-dependent transcription factor which is activated by various pharmaceutical agents and xenobiotic compounds [7]. It was originally classified as an orphan receptor since the endogenous ligand was not known when it was cloned. It was later shown that some kinds of secondary bile acids (such as lithocholic acid) could be endogenous ligands for this receptor [8, 9]. It forms a heterodimer with 9-cis-retinoid acid receptor (RXR) on ligand stimulation. This complex then binds to SXR-responsive elements (SXRE) in the promoter or enhancer regions of target genes (**Figure 1**). Some of its target genes are the drug-metabolizing enzyme, such as *CYP3A4*, and the ABC (ATP-binding cassette) family transporter, *MDR1*. Because of that, a function of SXR/PXR is considered as a xenobiotic sensor-inducing genes involved in detoxification and drug excretion [10] and named as such. The discovery of novel vitamin K function as a ligand for SXR/PXR indicated that physiological and pathological processes mediated by PXR/SXR would be affected by vitamin K.

There is another mode of vitamin K function which modulates activation of signal transduction pathway. This is inferred by existence of some genes induced by vitamin K, not by SXR agonist, rifampicin [11]. This induction was not affected by knocking down of GGCX suggesting that this is γ-carboxylation-independent pathway. Expression of those genes was suppressed by protein kinase A (PKA) inhibitor, showing the novel vitamin K function as a modulator of PKA activity (**Figure 1**).

Inhibition of another protein kinase, protein kinase C (PKC) α and ε, by vitamin K was also reported [12]. Inhibition of IKK (inhibitor of nuclear factor kappa B kinase) and subsequent inhibition of NFkB (nuclear factor kappa B) were observed. Whether this function of vitamin K is independent of mechanisms described above remains to be elucidated.

3. Epidemiological and clinical studies on vitamin K and aging-related skeletal diseases

A traditional Japanese food, "natto" (fermented soybeans) contains high concentrations of MK-7, a form of vitamin K2 (menaquinone), synthesized by microorganisms. Epidemiological study conducted in Japan revealed negative correlation of Natto intake and incidence of hip fracture [13], which drew attention toward possible link between vitamin K and osteoporosis.

Later, among several nutrients including vitamin D and calcium, vitamin K was shown to be the only nutrient that is significantly correlated with hip fracture incidence in Japanese population [14]. Furthermore, the fracture-preventing effect of vitamin K was observed in several clinical studies in Japan, which was confirmed by meta-analysis [15]. Based on these results, vitamin K2 is used for treatment of osteoporosis in several Asian countries. We previously reported a functional single nucleotide polymorphism (SNP) in *GGCX* that causes higher enzymatic activity correlated with higher bone mineral density in elderly Japanese women [16], suggesting bone-protective function of vitamin K is related to GGCX activity. Osteocalcin, one of the substrates of GGCX, is specifically expressed in osteoblastic lineage. The concentration of undercarboxylated form of osteocalcin (ucOC) in serum was reported to be positively correlated with fracture risk [17]. Measurement of ucOC has been clinically used to decide the indication of vitamin K for treatment of osteoporosis in Japan. These support the contribution of GGCX activity to bone-protective effect.

Vitamin K also has some epidemiological evidences in relationship with another skeletal disease, osteoarthritis. Low vitamin K intake was correlated to the prevalence of osteoarthritis both in North America and in Japan [18–20]. Unfortunately, therapeutic effect of vitamin K for established osteoarthritis was not proven by a trial [21], suggesting that the study period was too short or vitamin K has only preventive effect.

4. Paradoxical GGCX-mediated vitamin K functions on bone metabolism

It is difficult to evaluate vitamin K function on bone tissue mediated by GGCX *in vivo* due to its dominant effect on coagulation activity. For example, it is impossible to measure bone mineral density of adult mice systemically lacking GGCX because *Ggcx*-knockout mice die before birth or on the day of birth with massive bleeding [22]. To overcome this obstacle, we utilized Cre/loxP system which enables tissue-/organ-specific knockout of GGCX dependent on promoter activity [23] and generated osteoblast-specific GGCX-deficient mice by crossing with *Col1a1*-Cre mice [24]. Since osteoblasts express several substrates of GGCX including osteocalcin, we assumed bone-protective effect of vitamin K is mediated by GGCX activity in osteoblasts. Surprisingly, the bone mineral density was increased in osteoblast-specific GGCX-deficient mice and aberrant mineralization was observed in these mice by ultrastructural analysis. This result indicates that GGCX in osteoblast may not contribute to bone-protective effect of vitamin K. Moreover, it is contradicting to the clinical studies on *GGCX* SNPs or ucOC described above. We speculate that GGCX activity in other tissue is responsible for bone-protective effect of vitamin K and/or vitamin K function mediated by SXR/PXR that would be more important in the bone tissue. Further studies are necessary to clarify this enigma. It is noteworthy that osteocalcin-deficient mice have been shown to have mechanically stronger bone than wild-type mice [25], suggesting that the decrease of carboxylated osteocalcin, rather than increase of ucOC, has "bone strengthening effect."

5. SXR-mediated vitamin K functions on bone and cartilage

As described above, we proposed another mode of vitamin K function as a ligand of a nuclear receptor, SXR, and its murine ortholog, PXR. We showed that SXR is also expressed in osteoblastic cell lines and is activated by vitamin K2 [3]. We further identified SXR-dependent vitamin K-responsive genes by microarray analysis using human osteoblastic cell line, MG63 cells stably overexpressing SXR [26]. The identified genes included *Tsukushi* which encodes a protein that has a collagen-accumulating effect [27], *Matrilin2* which encodes a protein comprising extracellular matrix like collagen [28], and *Cd14* which regulates osteoblastogenesis [29] and osteoclastogenesis by inducing differentiation of B cells [30, 31]. These genes are induced even in the presence of warfarin, indicating their induction is independent of GGCX activity.

The involvement of SXR/PXR signaling in bone metabolism *in vivo* was suggested by the bone phenotype of systemic *Pxr* knockout mice [32]. We showed that 4-month-old female *Pxr* knockout mice had lower bone mineral density in femoral bone. Micro-CT analyses revealed fragile structure in the femoral trabecular bones of *Pxr* knockout mice. By histomorphometrical analyses, enhanced bone resorption and suppressed bone formation were observed in *Pxr* knockout mice. The mechanical strength of bone from *Pxr* knockout mice was weaker than that of wild-type mice. Negishi et al. reported the phenotype of systemic *Pxr* knockout mice from different origins [33, 34]. They also observed lower bone mineral density in *Pxr* knockout mice. They proposed a mechanism involving SLC34A2, a transporter of inorganic phosphate, expressed in the intestine. They showed *Slc34a2* is a PXR-responsive gene in the intestine and this was supported by the observation that serum levels of inorganic phosphate were significantly decreased in *Pxr* knockout mice. In con-

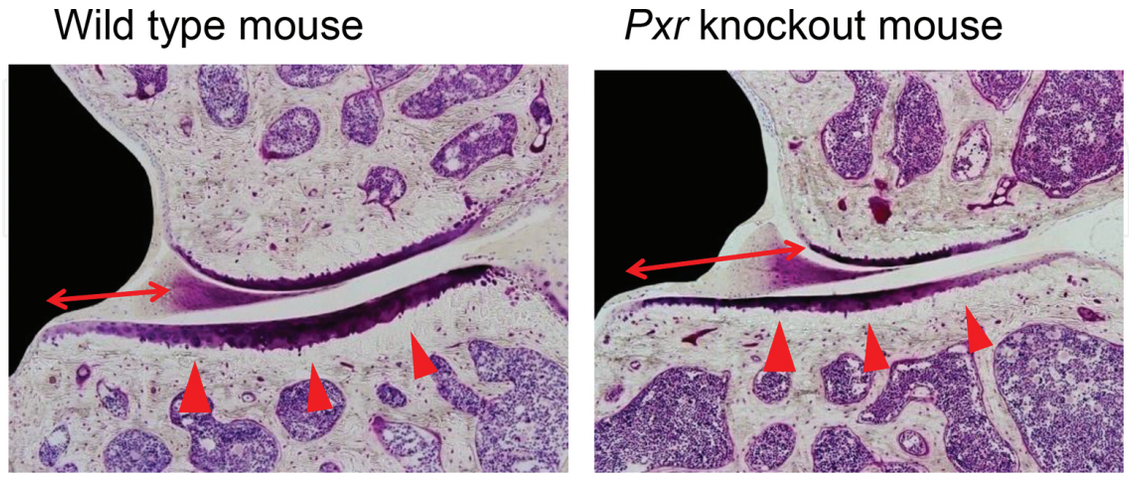


Figure 2. Aging-dependent wearing of articular cartilage of the knee joint in *Pxr* knockout mice. Representative microscopic images of articular cartilage of 13-month-old wild-type and *Pxr* knockout mice are shown. Arrowheads indicate lateral articular cartilage of the tibia. This difference was not significant in 4-month-old mice, suggesting this is aging-dependent process. Cited from Azuma et al. [35].

trast, we did not observe difference in the serum levels of inorganic phosphate between *Pxr* knockout mice and wild-type mice [32], suggesting the existence of different mechanisms according to the mouse strains and/or environment.

We also proposed SXR/PXR-dependent mechanism concerning vitamin K effect on articular cartilage [35]. We found that systemic *Pxr* knockout mice displayed aging-dependent wearing of articular cartilage of knee joints (**Figure 2**). Remarkable reduction of width and an enlarged gap between femoral and tibial articular cartilage were observed in *Pxr* knockout mice in 8-month-old and 13-month-old mice, but not in 4-month-old mice, indicating this is an aging-dependent process. With microarray analyses using ATDC5 chondrocytic cells overexpressing human SXR, we identified *Fam20a* (family with sequence similarity 20a) as an SXR-dependent gene induced by SXR ligands. We showed FAM20A related to the higher expression of COL2A1, a main component of extracellular matrix of the articular cartilages, suggesting the cartilage-protective effect of FAM20A. These results are consistent with epidemiological studies showing relationship between vitamin K intake and osteoarthritis and supporting the potential roles of vitamin K in preventing osteoarthritis caused by aging.

6. Conclusion

In this chapter, we described multiple mechanisms of vitamin K functions clarified so far and their involvement in aging-related skeletal diseases as examples for their biological significance. Besides blood coagulation, osteoporosis, and osteoarthritis, it became gradually aware that many physiological and pathological phenomena, such as fertility [36], atherosclerosis [37–39], brain development [40], dementia [41], and glucose metabolism [42–44], are related to the status of vitamin K sufficiency. We sincerely hope that vitamin K study leads to discoveries of new biological mechanisms and targets for disease prevention and treatment and eventually contributes to human culture and welfare.

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