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REVIEW

Vitamin K and hepatocellular carcinoma: The basic and clinic

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Abstract

Vitamin K (VK), which was originally identified as a cofactor involved in the production of functional coagulation factors in the liver, has been shown to be involved in various aspects of physiological and pathological events, including bone metabolism, cardiovascular diseases and tumor biology. The mechanisms and roles of VK are gradually becoming clear. Several novel enzymes involved in the VK cycle were identified and have been shown to be linked to tumorigenesis. The VKs have been shown to suppress liver cancer cell growth through multiple signaling pathways *via* the transcription factors and protein kinases. A VK2 analog was applied to the chemoprevention of hepatocellular carcinoma (HCC) recurrence after curative therapy and was shown to have beneficial effects, both in the suppression of HCC recurrence and in patient survival. Although a large scale randomized control study failed to demonstrate the suppression of HCC recurrence, a meta-analysis suggested a beneficial effect on the long-term survival of HCC patients. However, the beneficial effects of VK administration alone were not sufficient to prevent or treat HCC in clinical settings. Thus its combination with other anti-cancer reagents and the development of more potent novel VK derivatives are the focus of ongoing research which seeks to achieve satisfactory therapeutic effects against HCC.

Key words: Hepatocellular carcinoma; Vitamin K; Steroid and xenobiotic receptor; Nuclear factor-kappa B; Protein kinase A; Protein kinase C; Drug repositioning

Core tip: Vitamin K (VK) is essential nutrient initially identified as a cofactor to produce functional coagulation factors. In addition to the roles in hemostasis, pleiotropic effects of VK in bone health, atherosclerotic diseases and cancer have been attracting. VK has been shown to play tumor-suppressive roles in several cancers including hepatocellular carcinoma (HCC) and reported to have beneficial effects in the treatment of HCC although its anti-tumor effects remain to be improved. Currently novel VK derivatives are under developing and will be

applied to cancer treatment in the future.

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INTRODUCTION

Vitamin K (VK) is a well-known lipid-soluble vitamin that includes two natural types: VK1 and VK2, and synthetic types, known as VK3, VK4, and VK5. VK1, also known as phylloquinone, was first accidently identified by Dam[1] and Dam *et al*[2] for its anti-hemorrhagic activities in 1929. VK1 is ubiquitous and abundant in green leafy vegetables because it plays a direct role in photosynthesis. It performs the classic functions of VK that help the production of blood-clotting proteins[3-5]. VK2 is also known as menaquinone (MK), the subtypes of which are mainly synthesized by limited bacteria. They are mainly stored in animal products. The VK2 subtypes, which are characterized by the isoprenoid side chain length. MK-4 differs from the other MKs, which are synthesized by bacteria, such as MK-7, MK-8, and MK-9, in that it is the most common VK2 subtype in animals. It is a unique subtype because it is normally synthesized from VK1 *in vivo*[6-8]. In addition to VK1 and VK2, VK3 is an efficient coagulant[9]. Unlike the safe natural forms and other synthetic forms of VK, VK3 (menadione) is considered to be toxic because large doses have been shown to cause various adverse effects, such as allergic reactions, hemolytic anemia, and cytotoxicity in liver cells[10]. Aside from its clinical use as a hemostasis medicine, VK4 has recently been reported to have inhibitory effects on prostate cancer[11]. VK5 is used in many areas including the pet food industry to inhibit fungal growth[12] and has been shown to mimic the effect of insulin[13].

OVERVIEW OF VK METABOLISM

Dietary VK is absorbed from the small intestine along with dietary fat[14]. The latest findings have demonstrated that a cholesterol transporter, Niemann-Pick C1-like 1, is a key regulator of intestinal VKs absorption[15]. Despite VK's rapid metabolism in tissue, which results in comparatively low body storage[16], primary VK deficiency is rare in healthy adults. In addition to the average diet, which provides plenty of VK, other mechanisms maintain its balance within the human body. The VK cycle plays a critical role in maintaining VK function. The cycle proceeds through the coupled carboxylation and epoxidation carried out by gamma-glutamyl carboxylase (GGCX) and VK epoxide reductase (VKOR)[17,18]. The product, VK epoxide, plays an important role as a cofactor in blood coagulation factor production and is then reconverted to VK by VKOR[19]. It is well-known that warfarin and other 4-hydroxycoumarins block the activity of VKOR to inhibit coagulation[20,21], however, the identification of the *VKOR* gene was a recent finding[22,23]. More recently, it was demonstrated that VKOR deficiency caused early postnatal lethality in a knockout mice model due to severe intracerebral hemorrhage[24]. For decades it was believed that VK1 had the potential to transform into MK-4 endogenously in animals[8,25]. This was proven by mouse experiments[26,27]. Recently, the same group found that UbiA prenyltransferase containing 1 (UBIAD1), a human homologue of prenyltransferase menA, is a human MK-4 biosynthetic enzyme. Furthermore, they demonstrated that UBIAD1 is located in the ER and that it is not suppressed by warfarin[7].

THE INVOLVEMENT OF VK IN CELL AND TUMOR BIOLOGY

In addition to the initially identified role of VK as a cofactor in the production of functional clotting factors through Gla residue formation in the liver, Gla protein was identified in the bone matrix proteins such as osteocalcin in 1975[28], and the involvement of VK in the bone physiology has been studied[29]. Furthermore, since the 1980s researchers have shown the anti-proliferative effects of VK in several cancer cell lines, including (HCC)[30-33]. Although the novel attractive functions of VK were reported, the mechanisms of VK function beyond their role in activating hepatic coagulation factors remained unknown. In 2003, Tabb *et al*[34] identified the steroid and xenobiotic receptor (SXR), also known as PXR, as a ligand of VK2 and showed that SXR mediated gene expression in an osteosarcoma cell line. Interestingly, this research group further demonstrated that SXR is abundantly expressed in the liver and that it reciprocally regulates nuclear factor-kappa B (NF-κB)-regulated gene expression[35].

The anti-tumor effects of VK were attractive to investigators studying cancer biology. Otsuka *et al*[36] reported that VK2 inhibited the growth of HCC cells as well as their invasiveness *via* the activation of protein kinase A (PKA) and the subsequent inhibition of Rho activation. They also demonstrated the activation of the transcription factors AP-2-, USF-1- and CREB in HCC cells by showing the nuclear accumulation of Ser-phosphorylated CREB, although the roles of these factors in the VK2-induced suppression of cell growth and invasion are not known.

We have revealed that VK2 inhibits the growth of human HCC cells by suppressing cyclin D1 expression through the inhibition of NF-κB activation by suppressing IKK activity[37]. The suppression of NF-κB activation by VK2 was also observed in lipopolysaccharide-mediated macrophage activation[38] and in the VK-mediated suppression of the osteoclastogenesis of bone cells through the RANK/RANKL pathway[39,40]. It has been

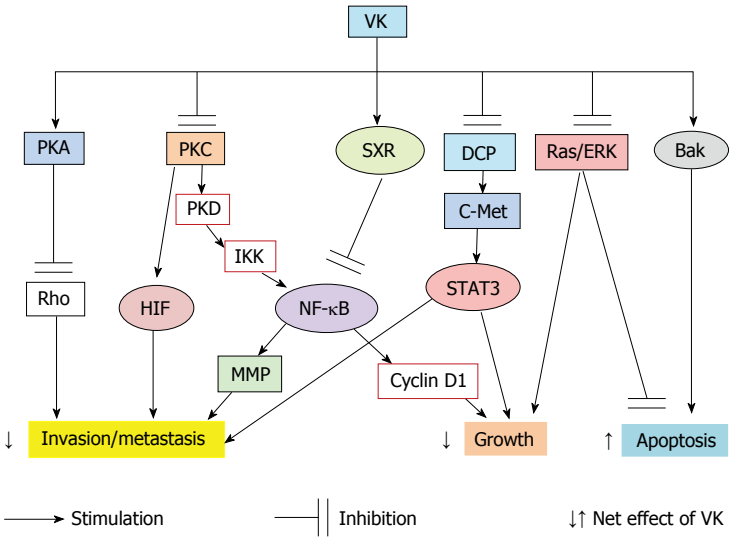

Figure 1 The effects of vitamin K on the multiple signaling pathways and the cellular behavior of liver cancer cells. PKA: Protein kinase A; PKC: Protein kinase C; PKD: Protein kinase D; DCP: Des-gamma-carboxy prothrombin; SXR: Steroid and xenobiotic receptor; ERK: Extracellular signal-regulated kinase; IKK: IκB kinase; NF-κB: Nuclear factor-kappa B; MMP: Matrix metalloproteinase; HIF: Hypoxia-inducible factor; VK: Vitamin K; STAT: Signal transducer and activator of transcription; Bak: Bcl-2 antagonist killer 1.

demonstrated that VK2 inhibits the expression of matrix metalloproteinases that contain NF-κB binding motifs in their promoter region[41], and augments the 5-fluorouracil-induced growth inhibition of HCC cells by inhibiting NF-κB activation[42]. Furthermore, we elucidated that VK2 inhibited the NF-κB activation through the inhibition of protein kinase C (PKC)-alpha and -epsilon kinase activities, as well as through the subsequent inhibition of PKD1 activation[43]. We have recently found that VK2 suppressed hypoxia inducible factor (HIF)-1 alpha activity through the inhibition of PKC by inhibiting the translocation of HIF to the nucleus[44].

Another interesting function of VK in the suppression of tumor development is its ability to induce apoptosis in certain cancer cells. Matsumoto *et al*[45] showed that VK2 induced apoptosis in Hep3B cells through the activation of AP-1. VK2-induced apoptosis is shown to be associated with p53 status in the human HCC cell line[46]. Recently Karasawa *et al*[47] demonstrated that VK2 covalently binds to Bcl-2 antagonist killer 1, a mitochondrial-mediated proapoptotic factor. The enhancement of apoptosis when VK2 was used in combination with acyclic retinoid (ACR) has been reported[48,49]. Kanamori *et al*[49] treated Huh7 cells with the combination of VK2 and ACR and found that VK2 plus ACR synergistically inhibited the growth of Huh7 cells by increasing apoptosis. When combined with ACR, VK2 inhibited Ras activation, followed by the inhibition of ERK phosphorylation. Interestingly, Suzuki *et al*[50] reported that des-gamma-carboxy prothrombin (DCP), also called protein induced by VK absence or antagonist Ⅱ, which is widely used as a tumor marker of HCC, has a binding affinity to c-Met, a hepatocyte growth factor receptor, and that it transmits aberrant STAT3 signaling[50]. They also reported the involvement of variant GGCX mRNA expression in the production of DCP in liver cancer[51]. Furthermore, Ma *et al*[52] showed the DCP-dependent growth advantage of HCC cells.

An interesting topic that has recently been reported in tumor biology is the role of UBIAD1, also called TERE1. UBIAD1 was recently identified as the menaquinone-4 biosynthetic enzyme[7]. UBIAD1 mRNA has been reported to be downregulated in prostate carcinoma cells and the overexpression of UBIAD1 inhibits the proliferation of tumor cell lines. UBIAD1 has therefore been considered to be a tumor suppressor in prostate cancer tumors[53]. Fredericks *et al*[54,55] reported that UBIAD1 controlled SXR-dependent gene expression in prostate cancer cells through several mechanisms. Since SXR transcription factor is a ligand of VK2 and because it has been shown to be involved in HCC cell growth[56,57], UBIAD1 expression might be linked to the effects of VK in HCC cells. More recently, UBIAD1 has been reported to be essential for embryonic development in mice[58] and VK2 has been shown to drive the metabolic maturation of pluripotent stem cells and fetal hepatocytes[59]. These findings suggest a novel role of VK metabolism in stem cells and that VK might be involved in cancer stem cell biology.

Collectively, the possible signal mechanisms of VK are summarized in Figure 1. VKs have been shown to have diverse effects on the phosphorylation states of various proteins[60]. Although the involvement of PKA, PKC, NF-κB, STAT, SXR and MAPK pathways are reported, the mechanisms by which VK2 modulates the protein kinases and/or phosphatases still remain to be elucidated. VK2 may reduce the growth and invasion of cancer cells through the modulation of protein kinases/phosphatases cascades.

VK DEFICIENCY BLEEDING IN NEWBORNS

Before the identification of VK as an essential cofactor for the production of functional coagulation factors, Townsend[61] (1894) reported 50 cases of a generalized bleeding tendency in neonates in a condition that was named the hemorrhagic disease of the newborn (HDN). He described that HDN differed from hemophilia in its earlier presentation, the lack of a family history and in its self-limiting course. Townsend[61] suggested a link between the mother's capacity to breast-feed and the hemostatic capacity of the newborn infant. After the identification of the role of VK in blood coagulation, the disease was shown to be related to VK nutritional deficiency and was renamed as VK deficiency bleeding (VKDB) by the ISTH Pediatric/Perinatal Subcommittee in 1999[62,63]. Although VK deficiency can occur in adults, it is common in newborns because of their limited VK storage, immature gastrointestinal absorption and due to the low placenta transfer of VK. The diagnosis of VKDB can be made in infants younger than 6 mo of age who present spontaneous bleeding, bruising, or intracranial hemorrhage with a prolonged clotting time but with a normal or elevated platelet count. Since the VKDB patients who present with intracranial bleeding are exclusively breastfed, Greer *et al*[64] investigated phylloquinone intakes in exclusively breast-fed infants in a North America and found that the average daily intake was one-tenth of that in healthy adults while formulated milk contained 50-fold higher concentration of phylloquinone than human milk. Although VKDB is rare in most developed countries, the consequences for the small number of patients who develop intracranial hemorrhage are often catastrophic. Nearly all cases of HDN/VKDB reported in the literature occur in infants who did not receive prophylactic VK supplementation in the newborn period. Consequently, many countries have introduced the routine prophylactic administration of VK at the time of birth to prevent hemorrhagic events[65,66].

THE INVOLVEMENT OF VK IN GENERAL HEALTH

Beyond the originally identified function of VK in blood coagulation system, it has been widely reported that VK has possible benefits on bone health and cardiovascular diseases[6,67]. Menatetrenone, a VK2 analog, has been used safely for the treatment of osteoporosis. Several clinical trials have shown it to be effective for treating osteoporosis in postmenopausal women, although the effects of VK2 alone might not be sufficient[68-70]. The potential benefit of VK in reducing cardiovascular disease risk is also reported and it might due to its function as a cofactor in the post-translational modification of the calcification-inhibiting matrix Gla protein[71,72]. An investigation revealed that UBIAD1-generated VK2 played an essential role in maintaining endothelial cell survival and overall vascular homeostasis[73].

A European large cohort study showed that dietary VK intake was associated with the reduced risk of cancer incidence in the prostate and the lung and that the effects were more pronounced in men than in women[74]. Furthermore, a more recent study demonstrated the association between the dietary intake of VK and the reduced risk of cardiovascular disease, cancer, and all-cause mortality in a Mediterranean population[75].

THE CLINICAL ASPECTS OF VK IN LIVER CANCER

In 1984, abnormal des-carboxy prothrombin was specifically detected in the plasma of patients with HCC[76]. It has since been used as specific diagnostic marker of HCC independent of α-fetoprotein[77,78]. Since the administration of VKs to patients with increased DCP levels showed a transient reduction of DCP levels, HCC was considered to exist under a condition of VK deficiency[79,80]. Earlier studies showed that the administration of VKs on cancer cells including HCC *in vitro*, resulted in anti-proliferative effects[30-33]. Thus, the anti-tumor effects of VK on HCC have been expected to be found *in vivo*.

In 2004 Habu *et al*[81] demonstrated that menatetrenone, a VK2 analog, suppressed the development of HCC in women with viral hepatitis-related cirrhosis. Since then, several randomized controlled studies reported the suppressive effects of menatetrenone on the recurrence of HCC after curative ablation therapy and surgical resection of the liver[82-86]. Although several initial reports with small study populations showed the favorable effects of VK2 in inhibiting the recurrence of HCC after treatment and improving tumor recurrence-free survival, a large randomized control trial (RCT) in which VK2 was administered after curative treatment, failed to show the advantage of VK2 administration[87].

Zhong *et al*[88] reviewed six RCTs and one cohort study, with a total of 930 patients and performed a meta-analysis. Although treatment with VK2 did not reduce the 1-year recurrence rate, there was a significant association between VK2 and reduced 2- and 3-year tumor recurrence. VK2 treatment was also associated with a significant improvement of 1-, 2-, and 3-year overall survival. However, the results might be considered to still be preliminary because the large scale RCT was evaluated at only 1 year. Therefore, a longer follow-up will be required to confirm the effects of VK2 on HCC.

FUTURE DIRECTIONS

Although various studies have reported the anti-HCC effects of VK2, the analogs in current use do not appear to exhibit dramatic anti-tumor effects when administered alone. One way to overcome this situation

is with the co-administration of VK and other reagents with anti-cancer properties. Yoshiji *et al*[85] reported the beneficial effects of VK2 combined with ACE inhibitor. Recently acyclic retinoid peretinoin showed beneficial effects on the recurrence and survival of hepatitis C virus-infected HCC patients after curative therapy[89]. VK2 plus ACR synergistically inhibited the growth of Huh7 cells[49]. Currently sorafenib is the only drug approved for the systemic treatment of HCC[90]. It has been shown to extend the survival period of end-stage HCC patients for several months. However, the effect of sorafenib on HCC is not yet satisfactory. Many novel-developed anti-cancer reagents that specifically target the signal transduction pathway of HCC cells have been tested clinically, but most of trials failed to demonstrate their non-inferiority to sorafenib[91,92]. A combination treatment with sorafenib and VK2 was examined *in vitro* and *in vivo* animal models and the studies showed that VK2 enhanced the tumor-suppressive effects of sorafenib[93-95].

Another way to enhance the effects of VK would be to develop a new VK derivative, which may be achieved by modifying the side chains of VK. Several approaches to develop novel VK analogs have been conducted. Since some of the effects of VK are considered to be mediated by SXR transcription factor as a ligand of VK2[34,56], Suhara *et al*[96,97] screened a series of chemically synthesized VK analogs by measuring the SXR-mediated transcriptional activity and found that the modification of the side chain of VK affects the SXR-mediated transcriptional activity. Setoguchi *et al*[98] synthesized a prodrug of an active form of menaquione-4 that is effectively delivered to HCC cells and which showed the enhanced anti-tumor effects on HCC cell growth.

Recently the repositioning (repurposing) of pre-existing drugs that have been safely used for long-term treatment in a clinical setting has been performed with many drugs such as aspirin and metformin[99,100]. Some of these drugs have begun to be used for chemoprevention and/or for the therapeutic purpose of enhancing anti-cancer effects. VKs seem to be one of the successful examples of repositioned drugs. After the discovery of VK as a cofactor of functional coagulation factor production, it has been shown to be beneficial for the maintenance of bone physiology and the prevention of cardiovascular diseases. Beyond these effects, the novel function of VK as an anti-tumor agent has been applied to the prevention and treatment of HCC, however, the beneficial effects of VK on HCC were found to be limited. The recent progress of novel technologies, such as a genome wide association studies and computational analysis, has been the first step to the repositioning of drugs[101,102]. These approaches will lead to novel applications of VKs and the development of novel VK-based reagents, and may be applied to the treatment of HCC in the future.

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