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Emerging role of UBIAD1 in embryonic development of mammals

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We recently demonstrated that dietary phylloquinone/vitamin K1 releases menadione/vitamin K3 by the cleavage of the side chain in the intestine, followed by delivery of menadione through the mesenteric lymphatic system and blood circulation to tissues, where menadione is converted into MK-4/vitamin K2, and accumulates in the form of MK-4. UBIAD1is a novel MK-4 biosynthetic enzyme screened and identified from the human genome database. Surprisingly, UBIAD1 was recently shown to catalyze the CoQ10 biosynthesis in zebrafish and human cells. Enzymatic analysis using site-directed mutagenesis revealed that UBIAD1 is capable of generating various menaquinones including MK-4, and UBIAD1 missense mutations in Schnyder Corneal Dystrophy (SCD) lower MK-4 biosynthetic activity significantly. To clarify the function of UBIAD1 *in vivo,* we attempted to generate mice completely lacking ubiad1, a homolog of human UBIAD1by gene targeting. Ubiad1-deficient (ubiad1-/-) mouse embryosfailed to survive beyond embryonic day 7.5, exhibiting small-sized body and gastrulation arrest. Ubiad1+/- mice developed normally, exhibited normal growth and fertility. Their tissue concentrations and synthetic activity of MK-4 were approximately half of the wild-type levels, whereas their tissue concentrationsand synthetic activity of CoQ9 were similar to the wild-type levels, respectively. Ubiad1-/-mouse embryos failed to be rescued, but their embryonic lifespans were extended to term by oral administration of MK-4 or CoQ10 to pregnant ubiad1+/- mice. These results suggest that ubiad1plays a critical rolein embryonic development through synthesizing MK-4, but may have additional functions beyond the MK-4 biosynthesis.

Biography

Toshio Okano received a Ph.D. in Pharmaceutical Sciences from Osaka University in 1979, and he is serving as a Professor and Chairman of the Department of Hygienic Sciences at Kobe Pharmaceutical University since 1996. He has made significant contributions to the basic and clinical sciences of vitamin D and vitamin K. In the past decade, his interests have been concentrating especially to explore additional functions and molecular mechanism of vitamin K beyond its canonical role as a co-factor for carboxylation in mammals. He and his co-workers succeeded in finding a first human vitamin K biosynthetic enzyme, UBIAD1 in 2010.

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