

Abstract

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Vitamin K, an example of triage theory: is micronutrient inadequacy linked to diseases of aging?

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BACKGROUND: The triage theory posits that some functions of micronutrients (the approximately 40 essential vitamins, minerals, fatty acids, and amino acids) are restricted during shortage and that functions required for short-term survival take precedence over those that are less essential. Insidious changes accumulate as a consequence of restriction, which increases the risk of diseases of aging.

METHODS: For 16 known vitamin K-dependent (VKD) proteins, we evaluated the relative lethality of 11 known mouse knockout mutants to categorize essentiality.

RESULTS: Results indicate that 5 VKD proteins that are required for coagulation had critical functions (knockouts were embryonic lethal), whereas the knockouts of 5 less critical VKD proteins [osteocalcin, matrix Gla protein (Mgp), growth arrest specific protein 6, transforming growth factor beta-inducible protein (Tgfbi or betaig-h3), and periostin] survived at least through weaning. The VKD gamma-carboxylation of the 5 essential VKD proteins in the liver and the 5 nonessential proteins in nonhepatic tissues sets up a dichotomy that takes advantage of the preferential distribution of dietary vitamin K1 to the liver to preserve coagulation function when vitamin K1 is limiting. Genetic loss of less critical VKD proteins, dietary vitamin K inadequacy, human polymorphisms or mutations, and vitamin K deficiency induced by chronic anticoagulant (warfarin/coumadin) therapy are all linked to age-associated conditions: bone fragility after estrogen loss (osteocalcin) and arterial calcification linked to cardiovascular disease (Mgp). There is increased spontaneous cancer in Tgfbi mouse knockouts, and knockdown of Tgfbi causes mitotic spindle abnormalities.

CONCLUSION: A triage perspective reinforces recommendations of some experts that much of the population and warfarin/coumadin patients may not receive sufficient vitamin K for optimal function of VKD proteins that are important to maintain long-term health.

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