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Commentary

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Biochemistry and Nutritional Aspects of Vitamin K

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Description

The term vitamin K refers to a variety of compounds containing a 3-position, 2-methyl-1,4-naphthoquinone ring with a hydrophobic side chain. Until the mid-1970s, when it was shown to be a substrate for a microsomal enzyme that converted protein-bound glutamyl residues to γ-carboxyglutamyl (Gla) residues, the biochemical function of the vitamin was not known. In relatively few proteins, this posttranslational modification has been found.

The first protein shown to be dependent on vitamin K for its synthesis, prothrombin (coagulating factor II), the zymogen of plasma procoagulant thrombin, was also the first protein shown to contain γ-carboxylglutamyl (Gla) residues. In patients with inherited bleeding disorders, plasma clotting factors VII, IX, and X were all originally identified and were subsequently shown to be vitamin K dependent. Until the mid-1970s, the only proteins known to require this vitamin for their synthesis were these four vitamin K-dependent clotting variables. These four vitamin K-dependent procoagulants are very homologous in their amino-terminal, Gla domains, and the 10-13 Gla residues in each are basically in the same position as in prothrombin. Three more Gla-containing plasma proteins with similar homology were discovered following the discovery of Gla. Protein C and protein S have an anticoagulant rather than a procoagulant role in normal hemostasis, and under some conditions, the seventh plasma protein containing Gla (protein Z) also has an anticoagulant function. They have been extensively studied, as these proteins play a crucial role in hemostasis, and the complementary DNA (cDNA) and genomic organisation of each of them are well known.

With this modification, the discovery of Gla residues in plasma vitamin K-dependent proteins led to the search for other proteins, and a 49-residue protein containing three Gla residues was isolated from the bone called osteocalcin (OC). It has no structural homology to plasma proteins that are dependent on vitamin K. While it is the second most abundant protein in the bone, it is not clearly described by its function. A second protein of low molecular weight (79-residue), matrix Gla protein (MGP), contains five residues of Gla and has also been isolated from bone for the first time; it is also synthesised in cartilage and many other soft tissues. The function of these two proteins has not been clearly established, but it has been shown that more dense bones develop in OC gene knockout mice, and MGP knockout mice die from spontaneous arterial and cartilage calcification. More recently, two extra Gla-containing bone proteins, periostin and Gla-rich protein have been described. Gas 6, a ligand for tyrosine kinase Ax1, and four integral membrane Gla proteins (PRGP-1, PRGP-2, TMG-3, and TMG-4) have been found to contain Gla residues in a small number of other mammalian proteins. Marine Conus snails secrete a large number of poisonous venom peptides containing Gla and are discovered in some snake venoms. A variety of vertebrates, the Conus snail, a tunicate, and Drosophila were cloned from the vitamin K-dependent carboxylase, suggesting the ancient evolutionary origin of this posttranslational alteration.

A biologically inactive form of prothrombin was found to be present in the plasma of oral anticoagulant-treated patients in the early 1960s. Subsequent experiments with hypoprothrombinemic rats were consistent with the existence of a rapidly synthesised hepatic precursor protein pool that could be transformed by posttranslational modification to prothrombin. The characterization of abnormal prothrombin isolated from the plasma of cows fed with dicoumarol anticoagulant led directly to an understanding of vitamin K's metabolic function. The unique calcium-binding sites found in normal prothrombin were absent from this protein. Gla residues were shown to contain acidic peptides obtained by the proteolytic enzyme digestion of prothrombin, but the proteolysis of abnormal prothrombin did not obtain Gla residues.

In 1975, it was shown that the microsomal preparation of the crude rat liver contained enzymatic activity (vitamin K-dependent carboxylase) that promoted the vitamin K-dependent incorporation of endogenous vitamin K-dependent protein precursors present in these preparations into Gla residues. This activity was maintained by detergent-solubilized microsomal preparations, and small peptides containing adjacent Glu-Glu sequences were found to be substrates for the enzyme. A general understanding of the properties of this unique enzyme was gained from studies utilizing this crude enzyme preparation, and these data have been adequately reviewed. The vitamin K-dependent carboxylation reaction does not require adenosine triphosphate, and the energy to drive this carboxylation reaction is derived from the oxidation of the reduced, hydro naphthoquinone form of vitamin K (vitamin KH2) by O2 to form vitamin K-2,3-epoxide.

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