VKOR and anticoagulant resistance – mutations, models and mechanisms

Müller, C.R., Rost, S.
Department of Human Genetics, University of Wuerzburg, Wuerzburg, Germany
crm@biozentrum.uni-wuerzburg.de

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Coumarin derivatives, e.g. warfarin, are in world-wide use for rodent pest control since they effectively repress blood coagulation. However, rodent populations developed resistance soon after the introduction of such compounds. Today, in many countries, effective pest control is hampered by the rapid spread of coumarin-resistant rodent populations. Chemically related compounds to those using in rodent control are the main class of drugs used for treatment and prevention of thrombo-embolic events in humans.

VKORC1, the warfarin-sensitive enzyme active in the reduction of vitamin K epoxide has been identified as the key component of the vitamin K redox cycle and the target of coumarin drugs (Li et al., 2004; Rost et al., 2004). Mutations in VKORC1 have been shown to confer resistance (*in vivo* and *in vitro*) to anticoagulants in humans as well as in laboratory and wild-caught *R. norvegicus* and *M. m. domesticus* (Pelz et al., 2005; Rost et al., 2009). Mutant animals and populations have been found world-wide. Apparently, VKORC1 mutations affecting different amino acid positions have arisen independently in different resistance areas. A single sequence variant in the VKORC1 promoter has been identified as the major genetic determinant of coumarin dosage requirement in humans (Oldenburg et al., 2007; Rieder et al., 2005).

Recently, X-ray crystallography has allowed delineating the three-dimensional structure of a bacterial homologue of VKOR. The resulting model can explain the topology of this membrane-bound protein and the mode of action of most mutations observed so far (Li et al., 2010).

VKORC1-like genes and proteins are present in organisms from all kingdoms of life. Apparently, vitamin K, and VKOR activity, are not only used for the carboxylation of proteins. Kinetic and expression studies of VKORC1-L1, the human paralogue of VKORC1, have shown that ancestral VKORs may play an important role in neutralizing reactive oxygen species which are generated during all oxidative reactions (Westhofen et al., 2011).

The presentation will review and update our present understanding of VKOR and anticoagulant resistance.

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