Mutations of the SPINK1 Gene and Their Relation to Chronic Pancreatitis

Volker Keim
Medizinische Klinik und Poliklinik II, Universitätsklinikum Leipzig, Leipzig, Deutschland

Since the discovery of mutations of SPINK1 in chronic pancreatitis (CP) several years ago, the relation of these mutations to the disease is discussed. In the original description of the major SPINK1 mutation, N34S was classified as sole polymorphism [1]. Later, the association of N34S to so-called ‘idiopathic’ [2], alcoholic [3], and tropical pancreatitis [4] was revealed. The paper of Kume and coworkers in the present issue of Pancreatology confirmed and extended these data and showed that in patients from all over the world both intronic and exonic alterations are relevant risk factors for pancreatitis.

Nevertheless, the importance of the SPINK1 mutation for pancreatic disease is controversial. Pfützer et al. [5] concluded that there is only a permissive and no causal role of SPINK1 mutations. This, however, is impossible to prove unless functional data are available. The mere frequency of any of these mutations does not tell us anything about the pathogenesis.

The easiest pathogenetic explanation would be an impaired inhibitory activity towards trypsin, but after expression in a bacterial system wild type and N34S-SPINK1 were equally effective [6]. In consequence, other and less simple mechanisms will have to be taken into consideration: firstly, but less likely, all SPINK1 variants could be in linkage disequilibrium with an adjacent gene that is the true cause of chronic pancreatitis. Second, SPINK1 mutations are part of a complex of several yet unknown genes. And finally, the numerous intronic variants could lead to a reduced synthesis, expression, or altered splicing that compromise the intracellular transport and/or activity of SPINK1. The latter could be clarified in a eukaryotic system and this will probably lead to a better understanding of the true role of SPINK1 in pancreatitis.

References