Expression, secretion and assembly of collagen I in non-classical osteogenesis imperfecta

Doctoral thesis
for
the award of the doctoral degree
of the Faculty of Mathematics and Natural Sciences
of the University of Cologne

submitted by
Alice Stephan

accepted in the year 2026

Abstract

Collagen I is ubiquitously expressed in the extracellular matrix of most organ systems. Expression, secretion and assembly of collagen I are complex processes with numerous crucial factors that need to be tightly controlled in order to form functional networks. As rare diseases provided countless insights into the pivotal regulators of collagen I, Osteogenesis imperfecta (OI) forms with so far unknown disease mechanisms provide fruitful model systems to deepen the knowledge on collagen I.

This thesis investigated homozygous variants in three genes of interest, namely c.448dupC mutation in *KDELR2*, c.323T>G in *TAPT1* and c.672G>T in *TENT5A*. Mutations in the KDEL ER protein retention receptor 2 (KDELR2) and non-canonical poly(A) RNA polymerase terminal nucleotidyltransferase 5A (TENT5A) were previously described to cause OI. Variants in the transmembrane anterior posterior transformation protein 1 (TAPT1) were only recently identified as OI-causing. To date, the exact changes in collagen I that occur in these OI types have not been precisely characterized and linked to the function of the altered gene.

All three variants lead to reduced collagen I quality caused by a loss of function in the affected protein. Bones of the newly generated *Kdelr2*-mutant mouse model displayed shorter and fewer collagen I fibrils, which is most likely caused by improper triplehelix formation. Patient-derived *TAPT1*-mutant fibroblasts showed impaired collagen I fibril assembly that was accompanied by morphological changes in the Golgi. Patient-derived *TENT5A*-mutant fibroblasts likewise showed impaired collagen I fibril assembly but with signs of improper collagen I triplehelix formation.

2 of the 3 forms investigated in this thesis and the majority of OI forms reported in the literature cause reduced collagen I quality due to defects in triplehelix formation. Improvement of triplehelix formation could therefore be a promising treatment strategy. Since HSP47 plays a key role in triplehelix folding and limitation of post-translational modifications, recently explored utilization of exogenous HSP47 might alleviate the phenotype of OI forms with impaired triplehelix formation. KDELR2- and TENT5A-related OI forms may also benefit from this treatment.