COLLAGEN-SPECIFIC MOLECULAR CHAPERONE HSP47 IS ESSENTIAL FOR THE CORRECT FOLDING AND/OR ASSEMBLY OF PROCOLLAGEN AND FOR THE DEVELOPMENT OF MOUSE EMBRYO

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HSP47 is a collagen-binding molecular chaperone located in the ER. HSP47 transiently binds to procollagens in the ER and disso- ciates from the substrate before transported to cis-Golgi. By adopting the synthetic peptide approach, HSP47 was shown to recognize typical collagen-like sequence (Gly-Pro-Pro)n repeats and to be dissociated from the substrate after the third Pro residues are hydroxylated, that is the most important post-translational modi- fication of procollagen to form the correctly assembled tight helix.

In addition to the binding specificity for various types of collagen, the expression of HSP47 is closely correlated with that of collagens under non-stressed conditions. HSP47 is expressed only in collagen-producing cells and tissues, which also suggests the collagen-related function(s) of HSP47 as a molecular chaperone.

Recently, we have succeeded to knockout the hsp47 gene and found that the disruption of hsp47 gene resulted in the failure in the accumulation of fully processed mature collagens of type I and type IV in the mouse embryo. This resulted in the failure of the formation of collagen fibrils as well as basement membranes and caused the apoptosis in mesenchymal cells resulting in the death of the embryo between 10.5 - 11.5 dpc. Thus, hsp47 is shown to be the essential gene for normal mouse development.

To elucidate the function of HSP47 in the molecular maturation of procollagen, hsp47-/- cell lines were established from the embryos of knockout mice and the conformation of the secreted procollagen was analyzed by protease treatment. Secreted type I procollagen from hsp47-/- cells was protease-sensitive whereas that from wild type cells was protease-resistant. When the cDNA encoding hsp47 was transfected into hsp47-/- cells, the secreted procollagen became protease-resistant, suggesting that HSP47 is essential for the correct folding/assembly of procollagens in the ER.

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