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The pathomechanism leading to nail-patella syndrome depends on the nature of the mutation

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Nail-patella syndrome (NPS) is an autosomal-dominant genetic disorder characterized by malformed fingernails and hypoplastic kneecaps. Approximately 40% of NPS patients develop a nephropathy caused by malfunctioning podocytes. Mutations in the gene LMX1B which encodes a transcription factor of the LIM-homeodomain family are known to be the cause of NPS. The pathomechanism underlying NPS is still unknown. Notably, only homozygous Lmx1b knock-out mice develop symptoms resembling those in NPS patients. We therefore hypothesized that patients suffer from missense mutations which confer a gain-of-function or a dominant-negative effect. To identify possible molecular pathomechanisms of NPS, knock-in mice were established with point mutations either in the first (H54L) or the second (C95F) LIM domain such as those described in patients. Heterozygous Lmx1b knock-in mice showed no NPS phenotype whereas homozygous knock-in mice displayed a reduced number of filtration slits in podocytes, similar to that of conventional Lmx1b knock-out animals. The presence of the mutated Lmx1b mRNA was confirmed but the protein was not detectable in podocytes. Detailed analyses of LMX1B mutants showed a reduced half-life of the mutant proteins in comparison to wild-type LMX1B. Another mutant LMX1B protein with a mutation in the homeodomain, V265D, showed a prolonged half-life compared to the wild-type protein. Due to protein instability, the knock-in mutations H54L and C95F lead to a loss of function in knock-in mice. As previously described, the mutation V265D within the homeodomain causes a dominant-negative effect. This suggests that different NPS mutations can lead to different pathomechanisms requiring distinct therapeutical approaches.

Biography

Lisa Lucke has completed her studies in biology at the University of Regensburg. In particular, she pursued her Master studies in a biotechnical company producing and testing antigens for T-cell diagnostics. Since 2016, she is working on her PhD at the chair of Prof. Dr. Ralph Witzgall, University of Regensburg. Her research area is based on a genetic disease, called nail-patella syndrome. Her topic deals with the analysis of different mutations in the transcription factor LMX1B that could lead to different pathomechanisms of nail-patella syndrome.

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