

7 Summary

The Growth and Differentiation Factor 5 (GDF5) is a secreted signaling molecule that belongs to the TGF β superfamily. GDF5 has an essential function during embryonic development, especially during the formation of the distal limbs. GDF5 signals via binding to its cognate receptor Bone Morphogenetic Protein Receptor 1B (BMPR1B) and determine pattern formation in the developing hand. Mutations in *GDF5* or *BMPR1B* cause different types of hand malformations, which are characterized by shortening of the phalanges and deviations of the finger joint regions. This PhD thesis is devoted to the functional in vitro analysis and genotype-phenotype correlation of newly identified mutations in *GDF5* (R438L, L441P, N445T) and *BMPR1B* (I200K, R486W). The molecular effects of these mutants were unknown and/or have led to atypical phenotypes in the patients.

Functional analyses with a micromass culture system revealed a strong inhibition of chondrogenesis by both mutant receptors. These findings imply that both mutations identified in human *BMPR1B* affect cartilage formation in a dominant-negative manner. The L441P mutation in *GDF5* causes a similar phenotype presumably because of a significantly reduced interaction with BMPR1B.

Moreover, proximal symphalangism and the multiple synostosis syndrome, which were previously only associated with mutations in *NOG*, could be identified in patients with point mutations in *GDF5*. Here, the interaction of the *GDF5* mutants with the inhibitor *NOG* were either disturbed or the mutant *GDF5* displayed an additional activity by also binding to BMPR1A.

The presented experiments with the newly identified mutations in *GDF5* and *BMPR1B* have identified some of the main determinants of *GDF5* for specific protein-protein interactions. Molecular details about the functional domains of *GDF5* became apparent, e.g. the identification of those interfaces that are important for receptor binding specificity or for the *GDF5*-*NOG* interaction.

Thus, these results broaden our understanding on the importance of *GDF5* and *BMPR1B* during the complex process of early bone development. The analyzed mutations expand the knowledge about *GDF5*-dependent phenotypes, i.e., mutations in *GDF5* or its interaction partners *BMPR1B* and *NOG*, respectively, can cause identical phenotypes if they impair their protein-protein interactions (Fig 28).