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The role of G-protein-mediated signal transduction processes in the development of mouse neural crest

Geboren am 16 Dezember 1974 in Gdansk, Polen
Diplom der Fachrichtung: Biotechnologie am 21.12.1998 an der Universität Gdansk, Polen

Promotionsfach: Pharmakologie
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In the present thesis project, we have characterized signalling mechanisms involved in neural crest cell development.
We were able to show that G_q/G_{11}-mediated signalling in neural crest cells, but not in other cells of the developing craniofacial system, is required for proper development of structures derived from the neural crest component of the first pharyngeal arch. We were also able to show that any combination of two functional alleles of $G\alpha_q$ or $G\alpha_{11}$ is sufficient for survival and normal craniofacial development. In contrast, after immunohistochemical analysis, we could show that absence of G_q/G_{11}- or G_{12}/G_{13}-mediated signalling did not affect the patterning of cranial ganglia.
Analysis of expression patterns of transcription factors seen in the developing pharyngeal arch mesenchyme and transcription factors known to be expressed in pharyngeal arches by migrating neural crest cells, indicate that the migration of neural crest cells into branchial arches 1 and 2 is not affected by the absence of G_q/G_{11}-mediated signalling in neural crest cells. However, our data support the model that the G_q/G_{11}-mediated signalling system mediates ET_A receptor-dependent differentiation of postmigratory neural crest cells of branchial arches 1 and 2 in a cell-autonomous manner and is crucial for determining the fate of cranial neural crest cells of the distal arch.
Interestingly, we did not observe any of developmental defects described in mutants of the endothelin system concerning defects of the outflow tract, aganglionic megacolon and defective skin pigmentation. We could show that $G\alpha_q/G\alpha_{11}$- and $G\alpha_{12}/G\alpha_{13}$-deficient embryos demonstrate proper formation and septation of the outflow tract of the heart and similarly, the presence of enteric neurons in distal colon as well as the distribution and

numbers of epidermal melanocytes are unaltered as well. Obtained data indicate that G_q/G_{11} or G_{12}/G_{13} alone do not mediate the effects of the ET-1/ET_A or ET-3/ET_B system on the development of the cardiac outflow tract, enteric nervous system and melanocytes.

Additionally, our data suggest that development of chromaffin cells and sympathetic neurons seem to be independent from absence of $G\alpha_q/G\alpha_{11}$ and $G\alpha_{12}/G\alpha_{13}$ in neural crest cells.

Interestingly, we could clearly show that $G\alpha_{12}/G\alpha_{13}$ deficiency in neural crest cell-derived cardiac cells resulted in characteristic and novel heart malformations, unrelated to any described neural crest-deficient animal model. We could clearly show that the loss of $G\alpha_{12}/G\alpha_{13}$ had no effect on the migration of cardiac neural crest cells, suggesting requirement for non-autonomous signalling from surrounding cells.

Taken together, in this work we provide genetic and histological evidence in support of a functional interaction between G-proteins in mouse neural crest cell development. Our data indicate that the loss of $G\alpha_q/G\alpha_{11}$ leads to defects in cranial neural crest differentiation *via* ET-1/ET_A receptor-mediated signalling pathway, but not in cranial neural crest migration. In contrast, $G\alpha_{12}/G\alpha_{13}$ are involved in the proper development of various cardiac structures independently of cardiac neural crest migration.