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Summary of the doctoral thesis

New functions of fibroblast growth factor homologous factors

Fibroblast growth factors (FGFs), by interacting with their receptors (FGFRs), regulate key cellular processes such as proliferation, migration, metabolism and apoptosis. The FGF family also includes fibroblast growth factor homologous factors (FHFs). The FHF subfamily consist of four proteins: FGF11, FGF12, FGF13 and FGF14 and is the least characterized group of FGF proteins. To date, due to the lack of signal sequence for secretion and mitogenic activity, these proteins have been considered intracellular proteins, not interacting with FGF receptors. Their main function has been attributed to the modulation of voltage-gated ion channels.

In my thesis, I have focused on elucidating the hitherto unknown functions of FHF proteins. To this end, I searched for new partner proteins interacting with FGF12, a representative member of the FHF subfamily. Among the identified intracellular proteins, a significant number were nuclear proteins, especially RNA-binding proteins involved in translation processes, including ribosome biogenesis (NOLC1 and TCOF1). I demonstrated for the first time that all FHF proteins localize to the nucleolus, where they interact with NOLC1 while only FGF12 forms a complex with TCOF1. The formation of FGF12 complexes with NOLC1 and TCOF1 is dependent on the phosphorylation of these proteins, and their binding site is located in the C-terminal fragment of the growth factor. Furthermore, I found that NOLC1 and TCOF1 do not interact with each other in the absence of FGF12. The data obtained suggest a novel and unexpected role for FHFs in ribosome biogenesis.

A further part of my dissertation is devoted to the search for extracellular functions of FHF proteins. I showed that that they undergo secretion, despite lacking a classical sequence for secretion, and that the mechanism of their export outside the cell is similar to that of FGF2 and requires the Na(+)/K(+) ATPase activity. I then confirmed a direct interaction of FHF proteins with FGFR. Unexpectedly, binding of FHF to FGFR on the cell surface resulted in activation of signaling pathways and internalization of FHF-FGFR complexes. However, in contrast to canonical FGF proteins, FHFs did not stimulate cell proliferation and glucose uptake, but their interaction with FGFR led to an anti-apoptotic cell response, allowing cells to survive under adverse conditions.