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**Discoidin Domain Receptor 1, Regulated by miR-199a-5p in Clear
Cell Renal Cell Carcinoma, Modulates Proliferation, Actin
Cytoskeleton Dynamics, and Cellular Migration**

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Clear cell renal cell carcinoma (ccRCC) is the most common form of renal cancer and represents 3-4% of all adult malignancies. Frequently difficult to detect, early diagnosis is often critical as the later stages of ccRCC are notoriously hard to treat with standard chemotherapies and drugs.

Many cases of ccRCC can be characterized by a loss-of-function mutation of the von Hippel-Lindau (VHL) tumor suppressor gene. This loss initiates an aberrant activation of several signaling pathways in the affected cells including the hypoxia-induced signaling cascade and the AKT pathway. The resulting tumor cells become highly vascularized and anti-apoptotic, and finally metastatic at later stages of the disease.

Accepted drug therapies include many receptor tyrosine kinase (RTK) inhibitors aimed at blocking the hyperactivation of these signaling pathways and have a variety of success rates. Many off-target effects have been reported, and questions arise as to the efficiency of these drugs to target the key molecular players in ccRCC.

In this work we strive to uncover new molecules that have a role in the progression of ccRCC. The RTK discoidin domain receptor 1 (DDR1) has recently entered the spotlight as a key regulator of migration and adhesion in a wide range of carcinomas. In the first part of this thesis we show that DDR1 is also highly active in ccRCC. Furthermore, we uncover several

novel functions for this receptor, including roles in proliferation and cyclin D1 expression, actin cytoskeleton dynamics and small GTPase regulation, as well as migration and invasion.

In the second part of this thesis, we focus on the role of microRNAs (miRNAs) deregulated in ccRCC. Using several high-throughput techniques, we created and analyzed the expression of miRNAs in ccRCC as compared to normal kidney tissue, revealing the deregulation of many miRNA families. The miRNA family hsa-miR-199-5p including hsa-miR-199a-5p was shown to be highly down-regulated in ccRCC. This miRNA was subsequently shown to target DDR1, providing evidence that this receptor is regulated post-transcriptionally in ccRCC.