EGFR signaling regulation by interaction with other membrane receptor pathways

Epidermal Growth Factor Receptor (EGFR) is a cell surface protein with tyrosine kinase activity, and a major effector of extracellular signals promoting cell proliferation. EGFR is also considered an oncogene, since its activity sustains cancer cell viability and growth. Due to its major impact in cell function, EGFR is subject to several regulatory mechanisms, at transcriptional, post-transcriptional, and post-translational levels. In particular, EGFR cross-talks with other cell surface receptors engaged by extracellular molecules.

Thus, we aim at elucidating novel mechanisms regulating EGFR signaling, via the cross-talk with other membrane receptor pathways, such as inflammatory cytokines, or the Neuropilins and their extracellular ligands. Our experimental models will employ normal and tumor cells dependent on the EGFR pathway. We will study 3D models growing in suspension, such as spheroids of epithelial cells or cancer cells, as well as patient-derived tumor organoids, available to the labs. Based on supportive evidence at cellular level, the relevance of the investigated mechanisms will be further validated in mouse models. In particular, we postulate a specific role of Interleukin1-Receptor (IL1R) signaling to enhance the EGFR pathway. Moreover, we implicate NRP1/NRP2 and their ligands in the regulation of EGFR expression in different cell types, and for rescuing cancer cell viability in response to oncogene-targeted therapies.

Investigating the crosstalk between EGFR and other membrane receptors is expected to unveil novel regulatory mechanisms controlling tissue development and homeostasis, as well as to advance our understanding of signaling escape mechanisms jeopardizing the efficacy of cancer therapy. In translational perspective, we will assay the therapeutic combination of EGFR-blockage and IL1R inhibitors. Moreover, since NRP1 and NRP2 cell surface receptors have been found to regulate EGFR expression and signaling, the targeting combination with inhibitors and extracellular ligands could improve the efficacy of EGFR inhibitors and prevent the onset of drug-resistance, as recently validated in our preliminary studies.

In sum, our project aims at elucidating novel mechanisms regulating EGFR signaling, via the cross-talk with other membrane receptor pathways; we anticipate that this new knowledge could be exploited for tackling issues relevant for personalized medicine.