

## Epigenetic silencing of microRNA in cancer associated fibroblasts mediates prostaglandin E2/interleukin 6 signaling in the tumor microenvironment

Running title: miR-149 mediates PGE2 and IL6 signaling in gastric cancer

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Tumor initiation and growth depend on its microenvironment in which cancer associated fibroblasts (CAFs) in tumor stroma play an important role. Prostaglandin E2 (PGE2) and interleukin (IL)-6 signal pathways are involved in the crosstalk between tumor and stromal cells. However, how PGE2-mediated signaling modulates this crosstalk remains unclear. Here, we show that microRNA (miR)-149 links PGE2 and IL6 signaling mediating the crosstalk between tumor cells and CAFs in gastric cancer (GC). miR-149 inhibited fibroblast activation by targeting IL6 and miR-149 expression was substantially suppressed in the CAFs of GC. miR-149 negatively regulated CAFs and their effect on GC development both *in vitro* and *in vivo*. CAFs enhanced epithelial to mesenchymal transition (EMT) and the stem-like properties of GC cells in a miR-149-IL6-dependent manner. In addition to IL6, PGE2 receptor2 (PTGER2/EP2) was revealed as another potential target of miR-149 in fibroblasts. Furthermore, *H. pylori* infection, a leading cause of human gastric cancer, was able to induce cyclooxygenase-2 (COX-2)/PGE2 signaling and to enhance PGE2 production, resulting in the hypermethylation of miR-149 in CAFs and increased IL6 secretion. Our findings indicate that miR-149 mediates the crosstalk between tumor cells and CAFs in GC and highlight the potential of interfering miRNAs in stromal cells to improve cancer therapy.