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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

Pu Li[1], Jing-Xuan Shan[3], Xue-Hua Chen[1], Di Zhang[2] and **Zheng-Gang Zhu[1]**

[1]Shanghai Key Laboratory of Gastric Neoplasms, Department of Surgery, Shanghai Institute of Digestive Surgery, Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, China

[2]State Key Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, China

[3]Laboratory of Genetic Medicine and Immnology, Weill Cornell Medical College in Qatar, Qatar

Tumor initiation andgrowth depend on its microenvironmentin 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 cellsand CAFs in gastric cancer (GC). miR-149 inhibited fibroblast activationby 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-149in fibroblasts. Furthermore, *H. pylori* infection, a leading cause of human gastric cancer, was able to inducecyclooxygenase-2 (COX-2)/PGE2 signaling and to enhance PGE2 production, resulting in thehypermethylation of miR-149 in CAFs and increasedIL6 secretion. Our findings indicate that miR-149 mediates the crosstalk between tumor cellsand CAFs in GC and highlight the potential of interfering miRNAs in stromal cells to improve cancer therapy.