Members of the miR-34 family are induced by the tumor suppressor p53 and are known to inhibit epithelial-to-mesenchymal transition (EMT) and therefore presumably suppress the early phases of metastasis. Here, we determined that exposure of human colorectal cancer (CRC) cells to the cytokine IL-6 activates the oncogenic STAT3 transcription factor, which directly represses the MIR34A gene via a conserved STAT3-binding site in the first intron. Repression of MIR34A was required for IL-6-induced EMT and invasion. Furthermore, we identified the IL-6 receptor (IL-6R), which mediates IL-6-dependent STAT3 activation, as a conserved, direct miR-34a target. The resulting IL-6R/STAT3/miR-34a feedback loop was present in primary colorectal tumors as well as CRC, breast, and prostate cancer cell lines and associated with a mesenchymal phenotype. An active IL-6R/STAT3/miR-34a loop was necessary for EMT, invasion, and metastasis of CRC cell lines and was associated with nodal and distant metastasis in CRC patient samples. p53 activation in CRC cells interfered with IL-6-induced invasion and migration via miR-34a-dependent downregulation of IL6R expression. In
Mir34a-deficient mice, colitis-associated intestinal tumors displayed upregulation of p-STAT3, IL-6R, and SNAIL and progressed to invasive carcinomas, which was not observed in WT animals. Collectively, our data indicate that p53-dependent expression of miR-34a suppresses tumor progression by inhibiting a IL-6R/STAT3/miR-34a feedback loop.