Metastasis is the major cause of poor prognosis in colorectal cancer (CRC), and increasing evidence supports the contribution of miRNAs to cancer progression. In this study, we found that high expression of miR-103 and miR-107 (miR-103/107) was associated with metastasis potential of CRC cell lines and poor prognosis in patients with CRC. miR-103/107 targeted the known metastasis suppressors death-associated protein kinase (DAPK) and Krüppel-like factor 4 (KLF4) in CRC cells, resulting in increased cell motility and cell–matrix adhesion and decreased cell–cell adhesion and epithelial marker expression. miR-103/107 expression was increased in the presence of hypoxia, thereby potentiating DAPK and KLF4 downregulation and hypoxia induced motility and invasiveness. In mouse models of CRC, miR-103/107 overexpression potentiated local invasion and liver metastasis effects, which were suppressed by reexpression of DAPK or KLF4. miR-103/107–mediated downregulation of DAPK and KLF4 also enabled the colonization of CRC cells at a metastatic site. Clinically, the signature of a miR-103/107 high, DAPK low, and KLF4 low expression profile correlated with the extent of lymph node and distant metastasis in patients with CRC and served as a prognostic marker for metastasis recurrence and poor survival. Our findings therefore indicate that miR-103/107–mediated repression of DAPK and KLF4 promotes metastasis in CRC, and this regulatory circuit may contribute in part to hypoxia-stimulated tumor metastasis. Strategies that disrupt this regulation might be developed to block CRC metastasis.