P-cadherin-mediated tumor-mesothelium interaction induces metabolic coupling as a determinant of metastatic outgrowth

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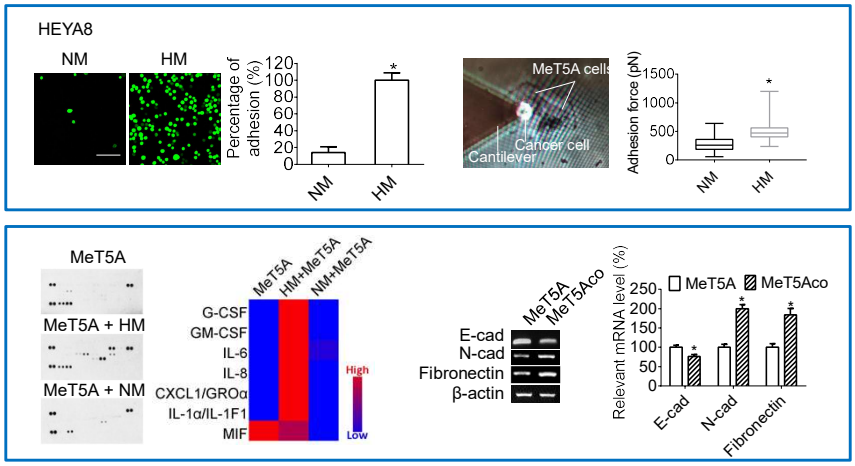
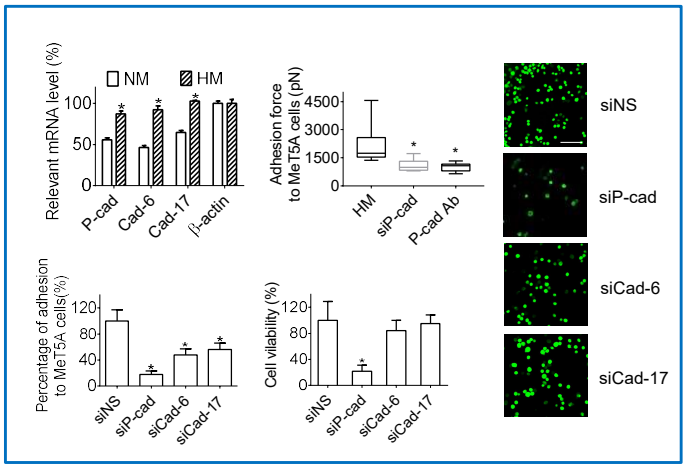
Introduction

Metabolic reprogramming is a hallmark of cancer. To survive the harsh tumor microenvironment, cancer cells frequently communicate with stromal cells to fulfill biosynthetic and bioenergetic demands. However, the mechanisms underlying tumor-mesothelial crosstalk remain elusive. Here, we show for the first time that P-cadherin (P-cad), a transmembrane adhesive protein, could act as a bidirectional activator of metabolic coupling in the ovarian cancer-mesothelium niche.

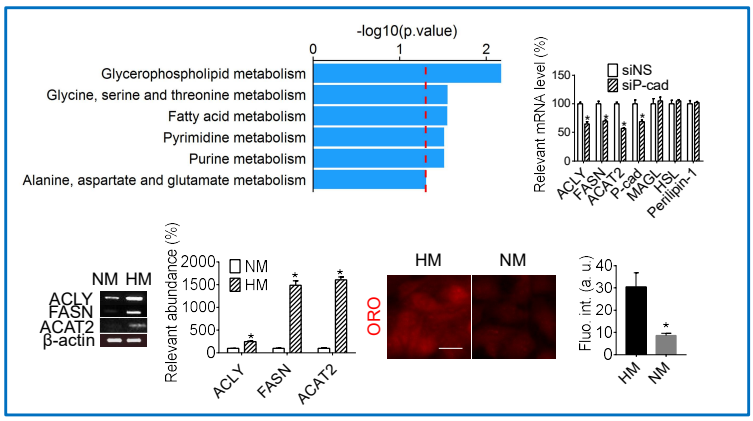
HM rather than NM cells adhere to and activate MeT5A cells



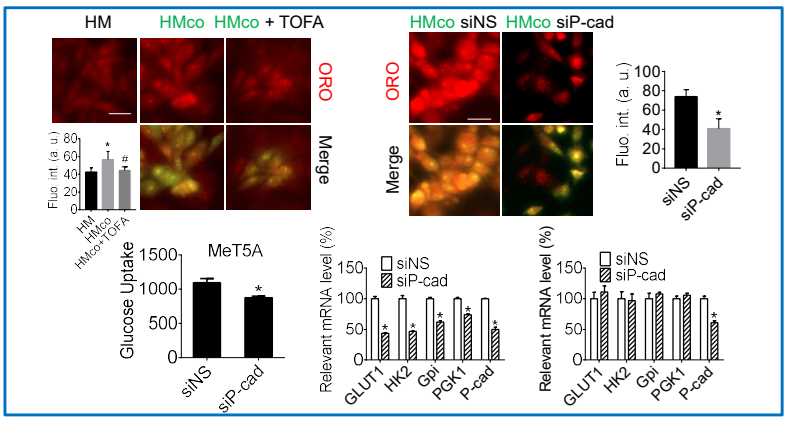
P-cad regulates adhesion and proliferation of HM cells



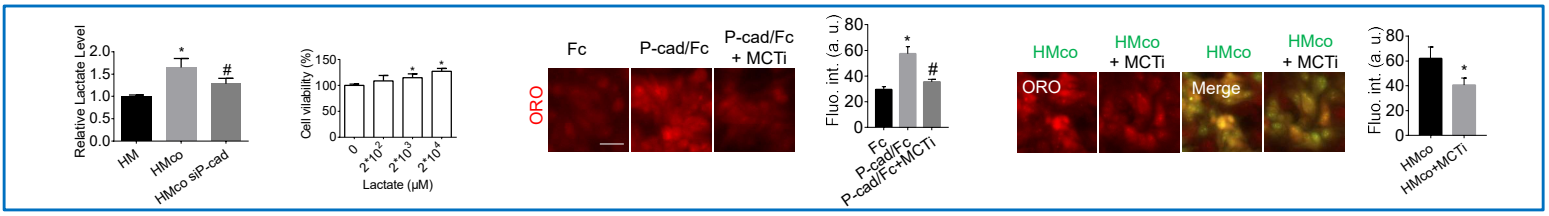
P-cad is positively related to lipogenesis in HM cells



P-cad modulates metabolic coupling in tumor-mesothelium niche



Blocking lactate shuttling efficiently inhibits lipogenesis in ovarian cancer cells



Conclusion

In this work, we unveil the important role of P-cad in the metabolic coupling of ovarian tumor-mesothelium niche, far from a transmembrane adhesive protein. Mechanistically, P-cad positively modulated the expression of lipogenic genes (ACLY, FASN, ACAT2) in cancer cells and glycolysis-related genes (GLUT1, HK2, Gpi and PGK1) in mesothelial cells. Moreover, mesothelial cells were found to fuel cancer cells in a P-cad dependent way, which opens a therapeutic window for ovarian cancer therapy. Taken together, our results unravel a critical role of P-cadherin in metabolic coupling and identify lactate shuttling in the tumor-mesothelium niche as a therapeutic window for ovarian peritoneal metastasis.

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