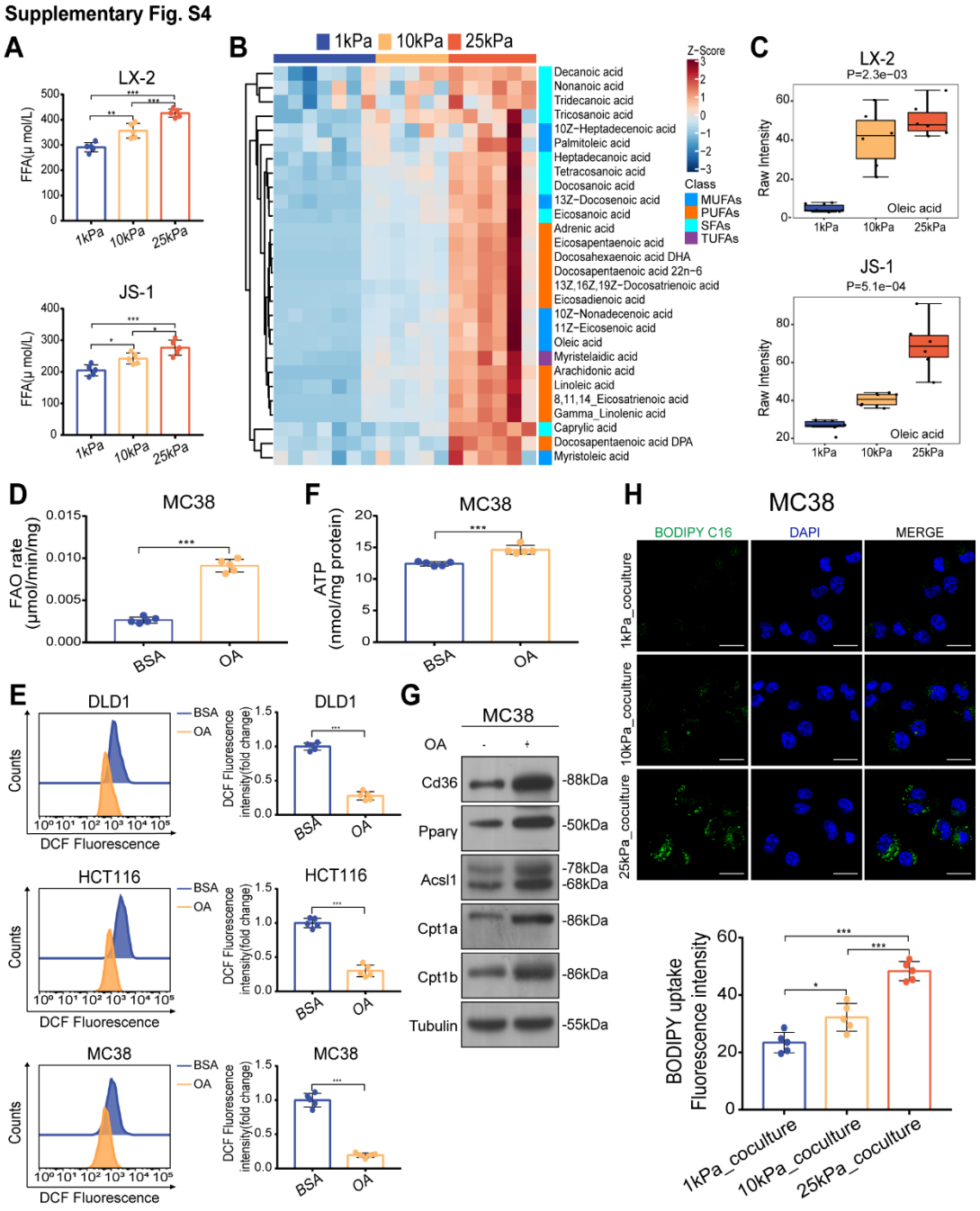

Supplementary Figure. S4 High stiffness-induced HSCs promote FAO metabolism in colon cancer cells through secreting FFAs. (A) FFA content in supernatant from LX-2 and JS-1 cells cultured on 1kPa, 10kPa and 25kPa polyacrylamide hydrogels (one-way ANOVA, n=5 independent experiments). **(B)** Heatmap of targeted lipidomic profiling of medium-and-long-chain fatty acids species in supernatant derived from JS-1 cells cultured on 1kPa, 10kPa and 25kPa polyacrylamide hydrogels (Kruskal-Wallis test, n=6 per group). **(C)** Raw intensity of oleic acid in supernatant derived from LX-2 and JS-1 cells cultured on 1kPa, 10kPa and 25kPa polyacrylamide hydrogels (Kruskal-Wallis test, n=6 per group). **(D)** Fatty acid oxidation rate of MC38 cells treated with either BSA or oleic acid (two-tailed paired *t*-test, n=5 independent experiments). **(E)** ROS content in DLD1, HCT116 and MC38 cells treated with

either BSA or oleic acid (OA, 100μM) (two-tailed paired *t*-test, n=5 independent experiments). **(F)** ATP level in of MC38 cells treated with either BSA or oleic acid (OA, 100μM) (two-tailed paired *t*-test, n=5 independent experiments). **(G)** Protein levels of Cd36, Pparγ, Acsl1, Cpt1a and Cpt1b in MC38 cells treated with either BSA or oleic acid (OA, 100μM). **(H)** Representative images (upper) and quantification (lower) of labelled lipids in MC38 cells after co-culturing with JS-1 cells treated as indicated. Scale bar: 5μm (one-way ANOVA, n=5 independent experiments). Data are graphed as the mean ± SD. **P*< 0.05; ***P* < 0.01; ****P* < 0.001.