Phenotypic alteration of tumor infiltrating macrophage by PHD inhibitor lead to improve tumor microenvironment in vivo mouse model.

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Tumor tissue environment is generally exposed to low oxygen, low nutrition and high interstitial pressure condition. These milieus are caused by vascular hyper-permeability, irregular vascularization and immature vessels. We previously reported that prolyl hydroxylase inhibitor (PHDi) induced tumor blood vessel normalization and improved tumor microenvironment (TME) in tumor bearing mouse. In this study, we examined whether improvement of TME by PHDi elicit phenotypic alteration of tumor infiltrating immune cells, especially macrophage (Mf). Lewis lung carcinoma cells were transplanted subcutaneously. Mice were treated with PHDi intraperitoneally at day10 after tumor transplantation. Then tumor tissues were collected at day16 and analyzed immune cells by flowcytometry and immunofluorescence staining. Mf ratio in total leukocyte were significantly increased in PHDi treated tumor in both immunohistochemical and flowcytometric analysis. Lymphocyte ratio didn't change in PHDi treated tumor. we performed Mf transplanted analysis using sorted Mf from tumor tissue. Our experiments showed that some Mf population contribute to maintain tumor vessel normalization and tumor microenvironment improvement in PHDi treatment. In addition, PHDi treatment didn't induce tumor progression in LLC mouse model.