Loss of TSC2 Signals for Altered Macrophage Function within Lymphangioleiomyomatosis: A Role for VEGF-D?

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Pulmonary Lymphangioleiomyomatosis (LAM) is a rare progressive, often-fatal lung disease associated with a mutation in either a TSC1 or TSC2 gene. LAM is manifested in three forms: slow-developing malignant tumors, lymph proliferation, and parenchymal tissue destruction. While scientific research has unveiled that LAM cells found in slow-developing malignancy tumors are responsible for lung tissue damage, it is not known how these cells cause destruction of the lung parenchyma, or whether this destruction can be prevented. We hypothesized that the Vascular Endothelial Growth Factor D (VEGF-D) produced from pulmonary LAM cells alters the macrophage phenotype and supports tumor growth. Furthermore, we reasoned by blocking the VEGF-D receptor could significantly improve targeted LAM therapy. By conducting a SEAP assay, a Nitrite assay, and qPCR on samples in vitro, we found that VEGF-D in LAM medium initiates a myeloid derived suppressor cell (MDSC) like phenotype. This altered phenotype results in lower NF-κB activation and less nitric oxide production- indicative of a weakened immune response. The in vitro study was complemented by an in vivo study, which concluded that higher levels of VEGF-D correlate to severe parenchymal destruction. Axitinib, a drug that blocks the VEGF-D receptor, was compared to Rapamycin, the drug currently approved for LAM treatment. From this comparison, Axitinib proved to be more effective than Rapamycin in suppressing the overactive innate immune system. While our research has significantly advanced knowledge circumventing LAM, there is still more to be uncovered about this rare pulmonary disease.