"Pulmonary Macrophage Transplantation Therapy of Hereditary Pulmonary Alveolar Proteinosis"

Takuji Suzuki M.D.,Ph.D.

Hereditary pulmonary alveolar proteinosis (hPAP) is characterized by pulmonary surfactant accumulation and respiratory failure due to defective GM-CSF receptor signaling caused by recessive genetic mutations in genes encoding the GM-CSF receptor (CSF2RA or CSF2RB), which impairs multiple alveolar macrophage (AM) functions including pulmonary surfactant clearance. An identical disease occurs in Csf2rb-/- (KO) mice. Whole lung lavage under general anesthesia is the only available therapy and is required in some patients every several months. Bone marrow transplantation corrected PAP in a murine hPAP model (KO mice) but was not successful in one child with hPAP who succumbed to lung infection before engraftment. We have recently developed a novel cell therapy, pulmonary macrophage transplantation (PMT). Murine WT bone marrow cells or KO cells transduced with a Csf2rb-expressing lentivirus were expanded/differentiated into macrophages, and administered into the lungs of KO mice without myeloablation. One PMT of WT macrophages resulted in a gradual increase in numbers of GM-CSF-Rb+ AMs that paralleled a synchronous decline in bronchoalveolar lavage (BAL) hPAP disease severity. One year after PMT, lung pathology and PAP biomarkers in BAL and AMs were markedly improved. PMT of WT or gene-corrected KO cells were equally efficacious. Importantly, the phenotype of macrophages before transplantation had changed to that of WT AMs and not KO AMs when evaluated one year after transplantation. PMT therapy of hPAP was highly efficacious, without adverse effects, and markedly improved survival. Results showed that GM-CSF and lung-specific factor(s) regulate AM phenotype, function and population size.