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LUNG ALERT

Pulmonary alveolar proteinosis: revealing a wider defect in host immunity

▲ Uchida K, Beck DC, Yomamoto T, *et al*. GM-CSF autoantibodies and neutrophil dysfunction in pulmonary alveolar proteinosis. *NEJM* 2007;**356**:567–79.

Pulmonary alveolar proteinosis (PAP) is a rare disorder of excessive accumulation of surfactant components in alveoli. The inhibition of granulocyte-macrophage colony-stimulating factor (GM-CSF) by blocking autoantibodies seems to lead to impaired surfactant clearance by alveolar macrophages. The authors explored the hypothesis that common and opportunistic pulmonary and disseminated infections reported in PAP are secondary to the effect of GM-CSF autoantibody (GM-CSF-Ab) on neutrophils by studying measures of neutrophil function.

In this prospective case-control study, neutrophils from five groups (12 subjects with PAP, 61 healthy controls, 12 patients with either cystic fibrosis (CF) or end-stage liver disease, 5 GM-CSF-/- mice (both alleles of the GM-CSF gene disabled) and 5 wild mice) were initially assessed using neutrophil count, ultra-structure and function. Both basal (cellular adhesion, basal phagocyte index, phagocyte capacity and oxidative burst) and GM-CSF primed neutrophil function (phagocytic capacity) and blood level of CD11b (a GM-CSF stimulated adhesion molecule promoting neutrophil-vascular endothelial adhesion) were measured. Basal and primed neutrophil functions were re-measured following incubation with GM-CSF-Ab in a dose-dependent fashion.

Neutrophil number and ultra-structure were similar in all groups. PAP cases had significantly low basal and GM-CSF augmented neutrophil functions. GM-CSF-/- mice had reduced basal but normal augmented neutrophil function. Patients with CF or end-stage liver disease had normal basal and augmented neutrophil function. The functions of normal human and wild mice neutrophils were reduced in a dose-dependent manner after incubating them with GM-CSF-Ab derived from PAP cases and mice, respectively.

The study provides support to the role of GM-CSF in the treatment of PAP. However, the absence of repeated lung infection is surprising given the magnitude of neutrophil defect in vitro. Minimal interstitial inflammation /fibrosis in PAP, possibly linked to reduced neutrophil function, may also raise the important question of whether monoclonal GM-CSF-Ab could be of use in diseases with excessive neutrophil activation like neutrophilic asthma and CF.

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