C/EBPβ-dependency of alveolar macrophages

Alveolar macrophages (AM) are the tissue-resident macrophages of the lung and are as such important for the immune defense against pulmonary pathogens, but also play a crucial role for the maintenance of lung integrity. In this regard one of their main functions is the clearance of surfactant lipoproteins from the alveolar space. Impaired AM function and the resulting excessive accumulation of surfactant lead to the development of pulmonary alveolar proteinosis (PAP), a disease associated with impaired respiratory function and increased susceptibility to pulmonary infections both in mice and humans. The transcription factor CCAAT-enhancer binding protein beta (C/EBPβ) is a key regulator of specific tissue-resident macrophages and previous studies in C/EBPβ-deficient mice suggest that AM depend on C/EBPβ. However, the exact functional role of C/EBPβ in AM biology remains unknown. We therefore investigate the role of C/EBPβ during AM development, homeostasis and inflammation. We employ various C/EBPβ knockout and knockin mouse mutant strains that affect the regulation or structure of C/EBPβ, its isoforms and its posttranslational modifications and examine the effects on AM. Using molecular genetics, RNA expression profiling and ATAC sequencing in combination with flow cytometry and immunohistochemistry we investigate the molecular functions as well as the regulatory networks of C/EBPβ in AM. Our data reveals that embryonic development and differentiation of classical AM (CD11b low) is C/EBPβ-dependent and adult C/EBPβ-/- mice show strongly reduced numbers of classical AM but the presence of CD11b high AM-like cells which are absent in wildtype controls. We have detected a strong increase of bronchoalveolar lavage fluid turbidity in C/EBPβ-deficient mice - similar to PAP disease - suggesting AM-like cells are not able to compensate for classical AM function. Furthermore, we were able to show that the described C/EBPβ-related phenotype depends on an AM-intrinsic expression of specific C/EBPβ protein isoforms and C/EBPβ-deficiency leads to strong transcriptional changes in AM and a decreased expression of AM signature genes. These results show that C/EBPβ is a key factor for proper AM development and function and indicate a potential role of C/EBPβ in the development of PAP-like diseases.

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