Long term maintenance of alveolar macrophage identity through massive ex vivo expansion in culture

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Macrophages are present in all tissues and play crucial roles in the maintenance of tissue integrity both during steady state and inflammation. It has become clear that tissue-specific functions of macrophages are strongly influenced by the respective environment imposed on each macrophage type. Recently, studies have shown that loss of tissue-specific signals e.g. by in vitro cultivation dramatically affects both the expression profile and enhancer landscape of macrophages. However, whether the phenotype acquired by in vitro cultured macrophages is stable or transient has not been studied yet.
Alveolar macrophages (AM) are adult resident macrophages capable of life-long self-maintenance through local proliferation. Previously, we found that AM can be maintained long-term in liquid culture without loss of proliferative capacity. Here, we show that a significant number of genes are deregulated in long-term cultured AM compared to freshly isolated, ex vivo AM, consistent with previous studies on other macrophage subsets. Interestingly, engraftment of cultured cells into their original tissue context by intratracheal transplantation of long-term cultured AM into wild-type mice restored gene expression to a transcriptional profile comparable to ex vivo AM. Furthermore, transplanted culture-derived AM stably integrated into the host and could be detected more than 7 months after transplantation. This demonstrates that the phenotype induced by adaptation to culture is transient and transcriptional changes of cultured AM can be reverted to gene signatures of bona fide AM by exposure to the natural tissue environment. Whereas transplantation of other mature macrophages populations into the lung as shown by previous studies resulted only in an incomplete adaptation of AM identity, our results are especially interesting given the possibility for ex vivo amplification of AM for therapeutic purposes without loss of AM identity upon transplantation. In conclusion, our findings represent the first example of cultured somatic cells, which not only retain the capacity to integrate into their natural niche but also restore their normal identity after encountering their natural niche.

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