Research paves the way for monocyte-based cell therapy

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Researchers from VIB-UGent reveal that adult circulating monocytes that get access to the macrophage niche in the liver or the lung can acquire identical tissue-specific macrophage functions and self-maintenance capacities as macrophages of embryonic origin. This paves the way towards monocyte-based cellular therapy in diseases associated with macrophage dysfunction, such as the disease known as pulmonary alveolar proteinosis. Using a mouse model for pulmonary alveolar proteinosis, the authors demonstrate that this rare disease can be cured by a single transfer of monocytes.

Elie Metchnikoff first identified macrophages in 1882 and was awarded the Nobel prize for his discovery in 1908 together with Paul Elrich. 2016 marks the centenary of the death of Elie Metchnikoff, yet we are still only scratching the surface with our understanding of these fascinating cells that, in addition to acting as sentinels of the immune system, are also essential for the day-to-day function of their organ of residence.

Until now scientists have speculated that the unique functional and self-maintenance capacities of tissue-resident macrophages are linked to their embryonic origin. This hypothesis was fueled by recent studies, showing that macrophages derived from embryonic progenitors are long-lived and self-maintaining whereas macrophages derived from adult circulating monocytes are short-lived. Validating this hypothesis experimentally has however been challenging as not only the precursors but also the tissues they colonize differ greatly.

Using unique mouse models, researchers at VIB-UGent under direction of Martin Guilliams now reveal that circulating monocytes can acquire identical tissue-specific functions and self-maintenance capacities as compared to embryonic precursors, provided that they get access to the steady state tissue-resident macrophage niches.

Using a novel model allowing the specific depletion of liver-resident embryonic-derived macrophages, called Kupffer cells, Martin Guilliams and colleagues demonstrated that blood monocytes colonize the emptied Kupffer cell niche in a single wave and rapidly differentiate into macrophages that are identical to their embryonic counterparts within 2 weeks. In addition, when transferred into the lungs of mice lacking alveolar macrophages, both adult monocytes and embryonic precursors developed into identical, fully functional alveolar macrophages that self-maintained and prevented disease for up to 1 year.

Charlotte Scott (VIB/UGent): "These studies addressed the question of nature versus nurture in macrophage development. The main factor controlling the functional specialization and self-maintenance capacity of macrophages is not the nature of the macrophage precursor, but rather nurture by the tissue of residence. Each progenitor receives tissue-specific signals which endow upon them the correct macrophage profile for that specific tissue. What these signals are and which cells produce them remains unknown but these are the next exciting questions we are working on."

Martin Guilliams (VIB/UGent): "In fact these findings would predict the existence of a restricted number of macrophage niches per tissue that would get colonized by embryonic macrophages before birth and remain inaccessible to circulating monocytes in adulthood as long as the niche is occupied. However, our data demonstrate that if we can empty these niches by depleting the resident macrophages then circulating monocytes colonize these niches rapidly and once they have, remain in these niches forever".

Lianne van de Laar (VIB/UGent): "The fact that circulating monocytes, which - as opposed to embryonic precursors - are easily accessible by blood donation, have the capacity to engraft permanently in tissues opens the way for monocyte-

based cellular therapy for diseases in which macrophages play a crucial role. We demonstrated the feasibility of this approach using a mouse model for a rare disease known as pulmonary alveolar proteinosis, as a single transfer of monocytes was able to durably prevent the development of the disease."

More information: Bone marrow derived monocytes give rise to self-renewing and fully differentiated Kupffer cells, Scott et., *Nature Communications* 2016

Yolk sac macrophages, fetal liver and adult monocytes are all able to colonize an empty niche and develop into functional tissue-resident macrophages, van de Laar et al., *Immunity* 2016

Tissue-Resident Macrophage Ontogeny and Homeostasis, Ginhoux, Guilliams, *Immunity* 2016

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