Human Mononuclear Phagocyte Kinetics in Health and Disease

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Introduction and Objectives
In humans, blood mononuclear phagocytes comprise of monocyte and dendritic cell (DC) subsets that circulate in equilibrium. The kinetics underlying their generation, differentiation and disappearance are critical to understanding both steady-state homeostasis and inflammatory responses. Here, using in vivo isotope labelling, the kinetics of circulating monocyte subsets was evaluated for the first time under healthy homeostasis in humans. In addition, the kinetic profile of circulating mononuclear phagocytes was examined in response to systemic inflammation.

Methods
To explore the circulating lifespan of human monocyte subsets in vivo, a stable isotope labelling approach was used to label dividing cells. After pulsing healthy volunteers with deuterated glucose, classical (CD14+ CD16-), intermediate (CD14+ CD16+) and non-classical (CD14lo/- CD16+) monocytes were isolated by FACS over 30 days. These cells were analysed for the presence of deuterium-labelled DNA by mass spectroscopy, of which the kinetic profiles were used to calculate the life-span of these circulating mononuclear phagocytes.
To understand the effects of systemic inflammation on mononuclear phagocytes, 2ng/kg endotoxin was administered i.v. to healthy volunteers.

Results
Under healthy homeostasis, monocyte subsets sequentially appeared in the circulation. Classical monocytes were the first to appear in the circulation, tailed by intermediate and then non-classical monocytes. Mathematical modelling suggested classical monocytes circulate for approximately 1 day, intermediate monocytes for 4.3 days and non-classical monocytes for 7.4 days.
In response to systemic inflammation, temporary monocytopenia was observed followed by the sequential repopulation of monocyte subsets, achieved by an early release of classical monocytes from the bone marrow. In addition to analysing monocytes, a loss of dendritic cells was also observed follow by a rapid repopulation of pDC and cDC1 and slower recovery of cDC2.

Conclusion
These data demonstrate differences in the turnover and relationship between human monocyte subsets under steady state and systemic inflammation. DC subsets also exhibited a distinct kinetic profile following inflammation warranting further investigation.

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