COMMON MONOCYTE PROGENITORS ARE NOVEL EFFECTOR CELLS IN MYCOBACTERIAL IMMUNITY

Mycobacterial tissue infections are characterized by the granuloma formation with multinucleated giant cells (MGC), a unique macrophage species. In order to define the hitherto elusive MGC progenitor, we analyzed monocyte progenitors from mouse bone marrow (BM). We found the common monocyte progenitor (cMoP) to have the highest potential to form MGC in response to mycobacterial glycolipids or whole mycobacteria. Moreover, mycobacteria induced robust formation of TNFα and nitric oxide in cMoP. Transcriptome analysis revealed a sustained synthesis and accumulation of cholesterol and fatty acids in cMoP, undergoing transformation into MGC. Oxidation and depletion of cholesterol, as well as inhibition of fatty acid synthase with orlistat impaired MGC formation, but not cytokine formation in cMoP. Thus the observed changes in lipid metabolism are a specific prerequisite for the MGC transformation program. In M. tuberculosis (M.tb) lung infection and in BCG spleen granuloma model, we identified a new circulating CD117-negative cMoP progeny, which we denominated induced monocyte progenitor (iMoP). We found an increased frequency of iMoP in the blood and BM of infected mice. Upon stimulation with mycobacterial effectors ex vivo, iMoP are, similar to cMoP, potent MGC progenitors. We hypothesize that cMoP generate iMoP which circulate in the peripheral blood and may serve as MGC progenitors in local mycobacterial infections. To confirm this, we are actually performing adoptive transfers of monocyte progenitors into M.tb infected mice. Together, we herewith introduce cMoP, which have been hitherto defined as precursors committed to renew monocytes only, specifically contribute to mycobacterial immunity.

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