Phenotypic profile of lipid-enriched macrophages spontaneously differentiated from blood-derived monocytes

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Background Macrophages are important in inflammation/tissue repair. Upon differentiation, they readily adapt to the tissue microenvironment, acquire specific phenotypes and become heterogeneous. Macrophage heterogeneity characterizes atherosclerotic lesions and may impact differently on plaque development/progression. Thus, the possibility to manipulate heterogeneity is attractive. Human tissue macrophages are not easily obtained and the various models currently used do not adequately reflect the heterogeneity and even the plasticity of resident macrophages. We have previously showed that two distinct morphotypes, i.e. round- and spindle-shaped, co-exist in the same culture of human macrophages spontaneously differentiated from adherent monocytes (MDMs). The aim of the present study was the characterization of the phenotype of these distinct MDMs. **Materials and Methods** Mononuclear cells were isolated from blood of six healthy donors by Ficoll-Paque density centrifugation and plated in 35 mm wells for primary cell culture. Adherent cells were cultured for 7 d in Medium 199 supplemented with antibiotics and 10% autologous serum. Antigen characterization was performed by immunofluorescence. Approximately 150 cells for each morphotype were collected from each culture dish by laser microdissection (PALM MicroLaser system), and their cytokine expression profile was determined by RT-qPCR after *in vitro* transcription. **Results** Both the spindle and the round morphotypes were positive for the leukocyte markers CD14 and CD45, and for the macrophage marker CD68, but differed for the amount of lipids spontaneously accumulated, which was markedly higher in the round cells. Lipid-enriched MDMs were positive for the scavenger receptor CD36 and for the fatty acid-binding protein 4/aP2 (FABP4/aP2), both involved in lipid handling, foam-cell formation and control of the inflammatory response. Moreover, they showed higher levels of the anti-inflammatory cytokines interleukin (IL)-10, and transforming growth factor (TGF)β2. Conversely, spindle MDMs were characterized by enhanced respiratory burst and higher expression of the pro-inflammatory chemokine (C-C motif) ligands 18 and 24 (CCL18 and CCL24). **Conclusions** Our data indicate that lipid-enriched MDMs show overall a non-inflammatory profile, reminiscent of the M2-like phenotype which has been shown to be atheroprotective, and suggest that intracellular lipids are key regulators of the inflammatory response. Moreover, since the up-regulation of CD36 and FABP4 has been observed in macrophages infiltrating human atherosclerotic lesions, our model may be a valuable approach to study the functional heterogeneity of tissue macrophages, which has been disclosed in multiple scenarios spanning from inflammatory and wound-healing responses to atherosclerosis.