METABOLIC REPROGRAMMING OF MACROPHAGES TOWARDS REGENERATIVE PHENOTYPE

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M2 macrophage activation is associated with the development of type 2 inflammation and tissue repair. Although it is known that lipid metabolism is important for M2 macrophage activation, it is still debatable whether it is required, and mechanisms are unclear. We found that the expression of 26 out of 32 M2-associated genes (e.g. Arg1, Chil3, Socs2, Cebpb, Irf4, Siglec-F) and oxidative phosphorylation (OXPHOS) in macrophages were strictly dependent on the presence of serum- derived lipids associated with high-density lipoproteins (HDLs). We identified that M2-inducing serum lipids were loaded on HDLs during blood coagulation, and the main sources of these lipids were activated granulocytes that secreted microparticles containing triglycerides and fatty acids (FAs). HDL-associated C18:0, C18:2cis, C18:3n3, C18:3n6, and C20:3n6 FAs were the most potent lipids that induced M2 activation. Blocking of scavenger receptors SR-B1 and SR-B3 on macrophages decreased by 90% and 70%, respectively the expression of M2 marker *Arg1*. We also found that the stimulation of macrophages by HDL-FA complexes resulted in the activation Akt pathway, which is downstream of scavenger receptors. Thus, our study identified a new pathway that mediates the metabolic reprogramming of macrophages toward the M2 phenotype.