Macrophages play distinct functions determined by the nature of the activators present in the microenvironment. From an academic point of view macrophage activation can be classified as pro-inflammatory or anti-inflammatory/pro-resolution/deactivation, these profiles coexisting in the course of the immune response, and playing a relevant functional role in the onset of inflammation. Several groups analyzed the metabolic aspects associated with macrophage activation trying to answer the question about what changes in the regulation of energy metabolism and biosynthetic precursors (NADPH, riboses, etc.) accompany the different types of polarization and to what extent these inputs are necessary for the activation phenotype. The interest of these studies is to envisage the possibility to regulate macrophage function by altering their metabolic activity as a complementary strategy to regulate their participation in the inflammatory response. Our data show that regardless of the challenges used and the availability of energy substrates, the macrophage is in more than 90% glycolytic, with limited use of other fuels for energy purposes; however, the pathways to generate metabolites from the TCA and glutaminolysis are fully functional and used for biosynthesis. In this context, we have investigated the role of macrophages in the development of atherogenesis, its diagnosis and its contribution to plaque stability and culprit and non-culprit acute coronary events. These studies allowed us to develop new strategies to evaluate functional atheromas and to stabilize them using specific metabolic-based signatures.