Targeting macrophage phenotypes and functions in atherosclerosis

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Heart attack and stroke are the most common forms of cardiovascular disease, and their underlying pathological process is atherosclerosis. Atherosclerosis is an inflammatory disease driven by hyperlipidemia. Macrophages mediate innate immune responses and lipid homeostasis and act as a key player in atherosclerosis. Lipid homeostasis is reprogrammed in the presence of inflammation, which results in excessive lipid accumulation in macrophages, and leads to the formation of lipid-laden foam cells. Foam cells are an indication of a build-up of atherosclerotic plaques. However, the cross talk among these processes in the development and progression of atherosclerosis are not fully defined. For the past few years, our recent studies successfully demonstrated the important role of the transcription factor CCAAT/enhancer-binding protein delta (CEBPD) in inflammation and cancer microenvironment over macrophages. In this current study, we aimed to dissect whether CEBPD functions at the junction of inflammation and macrophage lipid homeostasis. We found that CEBPD colocalized with macrophages in human and mouse atherosclerotic plaques and that *Cebpd* deficiency in bone marrow cells suppressed atherosclerotic lesions in hyperlipidemic *Apoe*$^{-/-}$ mice. In response to modified LDL, the p38^{MAPK}/CREB pathway contributed to CEBPD activation which promoted lipid accumulation in M1 macrophages but not in M2 macrophages. Through next generation sequencing (NGS) analysis, we found that the underlying mechanisms involved in this process included an increase in pentraxin 3 (PTX3)-mediated macropinocytosis of LDL and a reduction in ATP-binding cassette subfamily A member 1 (ABCA1)-mediated cholesterol efflux. Also, we found that zinc finger protein 202 (ZNF202) mediates CEBPD-repressed *ABCA1* gene transcription. Furthermore, we demonstrated that PTX3 can suppress ABCA1 expression through PPARγ down-regulation and reduce cholesterol efflux. In addition, we found that simvastatin (a HMG-CoA reductase inhibitor) can target CEBPD to block lipid accumulation in M1 macrophages. In conclusion, this study underscores the importance of cross talk between inflammation and lipid homeostasis and provides new insight into targeting macrophage phenotypes and functions in cardiovascular diseases. In addition, concerning the applicability and feasibility, we have developed a PTX3 inhibitor and are interested in applying it to atherosclerosis, and will hope to tailor treatments for cardiovascular diseases in the near future.

Keywords: CEBPD, inflammation, macrophages, PTX3, ZNF202, ABCA1, statins