Commentary

Lipid-Laden Macrophages cross the Border to Cancer

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ABSTRACT

Within atherosclerotic plaques, macrophages can take up cholesterol and thereby become lipid-laden cells. For long it has been thought that these foamy macrophages are the main contributors to chronic inflammatory responses in plaques. However, several publications lately highlighted that foamy plaque macrophages are less inflammatory than their non-foamy counterparts. Interestingly, a very recent *EMBO Molecular Medicine* paper by Wu et al. demonstrate that accumulation of lipids in tumor-associated macrophages (TAMs) elicits an immunosuppressive phenotype.

KEYWORDS: lipid-laden foam cell macrophages; metabolic rewiring; fatty acid metabolism; cholesterol metabolism; innate immunity; atherosclerosis; cancer

Macrophage translates as “big eater”, from Greek (macros = big and phagein = eat) and these innate immune cells engulf and kill microbes to protect us against infections. As proficient phagocytes macrophages also readily ingest lipids to acquire a foamy appearance. Foam cells are prevalent in all stages of atherosclerosis, leading to the common belief that they are the crucial drivers of chronic inflammation during this cholesterol-driven inflammatory disease. Yet, recent findings in cardiovascular research elicited a paradigm shift and highlight that “normal” macrophages, as opposed to lipid-laden foamy macrophages, are the main producers of inflammatory factors [1–3] (Figure 1).

Lipid-laden macrophages now also gained attention outside the atherosclerosis field and crossed borders to cancer research. Tumor-associated macrophages (TAMs) support tumor growth and metastasis by hampering anti-tumor immune responses and by facilitating angiogenesis.

Wu and colleagues recently reported in *EMBO Molecular Medicine* that this immunosuppressive phenotype of TAMs results from the accumulation of lipid droplets and associated metabolic rewiring [4]. They found lipid droplets to accumulate in TAMs from colorectal cancer patients. While numbers of macrophages did not differ between benign

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and tumor tissue in these patients, lipid droplet accumulation was specifically detected in TAMs. Hence, the quality but not necessarily the quantity of TAMs could serve as a prognostic prediction of cancer.

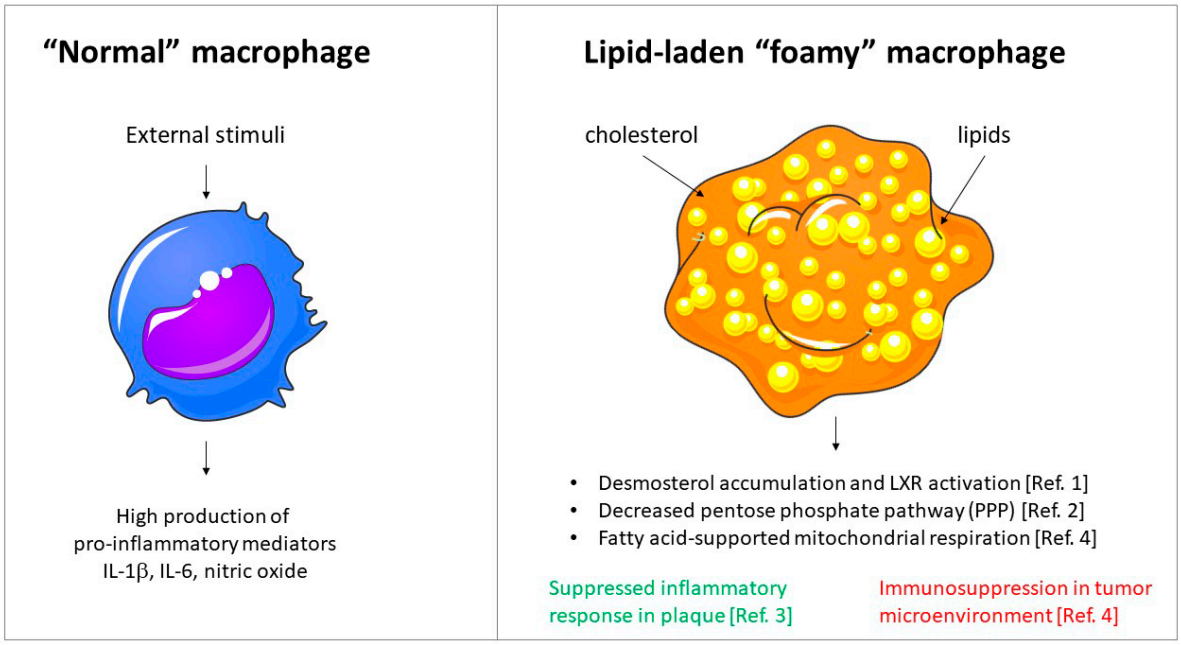

Figure 1. Properties of lipid-laden "foamy" macrophages.

Lipid droplet-derived fatty acids increased mitochondrial respiration and this metabolic shift towards increased fatty acid oxidation directly regulated the immunosuppressive function of macrophages. Consequently, disrupting lipid droplet formation in TAMs in vivo prevented the formation of a pro-tumor macrophage phenotype and impeded tumor growth. As such, the authors propose a potential therapeutic strategy that targets pro-tumor macrophages at an immunometabolic level.

Altogether, these discoveries in cardiovascular and cancer research indicate that lipid accumulation does not directly drive inflammation and rather elicits a suppressive macrophage phenotype. As such, we could consider lipid-laden macrophages as laidback couch potatoes that hang out without stoking inflammation and immunity? Maybe this is not the best description since they are not just passive and can actively suppress inflammation and anti-tumor immunity. Undoubtedly, recent literature demonstrates that lipid-laden macrophage are clearly less inflammatory than the current dogma states. This challenges the research community to have a more open vision on macrophage subtypes and their roles in disease progression.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest.

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