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TRPV4 calcium-permeable channel is a novel regulator of oxidized LDL-induced Macrophage foam cell formation

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Cardiovascular disease is the number one cause of death in developed world, and atherosclerosis, a chronic inflammatory arterial disease, is the most dominant underlying pathology. Macrophages are thought to orchestrate atherosclerosis by generating lipid-laden foam cells and by secreting inflammatory mediators. Emerging data support a role for a mechanical factor, e.g., matrix stiffness, in regulation of macrophage function and atherogenesis. We have obtained evidence that TRPV4, an ion channel in the transient receptor potential vanilloid family and a known mechanosensor, is the likely mediator of oxidized low-density lipoprotein (oxLDL)-dependent macrophage foam cell formation, a critical process in atherogenesis. Specifically, we found that: i) genetic ablation of TRPV4 or pharmacologic inhibition of TRPV4 activity by a specific antagonist blocked oxLDL-induced macrophage foam cell formation, and ii) TRPV4 deficiency prevented matrix stiffness or scratch-induced exacerbation of oxLDL-induced foam cell formation. Mechanistically, we found that: i) plasma membrane localization of TRPV4 was sensitized to the increasing level of matrix stiffness, and ii) TRPV4 activity regulated oxLDL uptake but not its internalization in macrophages. Altogether, these findings identify a novel role for TRPV4 in regulating macrophage foam cell formation by modulating uptake of oxLDL.

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