**PEROXIREDOXIN1 PROTECTS MACROPHAGES FROM IMPAIRED LIPOPHAGIC FLUX BY OXIDATIVE STRESS IN ATHEROSCLEROSIS**

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Oxidative stress activates autophagy and contributes to the atherogenesis via lipophagic flux, a form of lipid removal by autophagy. However, it has not been studied whether the endogenous anti-oxidant enzymes are involved in lipophagic flux. We demonstrated that anti-oxidant Peroxiredoxin1 (Prdx1) restored autophagic flux impaired by oxidative stress. Prdx1 was more highly-expressed than other anti-oxidant enzymes in macrophages in murine and human atherosclerotic plaque. Consistent with this observation, ApoE-/- mice transplanted with bone marrow (BM) cells from Prdx1-/-ApoE-/- mice had accelerated plaque formation upon high fat diet compared to ApoE-/- BM transplanted recipients. We revealed that Prdx1-deficient macrophages had higher intracellular cholesterol mass and lower cholesterol efflux compared to wild-type controls. Prdx-1 deficiency also inhibits maintenance of lipophagic flux in macrophages. This perturbation in cholesterol homeostasis was due to impaired lipophagic cholesterol hydrolysis by excessive oxidative stress, resulting in the inhibition of free cholesterol formation and reduction of LXRalpha activity. Notably, impairment of both lipophagic flux and cholesterol efflux was restored by the 2-Cys Prdx mimics ebselen and gliotoxin. This study reveals that Prdx1 is crucial to regulating lipophagic flux and maintaining macrophage cholesterol homeostasis against oxidative stress. We suggest that Prdx1-dependent control of oxidative stress may provide a strategy for treating atherosclerosis and autophagy related human diseases.