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Funding Acknowledgements: Type of funding sources: Foundation. Main funding source(s): Dutch Heart Foundation

Aging is an independent and dominant risk factor for atherosclerosis and is associated with a low-grade chronic inflammation termed inflammaging. This age-induced pro-inflammatory environment may have great impact on plaque-residing immune cells, including mast cells. Mast cells have been found to accumulate in the human atherosclerotic plaque upon disease progression and have been associated with plaque instability. However, it is currently unknown whether aging drives the pro-atherogenic effects of mast cells in atherosclerosis.

To assess the effects of aging on mast cell phenotype, we examined mast cell populations in young and old male Ldlr-/- mice fed either a chow (CD) or Western-type (WD) diet. We observed a 6-fold increase in the number of mast cells in the aged atherosclerotic aorta compared to young (Y-CD: 4.5±0.7 vs. O-CD: 279.4±9 cells, $p<0.01$; Y-WD: 45.3±15.2 vs. O-CD: 279.4±9 cells, $p<0.01$). Furthermore, we detected a marked increase in activation status with age as shown by the significantly augmented number of CD63+ mast cells in the atherosclerotic aorta (Y-CD: 1.8±0.6 vs. O-CD: 259.7±85.4 cells, $p<0.01$; Y-WD: 41.3±13.6 vs. O-CD: 259.7±85.4 cells, $p<0.01$). In line, we identified that aged bone-marrow derived mast cells displayed elevated basal CD63 expression compared to young cells, indicative of intrinsic low-grade activation. Moreover, we demonstrated that aging increases the amount of MHCII+ mast cells in atherosclerosis, allowing them to act as antigen-presenting cells, which correspondingly led to increased CD4+ T cell proliferation in vitro (young: 35.2±1.2% vs. old: 45.8±1.2%, $p<0.001$). Finally, single-cell RNA sequencing of human atherosclerotic plaques confirmed mast cell-specific expression of MHC-II orthologs.

To conclude, we established that aging induces phenotypic changes of mast cells in atherosclerosis, regarding both activation status and antigen presenting capacity, which can contribute to disease progression.