ABSTRACT

The low-grade, persistent chronic inflammation, forms one fundamental pillars of aging and underlies almost all leading causes of morbidity. Age-related inflammation is observed across different tissue throughout the organism, however visceral adipose is among the first tissue to exhibit this pathological state. Adipocytes and mesenchymal stromal cells that reside in the adipose tissue can produce pro-inflammatory cytokines and chemokines. The inflammatory phenotype of these cells is critical in recruiting immune cells to visceral adipose, which establishes and further promotes the chronic inflammatory state. However, the upstream cellular and molecular changes that underlie the inflammatory phenotype in adipocyte and stromal cells remain unclear**.** Complex lipids – lipids with more than one chemical moieties – are key structural components as well as signaling and metabolic molecules. Lipids such as oxidized phospholipids can directly stimulate inflammatory response. Moreover, dysregulation of membrane lipids can disrupt the secretory pathways and membrane-bound receptors that are integral in immune signaling transduction. These results raise the exciting possibility that studying the role of complex lipids in the development of chronic inflammation could reveal new strategies in combating aging and age-related diseases. However, despite emerging studies connecting the dysregulation of complex lipids with age-associated metabolic, cardiovascular and neurodegenerative diseases, our understanding of how complex lipids contribute to the chronic inflammatory state, or inflammaging, remains unexplored. I hypothesize that complex lipids dysregulation directly contributes to the chronic inflammation of visceral adipose through regulating the inflammatory phenotype in adipocytes and mesenchymal stromal cells. We will test our hypothesis by first identifying age-associated lipidomic changes in adipocytes and mesenchymal stromal cells from visceral adipose tissue of young and elderly human patients. We will then use a combination of genetic targeting and chemical supplementation approach to functionally test the effects of age-related lipid changes on the inflammatory phenotype of primary adipocytes and mesenchymal stromal cell cultures *in vitro.* Lastly, using genetic mouse models, we will assess the effects of lipid-regulating pathways on maintaining functional tissue homeostasis in visceral adipose *in vivo*. Leveraging visceral adipose as a powerful model, this project aims to uncover lipids and lipid-regulating pathways that functionally contribute to age-related chronic inflammation, a hallmark pathological state in aged population. Our lipidomic study with cellular resolution, together with functional studies *in vitro* and *in vivo* will provide new insight into the molecular mechanisms of aging. The specific lipids and pathways that we uncover will be of high value in therapeutic development in translational gerosceience research and pave ways for future mechanistic studies and funding opportunities.