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Recent clinical trials and human genetic studies implicate monocytes and macrophages (Mφ) in atherosclerotic cardiovascular disease (CVD). Yet, concerns on safety and specificity limit the potential of myeloid cell directed therapies for CVD and complex cardiometabolic disorders (CMD). This reflects knowledge-gaps in the identity of human monocyte subpopulations in homeostasis and disease. In the first cycle of R01-HL113147, the MPIs pursued highly productive bulk RNAseq and functional genomics of human monocyte-Mφ. However, "data averaging" in bulk RNAseq masks expression variation and limits capacity to identify monocyte subpopulations. Human monocytes and their regulatory features differ from mouse. So, despite elegant studies of rodent monocyte subpopulations and their "master regulator" proteins (MRs), the genetic and functional identities of human monocyte subpopulations remain unclear. Based on surface markers, human monocytes can be classified into three subsets, yet emerging data hint at greater diversity. Our preliminary single cell (sc)RNAseq in over 20,000 blood monocytes from multiple humans suggest (i) at least six monocyte subpopulations and (ii) variability in subpopulations distributions across CVD risk factor states. In this renewal, we propose cutting-edge scRNAseq profiling of human monocytes coupled to innovative population genetics and functional genomics to define the role of human monocyte subpopulations in CMD. In **Aim 1**, we will enroll 240 participants (60 healthy, 60 hypercholesterolemic, 60 type 2 diabetic and 60 cigarette smokers), perform 3'-end scRNAseq of ~5000 monocytes per subject in 60 participants to identify monocyte subpopulations, and use scRNAseq data to deconvolute subpopulation distributions from bulk RNAseq for all 240 subjects. Then, we will determine differentially expressed genes and MRs of monocyte subpopulations in health and in CVD risk states. **Aim 2** will combine scRNAseq and genome wide SNP data to identify monocyte subpopulation-specific *cis*-eQTL variants and genes with subpopulation-specific transcriptional bursting. These genetic tools will be used in large genetic datasets to test the association of specific subpopulations with CMD. In **Aim 3** we focus on subpopulation-specific long intergenic non-coding RNAs (lincRNAs), molecules implicated by our group and others in monocyte-Mφ functions and human diseases. Preliminary data reveals that most lincRNAs are expressed only in subsets of monocytes. We will use an imputation procedure for recovery of lincRNA expression to identify monocyte subpopulation-specific lincRNAs and association of their *cis*-eQTL variants and bursting features with CMD. Mechanistic studies of key subpopulation mRNAs and lincRNAs will use knockdown and overexpression in human monocyte-derived Mφ and gene-editing, for knockout, in human induced pluripotent stem cell-derived Mφ. We address a major knowledge gap in human monocyte biology by defining human monocyte subpopulations, interrogating their genetic relationship with CMD, and exploring functions of subpopulation-specific mRNAs and lincRNAs in human Mφs.