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Cell death, or apoptosis, is a routine part of homeostasis; up to tens of billions of our cells die every day and must be properly digested and recycled. Apoptotic cells normally are immunologically silent, unless they are allowed to remain unengulfed for prolonged periods of time, during which they become necrotic and inflammatory. Macrophages are the primary cell type responsible for the timely clearance of apoptotic cells, termed efferocytosis, which involves the recruitment and binding of macrophages, the ingestion of the apoptotic cell, and their digestion in lysosomes. Consequently, increased efferocytosis may reduce disease phenotypes that can occur from uncleared apoptotic cells, which is potentially relevant in the development of translational interventions. One underexplored component of efferocytosis is the maintenance of macrophage lysosomal function despite stress from digesting relatively massive apoptotic cargo. In other contexts, lysosomal stress is known to be sensed by two transcription factors, TFEB and TFE3, which translocate to the nucleus to drive expression of autophagy and lysosomal genes.

In our studies, we are evaluating the significance of TFEB and TFE3 on the effectiveness of efferocytosis. More specifically, we seek to identify how these transcription factors regulate the way macrophages recognize apoptotic cells, the efficiency of their degradation, and the characterization of autophagosomes generated within the macrophages. Preliminarily, we have developed a replicable procedure to use UV light to induce apoptosis in cells, protocols to fluorescently label them, and mouse models with modified TFEB and TFE3 expression for macrophage production, in preparation for both imaging and the quantification of gene expression through quantitative PCR. We plan to apply these procedures over time course experiments to observe how macrophages generate and receive efferocytosis signals. Our hypothesis is that TFEB and TFE3, through the induction of lysosomal-autophagy, are able to modulate the efficiency of macrophages in performing efferocytosis.