Molecular Determinants of Sarcoidosis

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Funding: This work was funded by the Ann Theodore Foundation and the Stead Scholarship Program of the Duke University Department of Medicine.

Background: Sarcoidosis is a multi-system inflammatory disease characterized by noncaseating granulomas, for which the current mainstay of treatment is steroids and/or other immunosuppressing agents. There is a need to better understand the intricacies of granuloma formation to develop targeted therapies and biomarkers to aid in diagnosis and monitoring of disease progression.
Methods/Results: We sought to establish a model of sarcoidosis using human induced pluripotent stem cells (iPSCs). We differentiated iPSCs into macrophages (iMacs) over the course of three weeks and then subjected these cells to agents known to induce multinucleated giant cell formation. We did not observe any characteristic giant cells after exposing unpolarized iMacs to a mammalian target of rapamycin (mTOR) activator or Kveim reagent. Furthermore, we did not observe any giant cell formation after simulating T-cell interactions with iMacs by exposure to soluble CD40 ligand, interferon gamma, and concanavalin A.
Conclusions: Considering the growing evidence that M2 macrophages play an important role in both mouse and human sarcoidosis granulomas, it is possible that polarization of iMacs towards an M2 phenotype may be necessary for giant cell formation *in vitro*. Additionally, the decreased expression of *HLA-DR* genes, which have been implicated in human sarcoidosis, in iMacs compared to macrophages derived from peripheral blood mononuclear cells may necessitate upregulation of *HLA-DR* in iMacs to induce a sarcoidogenic phenotype. Our iMacs may further be used to functionally validate markers of circulating cells that form sarcoidosis granulomas in humans.