Rose, T, Luder
L2
LSU Health Sciences Center, New Orleans, LA

Mentors: Augusto Ochoa, MD, Maria D. Sanchez-Pino, PhD
Louisiana State University Health Sciences Center, Department of Interdisciplinary Oncology, Department of Genetics & Stanley S. Scott Cancer Center

"Obese microenvironment contributes to MDSC phenotype through epigenetic mechanisms"

Obese patients are more susceptible to developing several different types of cancer. Myeloid derived suppressor cells (MDSC) promote tumor growth by blocking anti-tumor T cell responses. The expanded number and heightened function of MDSC have been found in mouse models of obesity. Our preliminary data show that patients with morbid obesity (body mass index [BMI] > 40 kg/m^2) also have increased numbers of MDSC in peripheral blood, which could contribute to the cancer risk. Here, we investigate *in vitro* whether the cholesterol, as a factor of obese microenvironment, regulates the immunosuppressive phenotype of MDSC via epigenetic mechanisms.

MDSC exert their immunosuppressive effects through the upregulation of several genes that codify for arginase 1 (*Arg1*), iNOS (*NOS2*), and PD-L1 (*CD274*). Transcriptome analysis by comparing purified MDSC from obese patients and normal weight controls (NWC) led us to hypothesize that expression of key genes such as arginase 1 is regulated by chromatin remodeling by the demethylase JMJD3. Additionally, ATAC-seq data obtained by comparing MDSC from mice fed with high-fat and low-fat diets led us to hypothesize that the function of MDSC might be modulated the methyltransferase EZH2. Mice fed a high fat diet showed open chromatin regions uncovering motifs for EZH2 in regulatory elements of *NOS2*, as compared to MDSC from low-fat diet mice. The RNA-seq and ATAC-seq data led us to hypothesize that the inflammatory milieu or deregulated metabolic factors, such as cholesterol, in obesity have a key role in the regulation of immunosuppressive gene expression in MDSC through epigenetic mechanisms involving EZH2 and JMJD3.

Here, we show that MDSC induced *in vitro* from mouse bone marrow in the presence of cholesterol-LDL show increased expression levels of arginase-1 and iNOS and enhanced immunosuppressive capacity. While expression of iNOS and suppression function on T cells are significantly reduced by inhibition of EZH2 with DZNeP, the inhibition of JMJD3 with GSK-J4 alters the expression of arginase-1 induced by LDL. These findings suggest that epigenetic modulators such as EZH2 and JMJD3 could be a promising druggable targets to modify the pro-oncogenic phenotype of MDSC in obesity and reduce their potential role in cancer development and progression.