Interferon-Induced Metabolic Perturbations Shape the Inflammatory Status of Human Monocytes: Implications for Innovative Therapeutic Engineering in SLE Autoimmunity

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Immune cells have unique metabolic requirements to support the energetic and biosynthetic burden during their activation. Delineation of the metabolic tuning of immune cells could lead to novel strategies in treating metabolically-demanding processes including autoimmune diseases. Among innate effectors, monocytes have a distinct role in systemic lupus erythematosus (SLE) pathogenesis. We have previously described robust type-I interferon (IFNα) signaling in patients with SLE. IFNα-stimulated monocytes from healthy individuals (IFN-Mo) develop mitochondrial hyperpolarization and increased oxidative stress resembling SLE monocytes (SLE-Mo).

Here we sought to delineate the metabolic repercussions of IFNα-mediated signaling that could explain metabolic shifts pertaining to autoimmunity. To this end, we combined transcriptomic data with metabolic flux analysis (Seahorse technology) and Gas Chromatography (GC-MS) in healthy monocytes, IFN-Mo and SLE-Mo. Our preliminary results indicate an increased, glucose-dose dependent glycolytic flux in IFNα-treated healthy monocytes recapitulating the SLE-Mo phenotype. Blockade of hexokinase 2 (HK-2)-dependent glycolysis with the use of 2-DG inhibitor attenuated proinflammatory cytokine secretion and the expression of surface markers characteristic of activated monocytes, supporting the deregulated metabolic profile in SLE autoimmunity.

Combination of these data with targeted metabolomics (LC-MS) analyses and the application of pathway-specific inhibitors are implemented in vitro to reverse the inflammatory state of SLE monocytes. Together, our data are expected to yield unique insights into the role of immunometabolism in SLE and the potential use of metabolites as novel therapeutic targets in autoimmunity.

Oxidative Stress in NK Cell and Its Correlation with Expression of Killer Immunoglobulin Receptors in SLE Patients

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Background Oxidative stress i.e. accumulation of reactive oxidative species has been found to be implicated pathogenesis of many autoimmune diseases including systemic lupus erythematosus. Although our body has natural process of scavenging reactive oxidative species but whenever balance inclines towards accumulation, oxidative stress begins to build in. These accumulated ions lead to damage at cellular level and at molecular levels also. In our NK cell specific study we evaluated oxidative stress and expression level of killer immunoglobulin receptors. Killer cell immunoglobulin like receptors binds to mhc class 1 receptors. They work in antagonistic manner they are either activating for NK cell activity or inhibiting. So the balance between two categories is critical for self tolerance. We have evaluated expression level of kIR2D4 which binds to HLA-G ligand and activating in nature and KIR3D1L on other hand interacts with HLA-Bw4 and prevent NK cell killing of healthy cells.

Methods Lupus Patient and healthy subjects Lupus patients are enrolled from outpatient department (OPD) of rheumatology clinic, PGIMER, Chandigarh.

Flow cytometric analysis PBMC isolated were incubated with antibodies conjugated to APC,PE, PerCP/cy5.5 for surface staining of antigens cd56, kIR2D4 and kIR3D1L. DCFDA dye based analysis was ad done for estimation cellular ROS levels.