Biological Design Doctoral Defense

Designing Metabolite-based Therapies to Rewire Immunometabolism and Treat Autoimmune Rheumatoid Arthritis

School for Engineering of Matter, Transport and Energy

Joslyn Mangal
Advisor: Dr. Abhinav Acharya

Abstract

Autoimmunity develops when the immune system targets self-antigens within the body. Rheumatoid arthritis (RA) is a common autoimmune disease, and its progression is characterized by pro-inflammatory immune cells rapidly proliferating, migrating, and infiltrating joint tissue to provoke inflammation. In order to fulfill this taxing autoreactive response, an increase in energy metabolism is required by immune cells, such as dendritic cells (DCs). Therefore, a shift in DC energy reliance from the Krebs cycle toward glycolysis occurs. This metabolic shift transitions DCs from anti-inflammatory properties toward an aggressive pro-inflammatory phenotype, in turn activating pro-inflammatory T cells and promoting RA pathogenesis. Given that cellular metabolism can control immune cell function, this work aims to harness the perturbations within RA immune cell energy metabolism and utilizes it as a therapeutic target by reprogramming immune cell metabolism via the delivery of metabolite-based particles. This was achieved by developing and delivering metabolite-based polymeric microparticles synthesized from the Krebs cycle metabolite, alpha-ketoglutarate (aKG; termed paKG MPs) to DCs to modulate their energy metabolism and promote anti-inflammatory properties (in the context of RA) in Aim 1. Furthermore, Aims 2 and 3 demonstrate that the two-time delivery of variations of these particles reduced RA inflammation in a RA collagen-induced arthritis (CIA) mouse model and generated desired responses with long-term effects. Specifically, Aim 2 treats RA in CIA mice using an antigen-specific approach by exploiting the encapsulation ability of paKG MPs to inhibit DC glycolysis in the presence of the encapsulated glycolytic inhibitor (PFK15) and CIA self-antigen (collagen type II (bc2)). In Aim 3, empty paKG nanoparticles (NPs) are delivered, in adjunct to a short, low dose of methotrexate (MTX – first-line approved RA therapy), to accelerate the paw inflammation resolution rate to half the amount of time observed in Aim 2. Overall, this work demonstrates that a two-time delivery of aKG-based particle formulations can reduce RA symptoms in CIA mice and induce long-term effects.

October 21, 2022; 10:30 AM; LSA 119;
Zoom Link: https://asu.zoom.us/j/3143472193