Targeting Granzyme K: New Therapeutic Approach Blocks Chronic Inflammation Across Diseases

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The complement system - a powerful component of our immune systems – is a network of proteins that work together to help the body fight infection, heal injury, and clear microbes. Our laboratory has made a paradigm-shifting discovery that fundamentally changes how we understand the complement system and its activation.

We discovered that granzyme K (GZMK) – produced by CD8 T cells that infiltrate diseased tissues – directly activates the entire complement cascade. It directly cleaves C4 and C2 proteins generating a classical C3 convertase which cleaves C3 and triggers a chain reaction that leads to formation of the C5 convertase and all the major inflammatory products of the complement cascade: signaling and chemotactic anaphylatoxin molecules (C3a and C5a), tagging proteins by opsonization with C3b that mark antigens for phagocytosis and cells for attack, and the membrane attack complex, which can activate or lyse cells.

In rheumatoid arthritis (RA) synovium, GZMK is most abundant in regions where complement activation is strongest. In fact, GZMK CD8 T cells dominate in the inflamed tissues not only in RA, but also in Crohn's Disease and ulcerative colitis gut, lupus nephritis kidney and other autoimmune diseases. In inflamed tissues, stromal fibroblasts produce large amounts of complement proteins (C2, C3 and C4) which are the major source of complement produced locally in inflamed tissues and acted on by GZMK. This represents a tissue focused process that differs from the previously known classical, alternative or lectin pathways of complement activation.

GZMK represents a novel and promising therapeutic target to inhibit complement activation across autoimmune and chronic inflammatory diseases. Unlike existing complement inhibitors that broadly suppress the entire system and compromise infection defense, GZMK inhibition offers precision targeting. This approach preserves essential anti-microbial complement functions while specifically blocking the harmful pathway driving chronic tissue inflammation such as in autoimmune diseases—addressing the key therapeutic limitation of current complement drugs.

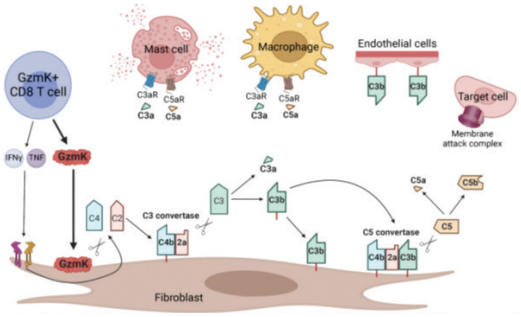
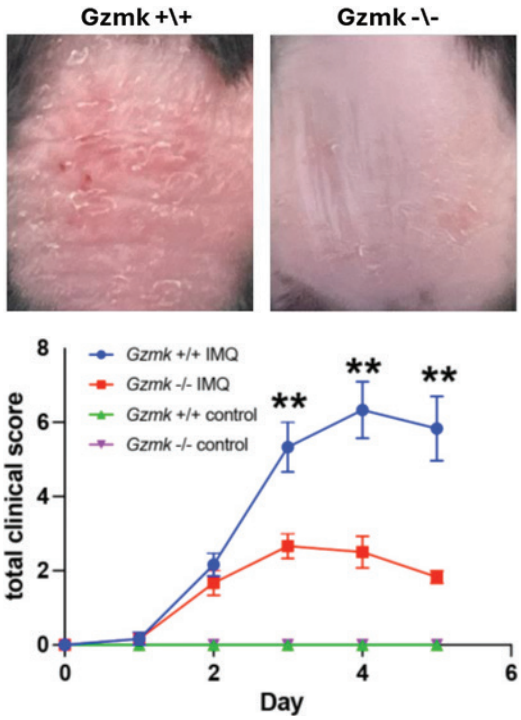


Figure 1: GZMK produced by CD8 T cells in inflamed tissues drives activation of the entire complement cascade with release of anaphylatoxins, opsonization and the full range of complement-mediated inflammation.



Figures 2-3: GZMK −/− mice have less severe psoriasiform dermatitis, and are protected from IMQ-induced dermatitis and complement activation.