Severe combined immunodeficiency (SCID), also known as the “bubble boy disease”, is a disease of the immune system where the body has difficulty fighting infections. The prevalence of SCID is 1 in 58,000 live births and infants with SCID experience severe opportunistic infections that are fatal in the first year of life if left untreated.1,2 The most common form of SCID is X-linked SCID (SCIDX1), which is caused by a mutation in the Interleukin-2 receptor gamma (IL2RG) gene, which leads to the death of T cells that regulate adaptive immunity. The IL2RG gene encodes one membrane gamma chain and a soluble gamma chain, both components of interleukin (IL) receptors. The soluble gamma chain is translated from an alternatively spliced version of the IL2RG gene.3 This soluble common gamma chain is implicated in inflammatory disease, but its specific role in this process is unclear.4,5

The **long-term goal** is to understand the function of the soluble gamma chain in the inflammatory response in order to better understand inflammatory diseases. I **hypothesize** that the soluble gamma chain will have conserved phosphorylation sites across vertebrates and interact with specific proteins involved in inflammation.

**Specific Aim 1: Identify conserved phosphorylation sites in the soluble gamma chain that are important for inflammation.**

**Approach 1:** Phosphorylation sites will be identified using Net Phos 2.0. Clustal Omega will then be used to identify amino acids that are conserved between vertebrate species. Then, the mouse model organism will be used with CRISPR to mutate these sites and examine inflammatory response using the inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) versus T cell proliferation by measuring T cell count.6

**Hypothesis:** Specific phosphorylation sites will be highly conserved and important for the inflammatory response.

**Rationale:** Conservation of phosphorylation sites will provide an understanding of the evolution of immunity and the function of the soluble gamma chain in inflammation.

**Specific Aim 2: Identify genes important for soluble gamma chain function in the inflammatory response.**

**Approach 2:** In the mouse model, take wild type, membrane gamma chain mutant, soluble gamma chain mutant (from Aim 1) and perform RNA-seq on different tissues. Identify genes, sort by Gene Ontology and observe changes in gene expression in each group. The genes that are enriched in the soluble gamma chain mutants may be important for inflammation. Test this by using CRISPR to knock out these genes and measure inflammation (with ESR and CRP) versus T cell growth (through measuring T cell count).

**Hypothesis:** Knocking out genes enriched in soluble gamma chain will decrease inflammation through lower levels of ESR and CRP compared to control.

**Rationale:** Understanding other genes involved in the inflammatory response will lead to an understanding of proteins the soluble gamma chain interacts with in the inflammatory process.

**Specific Aim 3: Identify novel protein interactors of the soluble gamma chain important for inflammation.**

**Approach 3:** Perform TAP tag analysis on the soluble and membrane gamma chain mutants from Aim 2, soluble gamma chain and membrane gamma chain in order to identify specific proteins that bind to the soluble gamma chain. Sort proteins by Gene Ontology, prioritize to do CRISPR knockouts and determine if these genes play a role in inflammation (measuring ESR and CRP) versus T cell proliferation (measuring T cell count).

**Hypothesis:** The soluble gamma chain will increase ESR and CRP, while the membrane bound gamma chain will interact with molecules involved in T cell growth, observed by a rise in T cell count.

**Rationale:** Identifying protein interactors of the soluble common gamma chain will lead to an understanding of the biological function of this protein.

Understanding the evolutionary conservation, gene expression and protein interactors of the soluble gamma chain will lead to a more in depth understanding of this protein’s role in inflammatory diseases. This may lead to drug treatments targeting the soluble gamma chain in order to ameliorate inflammation in disease.4

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