Macrophage Polarization Regulates Src-family Kinase Transcription

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BACKGROUND

The complexity of macrophage polarization is difficult to mimic in vitro. Studies thus often model polarization with canonical cytokines known to activate specific transcriptional programs.

HYPOTHESIS

To respond to the diverse array of polarizing signals, macrophages rely on cell surface receptors like immunoreceptor tyrosine-based activation motifs (ITAM)-associated receptors, which are essential for macrophage anti-inflammatory signaling through the activation of Src-family kinases.

METHODS

- Derive macrophages from murine bone marrow
- Polarize macrophages with different conditions
- Assess mRNA fold change from non-polarized controls via qRT-PCR

RESULTS

- Few studies have assessed the role of SFKs in macrophage polarization
  - LynA, one two equally expressed splice variants of lyn, is essential for macrophage anti-inflammatory signaling in response to weak ITAM receptor stimuli
  - Priming macrophages with inflammatory stimuli has been shown to upregulate LynA protein expression

CONCLUSIONS

- These preliminary data show a trend of LynA upregulation that is specific for a subset of strongly pro-inflammatory stimuli, consistent with prior data showing increased LynA protein expression with IFNγ
- Changes in Hck mRNA follow a similar pattern to LynA, but Fgr appears downregulated with inflammatory priming and upregulated with a subset of immunosuppressive polarization signals
- The hypothesized M1-polarizing signals, GM-CSF and IL-6, did not induce upregulation of Lyn or LynA, and future experiments will attempt to elucidate the role of these signals in our model

FUTURE DIRECTIONS

- Short-term: Assess transcriptional regulation of inhibitory SFK signaling components
  - Previous research has shown that priming macrophages with LPS leads to a decrease in expression of the inhibitory adaptor protein, Dok3

- Long-term: Investigate polarization-mediated changes in disease-associated macrophages
  - Macrophage polarization contributes to many different disease states including cancer and chronic inflammatory diseases like arthritis
  - Future studies will aim to assess SFK regulation in tumor-associated macrophages (TAMs), which have been described as having a more M2-like phenotype

REFERENCES