Background:

Giant Cell Arteritis (GCA) is a type of large vessel vasculitis that can cause blindness and aortic aneurysms. A significant unmet medical need remains in GCA, as current treatment options are limited, and relapse increases corticosteroid (CS) exposure and toxicity.

The primary role of macrophages/dendritic cells (DCs) and T_H1/T_H17 lymphocytes in GCA pathogenesis has been highlighted previously. Granulocyte-macrophage colony stimulating factor (GM-CSF) may contribute to GCA pathogenesis by stimulating giant cell formation.[1] GM-CSF produced by $CD4^+$ T helper T_H1 and T_H17 cells can stimulate conventional DCs and promote differentiation of monocyte-derived DCs.[2] GM-CSF may drive DCs to program naïve $CD4^+$ cells to T_H1, T_H17, and T follicular helper phenotypes (IFNγ/IL-17/IL-21). Notably GM-CSF RNA has been reported in GCA lesions[3] and in peripheral blood mononuclear cells of symptomatic patients.[4]

Objectives:

We hypothesized elevation of the GM-CSF pathway signature in GCA vessels versus controls.

Methods:

Two independent sources of temporal artery biopsies were utilized. First, GCA (n=17) and control (symptomatic patients suspected for GCA, but with a normal temporary artery biopsy; n=5) biopsies were analyzed for 15 mRNA transcripts representing T_H1, T_H17, and GM-CSF signaling (RNAscope; RS) and for mRNA transcripts representing the autoimmune panel (Nanostring; NS). Semi-quantitative scoring was performed on RS images, and fold-change of representative T_H1, T_H17 and GM-CSF related mRNA transcripts were calculated via NS nCounter analysis. Additional GCA and control biopsies were obtained and analyzed by RT-PCR for a subset of transcripts (n=10 each) and by confocal microscopy for GM-CSF and GM-CSF-Rα protein (n=2 each).

Results:

The GM-CSF signaling pathway molecular signature was confirmed to be upregulated by 4 independent analyses.

GM-CSF-associated and T_H1-associated genes were upregulated in GCA biopsies versus control (GMCSF: 3-4x RS; GM-CSF-Rα: 6.7x NS, 6x RS; and CD83: 3.9x NS, 6x RS; TNFα: 2x NS, 3x RS; IFNγ: 2x RS; IL-1β: 6x RS). T_H17 associated genes were not elevated, potentially due to concomitant CS treatment.

Upregulation of both GM-CSF (12x) and GM-CSF-Rα (3x) mRNA was confirmed in a separate cohort of biopsies from GCA patients vs. controls by RT-PCR (Figure). GM-CSF and GM-CSFRα proteins were detected in the luminal endothelium, neovessels and inflammatory cells of GCA patients. In normal temporal arteries, GM-CSF protein was not detected, and some GM-CSFRα expression was observed in the luminal endothelium.

Pu.1, a transcription factor downstream of GM-CSF signaling, was increased 8x in GCA vs. controls (RS, NS) (Figure).

Conclusion:

GM-CSF and T_H1 pathway signatures were demonstrated in GCA patient temporal arteries by independent analytical techniques. Active GM-CSF signaling in diseased tissue is evidenced by increased expression of Pu.1 in the vessel wall. These data implicate the GM-CSF pathway in GCA pathophysiology and increase confidence in rationale for targeting GM-CSF in GCA.

References:

1. M-CSF and GM-CSF promote alveolar macrophage differentiation into multinucleated giant cells with distinct phenotypes. Lemaire *et al,* 1996. Journal of leukocyte biology, 60(4):509-18.
2. Targeting GM-CSF in inflammatory diseases. Wicks & Roberts, 2016. Nature reviews. Rheumatology, 12(1):37-48.
3. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. Weyand *et al,* 1994. Annals of internal medicine, 121(7):484-91.
4. Interleukin-21 modulates T_H1 and T_H17 responses in giant cell arteritis. Terrier *et al*, 2012. Arthritis and rheumatism, 64(6):2001-11.