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Inhibition of JAK-STAT Signaling Suppresses Pathogenic Immune Responses in Medium and Large Vessel Vasculitis

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BACKGROUND: Giant cell arteritis, a chronic autoimmune disease of the aorta and its large branches, is complicated by aneurysm formation, dissection, and arterial occlusions. Arterial wall dendritic cells attract $CD4^+$ T cells and macrophages to form prototypic granulomatous infiltrates. Vasculitic lesions contain a diverse array of effector T cells that persist despite corticosteroid therapy and sustain chronic, smoldering vasculitis. Transmural inflammation induces microvascular neoangiogenesis and results in lumen-occlusive intimal hyperplasia. We have examined whether persistent vessel wall inflammation is maintained by lesional T cells, including the newly identified tissue-resident memory T cells, and whether such T cells are sensitive to the cytokine-signaling inhibitor tofacitinib, a Janus kinase (JAK) inhibitor targeting JAK3 and JAK1.

METHODS: Vascular inflammation was induced in human arteries engrafted into immunodeficient mice that were reconstituted with T cells and monocytes from patients with giant cell arteritis. Mice carrying inflamed human arteries were treated with tofacitinib or vehicle. Vasculitic arteries were examined for gene expression (reverse transcription polymerase chain reaction), protein expression (immunohistochemistry), and infiltrating cell populations (flow cytometry).

RESULTS: Tofacitinib effectively suppressed innate and adaptive immunity in the vessel wall. Lesional T cells responded to tofacitinib with reduced proliferation rates (<10%) and minimal production of the effector molecules interferon-γ, interleukin-17, and interleukin-21. Tofacitinib disrupted adventitial microvascular angiogenesis, reduced outgrowth of hyperplastic intima, and minimized $CD4^+CD103^+$ tissue-resident memory T cells.

CONCLUSIONS: Cytokine signaling dependent on JAK3 and JAK1 is critically important in chronic inflammation of medium and large arteries. The JAK inhibitor tofacitinib effectively suppresses tissue-resident memory T cells and inhibits core vasculitogenic effector pathways.

Key Words: cytokines ■ giant cell arteritis ■ inflammation ■ Janus kinases ■ STAT transcription factors ■ T-lymphocytes ■ vasculitis

Sources of Funding, see page 1946

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Clinical Perspective

What Is New?

- Signal transducer and activator of transcription (STAT) 1 and STAT2 target genes, the transcription factors STAT1 and STAT2, and the STAT pathway activators type I and type II interferon are abundant in the tissue transcriptome of arteries with giant cell arteritis.
- The Janus kinase/STAT inhibitor tofacitinib suppresses the ex vivo induction of interferon-γ–positive T cells in patients with giant cell arteritis.
- Chimeric mice carrying human arteries and immune cells from patients with giant cell arteritis develop persistent vasculitis.
- In the chimeras, tofacitinib efficiently suppresses T-cell invasion into the artery, inhibits proliferation and cytokine production of vasculitogenic T cells, and curbs survival of artery-resident T cells.
- Tofacitinib treatment prevents neoangiogenesis and intimal hyperplasia in inflamed arteries.

What Are the Clinical Implications?

- The Janus kinase/STAT inhibitor tofacitinib effectively targets multiple disease-relevant processes in inflammatory vasculopathy and represents a potential disease-modifying agent.

Vasculitides of large elastic arteries are infrequent but potentially fatal diseases, damaging vital blood vessels, such as the aorta, the subclavian-axillary bed, the carotid branches, and mesenteric arteries. Giant cell arteritis (GCA) accounts for most cases of autoimmune large vessel vasculitis, typically causing vision loss, aortic arch syndrome, aortic dissection, and aortic aneurysms. Extravascular GCA, consisting of an intense hepatic acute-phase response, gives rise to highly elevated laboratory markers of inflammation. Whether the hepatic acute-phase response precedes or follows vascular inflammation is unresolved. GCA is a chronic condition, which persists despite long-term therapy with high-dose corticosteroids,[1,2] and disease risk genes have been localized to multiple biological pathways.[3]

CD4+ T cells and macrophages dominate the transmural lesions of this granulomatous vasculitis. Arterial wall dendritic cells function as gatekeepers and by providing access to invading T cells and macrophages fail to protect the artery's immune privilege.[4,5] In GCA arteries, wall-resident dendritic cells express low concentrations of the immunoinhibitory ligand PD-L1, disarming the protective PD-1 immune checkpoint.[6,7] Tissue-infiltrating CD4+ T cells are PD-1+, yet are highly activated, are nonexhausted, and cover multiple effector functions. Most prominent are tissue T helper (Th) 1 and Th17 cells, but interleukin (IL)–21— and IL-9–producing T cells are also present.[8,9] Heterogeneous T-cell effector populations in the lesions are indicative of an unopposed T-cell response.

GCA's chronicity suggests a role for tissue-resident memory T cells (T_{RM}), a recently discovered T-cell lineage residing in tissues, where they provide fast and powerful helper functions.[10] Different from central memory and effector memory T cells, T_{RM} cells receive localizing signals in the tissue niche and do not recirculate to secondary lymphoid organs. Two phenotypic markers, CD69 and CD103 (a receptor recognizing E-cadherin), have been identified.[11] T_{RM} cells in E-cadherin^{low} tissues lacking epithelium possibly express alternative markers, such as type I collagen receptors. Originally considered crucial for rapid antipathogen responses, T_{RM} cells may also drive autoimmune tissue inflammation.[12] Functional heterogeneity, being able to release interferon (IFN)–γ, IL-17, IL-9, and tumor necrosis factor–α, enables the proinflammatory effector functions of T_{RM} cells.[13] Tissue-derived IL-7, IL-15, and transforming growth factor–β are believed to guide T_{RM} recruitment, differentiation, and maintenance.[13] Whether T_{RM} cells are involved in building and sustaining GCA's granulomatous lesions and the arterial wall remodeling process is unknown.

T cells depend on signals through their T-cell receptor, but require input from the cytokine milieu to direct their clonal expansion, persistence, and functional differentiation. Environment-cell communications rely on cytokine signals that trigger the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway.[14] The JAK/STAT signaling pathway has been implicated in cancer cell growth and autoimmunity.[15] Th1 lineage commitment is strictly linked to STAT1- and STAT4-mediated gene induction.[16] STAT3 is considered the master regulator for Th17 cell differentiation. Gene polymorphisms encoding type I cytokine receptors and their signaling elements (IL-23R, IL-12B, JAK2, and STAT3) are linked to inflammatory bowel diseases and psoriasis.[17] STAT4 polymorphisms are associated with rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus.[18,19] The critical role of JAK/STAT in immune-mediated disease has been therapeutically exploited with the development of JAK inhibitors (Jakinibs), small-molecule inhibitors that block the action of type I/II cytokines. The JAK3/1 inhibitor tofacitinib[20] has been approved for rheumatoid arthritis treatment.[21] JAK3-activating mutations in T-cell acute lymphoblastic leukemia and JAK3-inactivating mutations in severe immunodeficiency emphasize the critical role of JAK3 in T-cell biology.[22,23] Most prominently, JAK3 inactivation results in the loss of function of the common γ-chain (γc), causing X-linked severe combined immunodeficiency.[23,24] Cytokines central in regulating T-cell activa-