Sympathetic Nerve-driven CD200-CD200R1 Interactions Between Macrophages And Endothelial Cells In Sustained Prosthetic Joint Infection

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INTRODUCTION: Chronic infections, stress, and inflammation can activate the sympathetic nervous system (SNS), which modulates immune responses through the release of neurotransmitters such as norepinephrine (NE). Periprosthetic joint infection (PJI) remains a severe complication following total joint arthroplasty. Although surgical interventions, such as one- or two-stage revision with thorough irrigation, are among the most effective treatments, many patients experience recurrent infections, suggesting the presence of a localized immunosuppressive microenvironment in PJI. In this study, we identified localized SNS activation in PJI patients. Disruption of SNS activity in a PJI mouse model significantly reduced bacterial burden. Moreover, pharmacological inhibition of the beta-2 adrenergic receptor (β2AR) or application of a CD200R1-blocking antibody replicated these effects.

METHODS: To investigate sympathetic activation and receptor expression in PJI, we performed IHC and ELISA on synovial tissues from patients with PJI and aseptic failure (AF). Additionally, we analyzed single-cell RNA sequencing data from synovial tissues of PJI patients, derived from our previous studies. We established a PJI mouse model and a chemically sympathectomized PJI mouse model using 6-hydroxydopamine (6-OHDA). Synovial bulk RNA sequencing was conducted to evaluate changes in immune cell phenotypes within the tumor microenvironment. In vitro, THP-1 and HUVEC cell lines were stimulated with a β2-adrenergic receptor (β2AR) agonist, followed by Western blot, qRT-PCR, and co-immunoprecipitation (Co-IP) analyses. Finally, we treated PJI mice with intra-articular injections of a β2AR inhibitor combined with antibiotics to assess therapeutic outcomes.

RESULTS: Immunohistochemical staining for tyrosine hydroxylase (TH) in synovial tissues and ELISA analysis of serum and synovial fluid from patients with PJI and AF revealed heightened sympathetic activation in PJI patients, with even greater activation in those with recurrent infections. To investigate the role of sympathetic innervation in PJI, we established a PJI mouse model following chemical sympathectomy with 6-hydroxydopamine (6-OHDA). Compared to controls, 6-OHDA-treated mice exhibited significantly reduced bacterial burden, improved bone density, and decreased biofilm formation. Bulk RNA sequencing of synovial tissues showed upregulated phagocytosis-related genes and downregulated immunosuppressive genes in the 6-OHDA group. Notably, treatment with propranolol, a β-adrenergic receptor antagonist, yielded effects similar to 6-OHDA. Reanalysis of single-cell RNA sequencing data from PJI patient synovia revealed that immune cells, particularly macrophages, predominantly expressed ADRB2 (β2-adrenergic receptor). Further analysis of ADRB2+ macrophages indicated high expression of CD200R1, while its ligand, CD200, was primarily expressed on endothelial cells. Given reports that the CD200-CD200R1 axis inhibits macrophage phagocytosis, we conducted in vitro experiments using THP-1 macrophages and HUVEC endothelial cells. Stimulation of β2-adrenergic receptors activated the cAMP-PKA-CREB pathway, upregulating CD200R1 expression in macrophages and CD200 expression in endothelial cells. Co-culture of β2-agonist-stimulated HUVECs or recombinant CD200 with β2-agonist-stimulated THP-1 cells significantly impaired macrophage phagocytosis and downregulated phagocytosis-related gene expression. Finally, intra-articular injection of a β2-adrenergic receptor inhibitor or CD200R1-blocking antibody combined with antibiotics in PJI mice significantly reduced bacterial burden, biofilm formation, and inflammation compared to antibiotic treatment alone.

DISCUSSION: PJI is a severe complication following total joint arthroplasty. In this study, we identified SNS activation in PJI patients, with a notable correlation to infection recurrence. While prior studies have reported the regulatory roles of sensory and sympathetic nerves in immune responses, their specific contributions to PJI remain unexplored. Chronic SNS activation, triggered by factors such as stress, emotions, or infections, modulates the immune system through the release of NE. Using a chemically sympathectomized PJI mouse model induced by 6-OHDA, we demonstrated that suppressing SNS activity improves PJI outcomes, evidenced by reduced bacterial burden, attenuated inflammation, decreased biofilm formation, and ameliorated bone erosion. Previous research has established CD200R1 as an immune checkpoint on macrophages, where its interaction with CD200, expressed on tumor cells, impairs phagocytosis and promotes M2 polarization. Similarly, we found that β2AR activation upregulates CD200R1 expression in macrophages via the cAMP-PKA-CREB signaling pathway, with its ligand CD200 specifically expressed on endothelial cells. This CD200-CD200R1 interaction suppressed macrophage phagocytosis in vitro. In our PJI mouse model, intra-articular administration of a β2AR inhibitor or CD200R1-blocking antibody, combined with antibiotics, significantly reduced bacterial burden, inflammation, and biofilm formation compared to antibiotics alone. These findings highlight the immunomodulatory role of SNS in PJI and suggest that targeting the β2AR-CD200-CD200R1 axis may offer novel immunotherapeutic strategies for PJI management.

CLINICAL RELEVANCE: The sympathetic activation in PJI patients is one of the reasons for their chronic persistent infection. Local or systemic use of β 2 receptor inhibitors can enhance the efficacy of antibiotic treatment for PJI.