Periprosthetic Joint Infection and Immunity – Understanding the Host

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Introduction: Periprosthetic joint infection (PJI) is a serious complication of total joint arthroplasty. Even with current treatments, failure rates are still quite high with a 5-year mortality rate of 26%. Majority of the literature in the field has focused on development of better tools for diagnostics and treatment strategies including innovate antibiotic delivery systems, anti-biofilm agents, and bacteriophages. Nevertheless, the role of the immune system, which is supposed to be the first line of defense, during PJI is not fully understood. Can understanding immune system fate during biofilm associated PJI and how to reverse or block purported pathogenic pathways lead to better outcomes in PJI?

Methods: A literature search was conducted using PubMed from 1995-2023 to identify reports on immune system function *in vitro*, *in vivo* animal models, and in clinical studies in periprosthetic joint infection with orthopaedic relevant bacteria.

Results: Immune cell products are found within the circulation, synovial fluid, and tissue during infection including cytokines, byproducts, antimicrobial peptides, and soluble receptors, many of which are part of the workup for PJI diagnosis. Biofilm-associated bacteria can modulate host responses directly or indirectly at multiple levels. The major population recruited into the joint during infection are anti-inflammatory myeloid derived suppressor cells (MDSCs) which decrease proliferation of inflammatory populations and promote anti-inflammatory populations including M2 macrophages. Bacteria are able to block effector functions by inhibiting receptor interactions, degrading effector products, and intracellular survival (Figure 1).

Discussion: Host immune cells and microbial interactions have been extensively researched in animal models but how this correlates with human infection needs to be further clarified. Nevertheless, effector functions by the immune system are severely inhibited leading to a chronic infection.

Significance/Clinical Relevance: Understanding the shortcomings and mechanisms by which bacteria can subvert the immune system may open new avenues to harbor our own immune system to combat PJI.

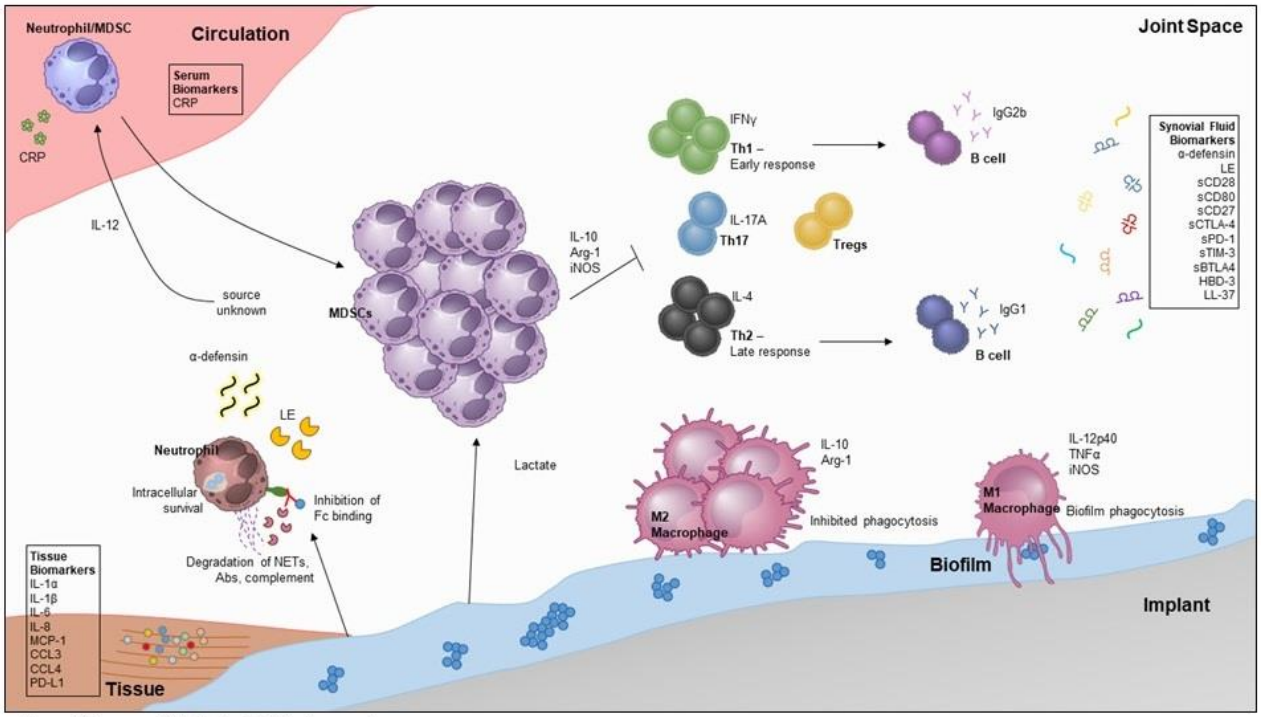

Figure 1. Immune Cells in the PJI Environment
Immune cell products are found within the circulation, synovial fluid, and tissue during infection including cytokines, byproducts, antimicrobial peptides, and soluble receptors, many of which are part of the workup for PJI diagnosis. Biofilm associated bacteria are able to modulate host responses directly or indirectly at multiple levels. The major population recruited into the joint during infection are MDSCs which decrease proliferation of inflammatory populations and promote anti-inflammatory populations including M2 macrophages. Bacteria are able to block effector functions by inhibiting receptor interactions, degrading effector products, and intracellular survival. LE – Leukocyte Esterase, CRP – C-reactive protein, MDSC – Myeloid derived suppressor cell, Th – T helper, IL – Interleukin, IgG – Immunoglobulin, CD – Cluster of differentiation, Abs – Antibodies, NETs – Neutrophil extracellular traps, Arg – Arginase, iNOS – Inducible nitric oxide synthase, TNF – Tumor necrosis factor, PD-L1 – Programmed death ligand 1, CCL – Chemokine (C-C motif) ligand, MCP – Monocyte chemoattractant protein, CTLA - Cytotoxic T-lymphocyte-associated protein, TIM – T cell membrane protein, BTLA – soluble B and T lymphocyte attenuator, HBD – human beta-defensin, LL – cathelicidin.