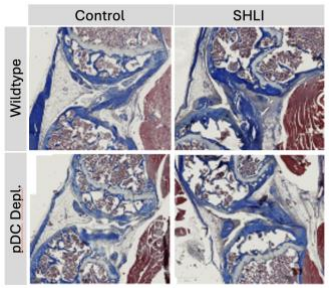
Abstract: Plasmacytoid dendritic cells contribute to the establishment of periarticular fibrosis in the SHLI model.

Anne Consalus[1], Marie Dominique Ah Kioon,[1] Raylin Xu[1,2], Laura Moore[1,2], Franck Barrat[1]
[1]HSS Research Institute, Hospital for Special Surgery, New York, New York, [2]Department of Orthopedic Surgery, Hospital for Special Surgery, New York, New York

INTRODUCTION: Fibrosis is a biological process by which the body responds to injury by depositing extracellular matrix, leading to scar formation. However, under certain conditions, this physiologic process can become dysregulated.[1] Pathologic joint fibrosis, also known as arthrofibrosis, is a condition characterized by excessive deposition of extracellular matrix[2] and may occur following injury, surgery, or immobilization.[3] Previous work has demonstrated that the mouse single hindlimb immobilization (SHLI) is a robust model with many similarities with the human condition. In this model system, knee immobilization leads to robust fibrosis of both the anterior and posterior knee joint.[4] Recent studies have highlighted the role of plasmacytoid dendritic cells (pDCs) in pulmonary and dermal fibrosis, particularly in systemic sclerosis.[5] pDCs are rare but highly secretory cells immune cells capable of driving a robust inflammatory and fibrotic response, through cytokines such as interferon. Previous work has demonstrated that depletion of pDCs protects mice from developing skin fibrosis, reducing collagen deposition and myofibroblasts activation. The aim of this pilot study is to investigate the role of plasmacytoid dendritic cells in arthrofibrosis.

METHODS: Age-matched male C57BL/6J and their littermate BDCA2-DTR mice aged between 13 and 16 weeks underwent single hindlimb immobilization for 3 weeks using a custom 3D-printed clamshell cast to induce arthrofibrosis. Three days prior to hindlimb immobilization and twice per week during the immobilization period, pDCs were depleted in BDCA2-DTR mice by intra-peritoneal (i.p) injection of diphteria toxin. Casts were changed weekly and hindlimbs were released at 3 weeks. Mice were euthanized 4 days after cast release and tissues were harvested for histology and immunohistochemistry. Mouse knee joints were fixed in 4% formaldehyde, decalcified in EDTA and embedded in paraffin for sectioning. Serial 5µm sections were stained with hematoxylin and eosin (H&E), Masson's Trichrome and Picrosirius Red for histological analyses. Histological quantification was done using ImageJ and statistis in GraphPad Prism.

RESULTS: Preliminary results show that depletion of pDCs reduces arthrofibrosis in the SHLI model. Histological results show that the area of fibrosis is smaller in the immobilized limb of pDC-depleted mice compared to the immobilized limb of control mice. This is associated with less deposition of collagen in the immobilized limb of pDC-depleted mice as compared to the wild-type controls. There are no notable differences in the control limb for intra-articular fibrosis.



DISCUSSION: Previous work on pDCs indicate that these cells may play a key role in the pathogenesis of systemic sclerosis by secreting type 1 interferon. While inflammatory cytokines have previously been implicated in the development of pathogenic joint fibrosis, their origin remains unclear. This preliminary work implicates pDCs as a key effector cell in the development of arthrofibrosis. These results are of additional interest as pDCs have predominantly been studied in autoimmune conditions and infections, and the mouse SHLI model does not rely on immune modulation.

CLINICAL RELEVANCE: Despite advances in musculoskeletal medicine, the prevention and management of joint stiffness remains an unresolved challenge and remains a significant clinical issue for patients following injury, immobilization, or operation due to impaired mobility and quality of life. The underlying pathogenesis for arthrofibrosis is not well understood, and there are currently no specific markers for diagnosing this disease, which complicates patient management as well as the development of novel treatments. pDCs represent a novel target for both the diagnosis and treatment of arthrofibrosis. Importantly, pDC targeting therapeutics are currently in development and have shown efficacy in both preclinical data[6] and a phase 3 clinical trials for lupus.[7]

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