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TITLE: **Endogenous and Exogenous Pericytes in the Pathobiology and Treatment of Osteoarthritis**

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14. ABSTRACT
Pdgfrb transgenic reporter animals represent a tool for the visualization of pericytes within joint associated tissues. Destabilization of the medial meniscus in the mouse induces osteoarthritic changes associated with dynamic changes in the vasculature and Pdgfrb reporter activity within the infrapatellar fat pad. These changes implicate endogenous pericytes as a key cellular player in post-traumatic osteoarthritis.

15. SUBJECT TERMS
Osteoarthritis, post-traumatic osteoarthritis, pericyte, perivascular cell

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1. INTRODUCTION:

Pericytes have mesenchymal stem cell (MSC)-like properties and perform critical roles in immune regulation in diverse organ systems. The current project seeks to explore the entirely novel hypotheses that: *(1)* endogenous synovial pericytes may exert protective / immunomodulatory effects in osteoarthritis (OA), and *(2)* intra-articular administration of purified pericytes will improve OA disease progression. Aim 1 seeks to develop and evaluate a post-traumatic osteoarthritis model within pericyte reporter mice. Next, Aim 2 evaluate the therapeutic potential of intra-articular pericyte delivery in mouse post-traumatic osteoarthritis.

2. KEYWORDS:

Arthritis, osteoarthritis, post-traumatic osteoarthritis, PTOA, inflammation, pericyte, perivascular stem cell, mesenchymal stem cell, MSC, immunomodulation, platelet derived growth factor receptor beta, PDGFRB.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

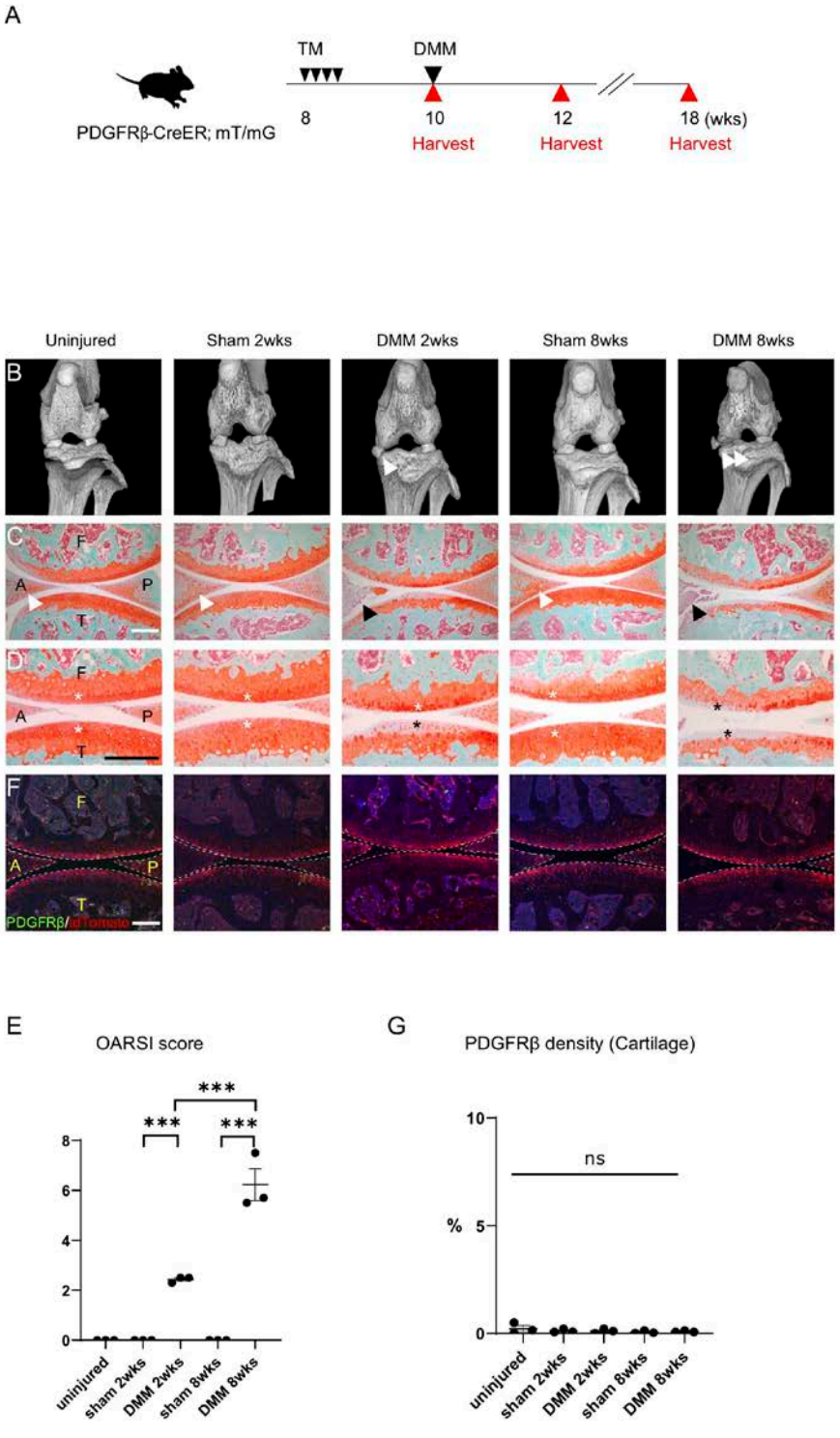
Major Task 1: Develop PTOA model in pericyte reporter animals
- 90% complete, estimated completion date: 08/15/2019.

Major Task 2: Determine the therapeutic potential of intra-articular pericyte injection.
- 80% complete, estimated completion date: 12/31/2019.

What was accomplished under these goals?

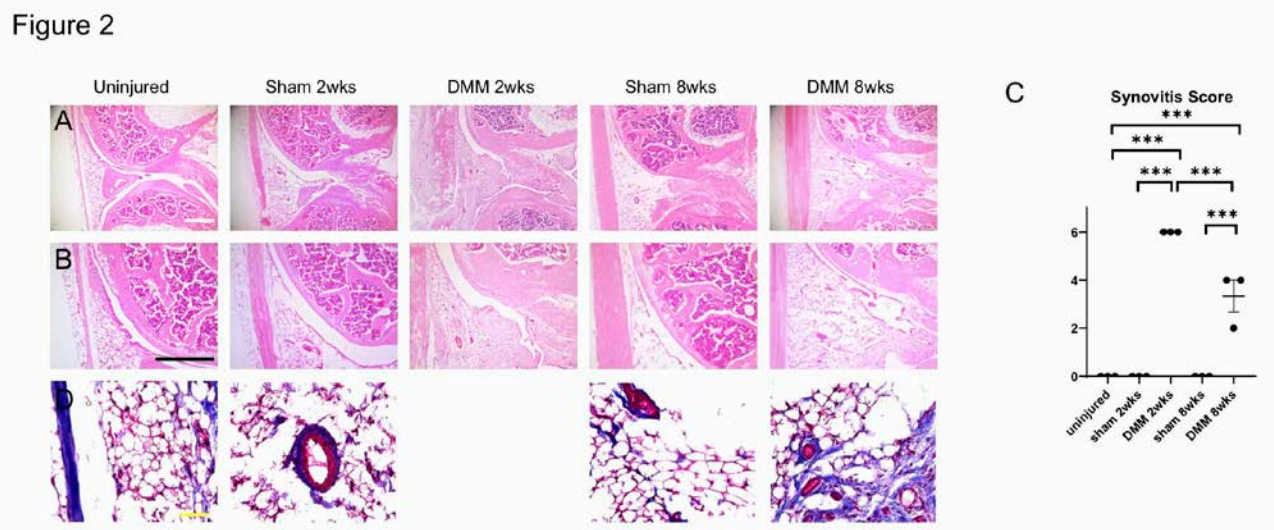
1) Major activities
    a. In the first year of this Discovery award, and in reference in major task 1 we have used a Pdgfrb reporter animal in order to develop a pericyte reporter in a model of PTOA. We have examined Pdgfrb reporter activity within the stifle joint under uninjured, sham operated, or PTOA conditions (destabilization of the medial meniscus). As we will discuss, we have demonstrated that inducible Pdgfrb reporter mice represent a method to perform lineage tracing for pericytes within the joint-associated subsynovial tissue. Further, we have observed dynamic changes in domains of Pdgfrb+ cellular descendants after DMM surgery. We have also determined that Pdgfrb reporter activity is not entirely specific to pericytes, and that reporter activity exists in other cell types within the joint, including most ligamentous cells and a small portion of synoviocytes.
    b. In reference to major task 2, we have isolated and applied Pdgfrb+ pericytes to the stifle joint of sham- or DMM-operated animals. Animal surgeries have been conducted, and histologic analysis is ongoing (Major task 2, subtask 3).
2) Specific objectives
    a. Our first specific objective was to evaluate an inducible Pdgfrb reporter mouse as a pericyte reporter within the stifle joint. As we will describe, Pdgfrb reporter activity is highly localized to pericytes, but is also found in a ligamentous cells and a portion of synoviocytes. Therefore, Pdgfrb reporter mice appear to be a strong pericyte reporter, but also highlight other joint-associated cells.
    b. Our second objective was to map Pdgfrb reporter activity among sham-operated and DMM-operated conditions. As we will describe, DMM induced a dramatic change in Pdgfrb reporter activity. DMM induced microvascular proliferation within the subsynovium, with a concordant proliferation of Pdgfrb+ descendants.
    c. Our third objective was to isolate and apply Pdgfrb+ pericytes so as to mitigate DMM induced cartilage damage. We found that the isolation, purification, and culture propagation of Pdgfrb+ pericytes was feasible. Ongoing analyses are determining the phenotypic consequences of Pdgfrb+ cell therapy.
3) Significant results
    a. First, we confirmed that Pdgfrb reporter animals undergoing degenerative changes after destabilization of the medial meniscus (DMM) surgery (Fig. 1). For these experiments, tamoxifen (TM) was administered to Pdgfrb-CreER ; mT/mG transgenic mice according to a previously validated schedule at 8 weeks of age (Fig. 1A). Thereafter, animals were subjected to DMM or sham surgery at 10 weeks of age, and analyzed 2 and 8 weeks thereafter. Microcomputed tomography of the stifle joint confirmed destabilization of the medial meniscus among the DMM treatment groups at 2 and 8 weeks post-operative (Fig. 1B, white arrowheads). Sagittal histologic sections of the joint were next stained with Safranin O / Fast Green (Fig. 1C,D). Results confirmed a significant and progressive loss of Safranin O staining among DMM but not sham operated animals, which was most notable within the proximal tibial articular cartilage (T), but also evident within the distal femoral cartilage (F). Pdgfrb reporter activity was examined across samples (Fig. 1E). Overall and as expected, minimal Pdgfrb reporter activity was observed among articular chondrocytes or bone-associated cells. Confirmation of degenerative changes was further obtained using the OARSI scoring system (Fig. 1F). Finally, lack of Pdgfrb reporter activity within articular chondrocytes was confirmed quantitatively (Fig. 1G).

Figure 1


A
TM
DMM
PDGFRβ-CreER; mT/mG
8
10
Harvest
12
Harvest
18 (wks)
Harvest
Uninjured
Sham 2wks
DMM 2wks
Sham 8wks
DMM 8wks
B
C
D
F
F
A
P
T
PDGFRβ/tdTomato
E
OARSI score
***
***
***
uninjured
sham 2wks
DMM 2wks
sham 8wks
DMM 8wks
G
PDGFRβ density (Cartilage)
ns
%

b. Having confirmed osteoarthritic changes after DMM, we next examined in detail the histologic changes within the infrapatellar fat pad (IFP) after either sham or DMM surgery. For this purpose, sagittal sections of the knee joint were obtained at the level of the posterior cruciate ligament after either sham or DMM surgery (Fig. 2). Results using routine H&E stained sections showed dynamic changes in the appearance of the IFP (Fig. 2A,B). At two weeks after DMM, an inflammatory infiltrate was noted in the IFP, composed primarily of mononuclear inflammatory cells. At 8 weeks after DMM, increased fibrosis of the IFP was noted. Inflammatory changes within the IFP and overlying synovium were next quantified using a semi-quantitative scoring system (Fig. 2C). Synovitis score was highest at 2 weeks post DMM, and remained elevated above baseline at 8 weeks post DMM (Fig. 2C). Immunohistochemical confirmation of the cell composition of the inflammatory infiltrate is ongoing. In comparison and as expected, no significant synovitis was observed among uninjured or sham operated animals. Fibrotic change within the IFP was next confirmed by Masson's Trichrome staining (Fig. 2D). Here fibrotic change was most notable within the IFP at 8 weeks post DMM, while not observed under uninjured or sham operated conditions.

Figure 2



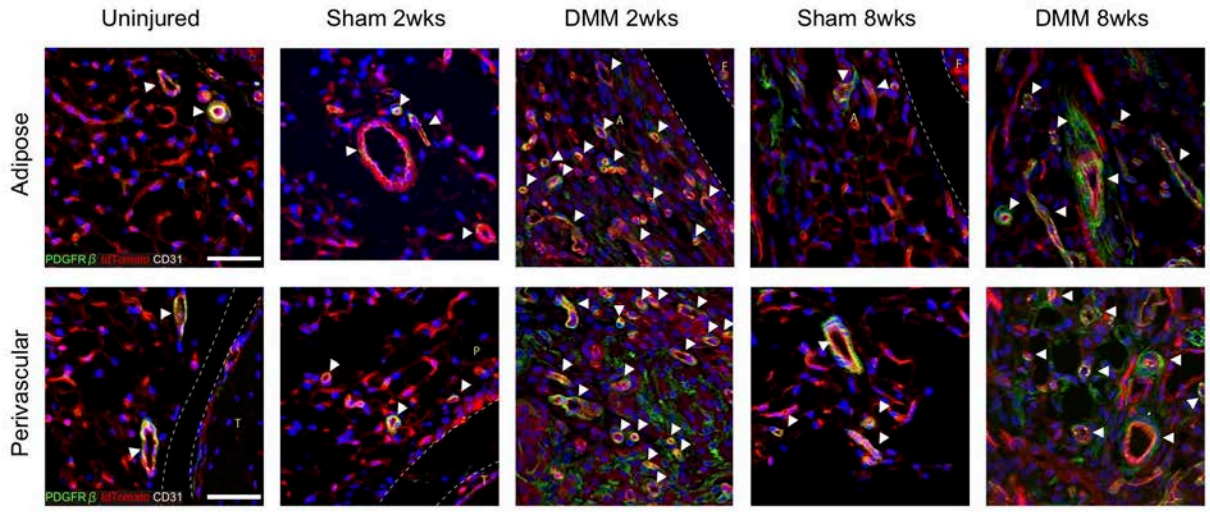
c. Having confirmed temporally patterned changes within the IFP elicited by DMM surgery, we next set out to examine pericyte reporter activity within the IFP using Pdgfrb reporter animals. For this purpose, the IFP was separated for analysis into adipose and perivascular areas (Fig. 3). Immunohistochemical staining for CD31 was performed to mark endothelium (appearing red), while Pdgfrb reporter activity appears green. Under uninjured conditions within the IFP, Pdgfrb reporter activity was found essentially exclusively within an abluminal 'pericytic' location. These findings were essentially confirmed among the IFP of sham-operated animals at both 2 and 8 weeks post-operative. In contrast, vascular changes and perivascular reporter activity showed dynamic changes after DMM surgery. At two weeks, numerous thin-caliber, capillary type vessels were observed within the IFP, either within adipose or perivascular locations (white arrowheads, middle column). These apparent increase in microvascular density was accompanied by a robust increase in the number of Pdgfrb reporter positive cells. Interestingly, DMM induced a significant expansion of Pdgfrb positive cellular descendants which was most notable at 2 weeks post-destabilization. Interestingly, cellular descents of Pdgfrb reporter positive cells were frequent both in a pericytic location, but also in cells completely unassociated with microvessels. Similar observations were observed at 8 weeks after DMM (far right column). Here, microvessels were still more apparent in comparison to uninjured or sham-operated conditons. Pericyte Pdgfrb reporter activity was likewise increased over baseline. Again, both vascular-associated with non-vascular mGFP reporter activity was observed. These findings led us to several conclusions:

1 – Pdgfrb reporter activity is specific to pericytes within the infrapatellar fat pad

2 – Minimal changes in vascular patterning or Pdgfrb reporter activity are seen within sham-operated conditions.

3 – DMM induces temporally dynamic changes in vascular patterning and Pdgfrb reporter activity, including a pronounced microvascular proliferation accompanied by expansion of Pdgfrb reporter activity.

Figure 3



d. These qualitative changes in vascular patterning as well as cellular descendants of Pdgfrb-expressing pericytes induced by DMM were next quantified by histomorphometric analysis. First, vascular histomorphometry was performed on serial sections of IFPs under each treatment condition (Fig. 4A-C). Vascular histomorphometry was performed specifically within adipose areas (left column), perivascular areas (middle column), or total area (right column). A significant increase in vascular numbers per high powered field was observed at both 2 and 8 weeks post DMM in comparison to either uninjured or sham-operated conditions (Fig. 4A). No statistically significant changes in mean vascular density were found (Fig. 4B). Total vascular area showed a significant increase at both 2 and 8 weeks post DMM in comparison to either uninjured or sham-operated conditions (Fig. 4C). Pdgfrb pericyte reporter activity was next quantitatively examined within the IFP under each treatment condition and timepoint (Fig. 4D-F). Consistent with our prior observation, the density of Pdgfrb reporter activity was most notably increased at 2 weeks post DMM (Fig. 4D). A non-significant trend toward increased Pdgfrb reporter activity was also seen at 8 weeks post-DMM (Fig. 4D). The density of Pdgfrb reporter activity that was not associated with the vasculature was next quantified (Fig. 4E). Consistent with our prior observations, uninjured animals essentially showed minimal non-vascular Pdgfrb reporter activity within the IFP. These findings of rare to absent non-vascular reporter activity were likewise observed under sham-operated conditions. In contrast, significant increased numbers of non-vascular Pdgfrb reporter activity was observed at 2 weeks post-DMM (Fig. 4E). This remained elevated above baseline at 8 weeks post-DMM, albeit without statistical significance (Fig. 4E). Finally, the frequency of Pdgfrb+ pericytic coverage of microvessels within the IFP was assessed (Fig. 4F). Under uninjured conditions, essential 100% coverage of microvessels by Pdgfrb+ pericytes was observed. These findings of near universal Pdgfrb+ pericyte coverage were conserved among sham-operated animals. In contrast, Pdgfrb+ pericytic coverage was reduced after DMM. This finding was most notable at 2 weeks after injury, but found at 8 weeks post-DMM as well.

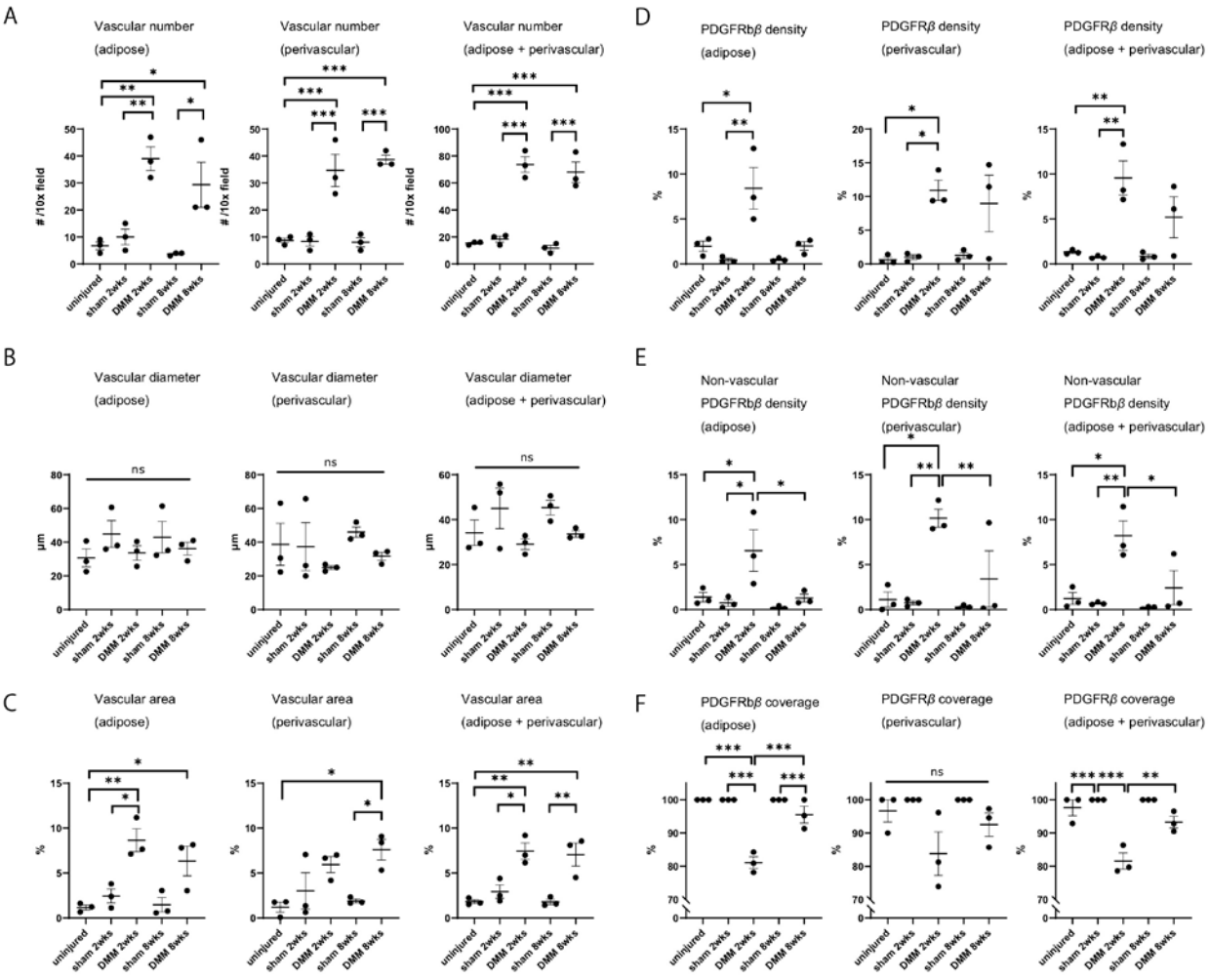
These findings led us to several conclusions:

1 – Pdgfrb-expressing pericyte coverage is a near universal feature of microvessels within the IFP at baseline.

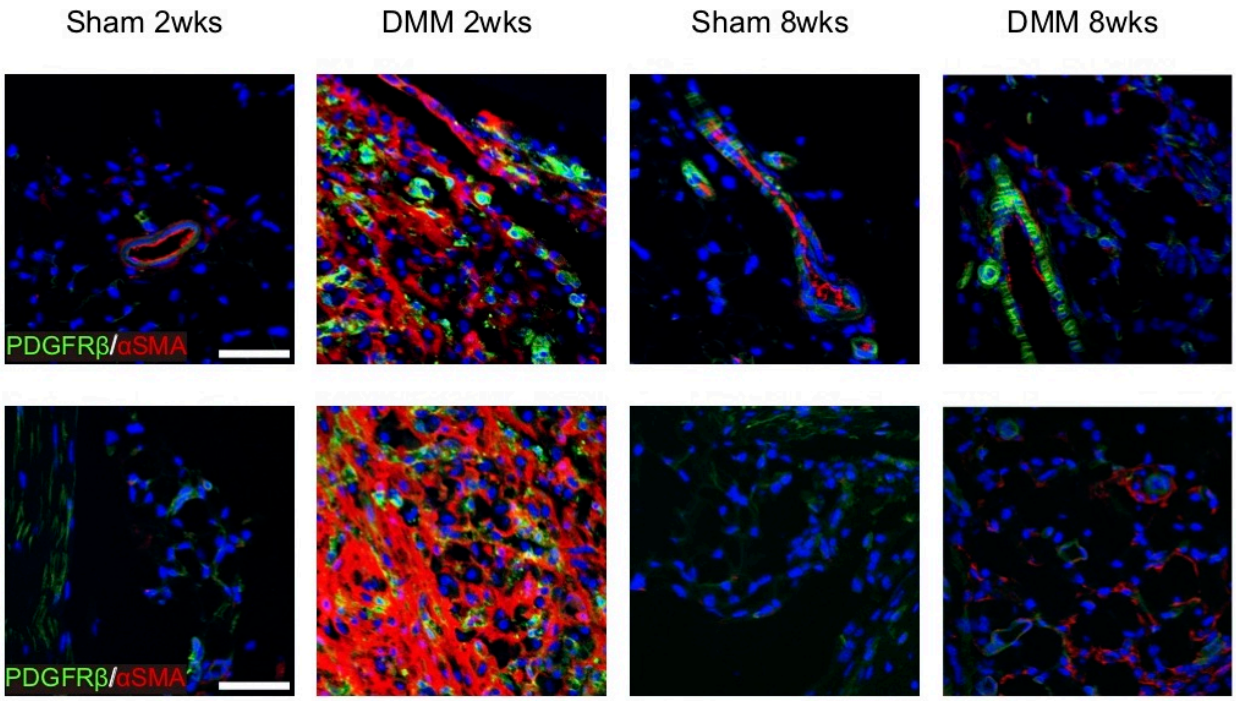
2 – DMM induces acute changes in the IFP at two weeks post-injury, including increases in microvascular density and area, accompanied by increased dettachemnt of Pdgfrb-expressing cellular descendants from vessel walls, and reduced coverage of vessels by Pdgfrb-expressing pericytes.

3 – Finally, timepoint corresponding to later cartilage catabolism demonstrate further vascuarl changes, including a sustained increase in vascular numbers and vascular area, but also a n apparet ‘maturation’ of blood vessels, with reduced non-vascular Pdgfrb-expressing cells, and a return to Pdgfrb-expressing pericyte coverage of IFP microvessels.

Figure 4

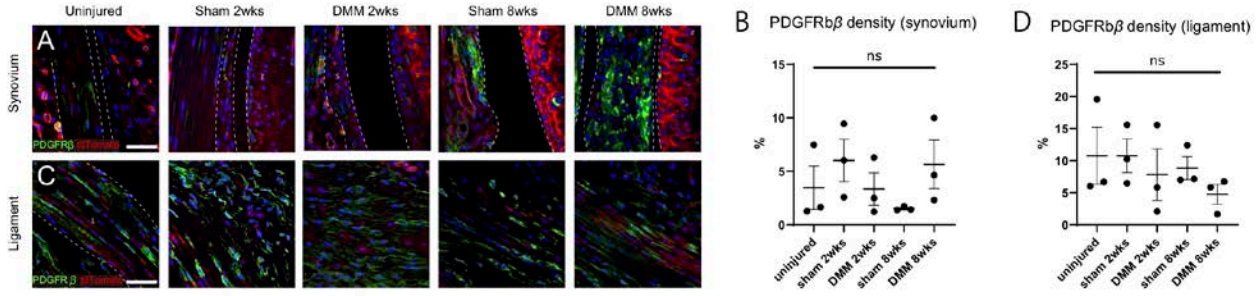

A
Vascular number (adipose)
Vascular number (perivascular)
Vascular number (adipose + perivascular)
/10x field
B
Vascular diameter (adipose)
Vascular diameter (perivascular)
Vascular diameter (adipose + perivascular)
ns
μm
C
Vascular area (adipose)
Vascular area (perivascular)
Vascular area (adipose + perivascular)
%
D
PDGFRbβ density (adipose)
PDGFRβ density (perivascular)
PDGFRβ density (adipose + perivascular)
E
Non-vascular PDGFRbβ density (adipose)
Non-vascular PDGFRbβ density (perivascular)
Non-vascular PDGFRbβ density (adipose + perivascular)
F
PDGFRbβ coverage (adipose)
PDGFRβ coverage (perivascular)
PDGFRβ coverage (adipose + perivascular)
uninjured
sham 2wks
DMM 2wks
sham 8wks
DMM 8wks

e. Our findings thus far suggested that DMM induces Pdgfrb+ pericyte vascular detachment and expansion within the IFP, which was followed by fibrotic change of the IFP. These findings suggested the potential transdifferentiaton of Pdgfrb-expressing pericytes to myofibroblasts within the IFP. To begin to investigate this possibility, immunohistochemistry for Smooth Muscle Actin (SMA) was performed on the IFP of sham-operated or DMM-operated animals (Fig. 5). Results among sham-operated animals showed that SMA immunostaining highlighted only a thin-rim of tissue within a pericytic / perivascular location (observed at both 2 and 8 weeks after sham-surgery). In marked contrast, a high density of SMA immunoreactivity was observed at 2 weeks post-DMM, again corresponding to non-vascular mGFP/Pdgfrb reporter activity. At 8 weeks post DMM, some residual SMA immunohistochemical staining was observed within non-vascular components of the IFP. Thus, transient and robust SMA expression is observed within pericyte descendants within the IFP. These findings are suggestive of pericyte-to-myofibroblast transdifferentiation within the IFP elicited by destabilization surgery, which will be further pursued using additional markers of putative myofibroblasts. These findings will also be confirmed by ongoing flow cytometry examination of Pdgfrb+ cells within the IFP.



f. The specificity of Pdgfrb reporter for putative ‘pericytes’ within joint-associated tissues was next assessed. Previously we found that Pdgfrb reporter activity was indeed a highly specific marker of ‘pericytes’ within the IFP. Our findings did however show that Pdgfrb reporter activity was present in other cell types within joint-associated tissues. First, a small population of synoviocytes demonstrated Pdgfrb reporter activity (Fig. 6A,B). Interesting, a slight and non-signficant increase in numbers of Pdgfrb+ synoviocytes was observed after DMM surgery, especially at the 8 week timepoint. Second, a significant portion of intra-articular ligamentous cells were found to have Pdgfrb reporter activity (Fig. 6C,D). No significant changes in Pdgfrb frequency within ligamentous cells was observed across treatment groups or timepoints. In summary, transgenic Pdgfrb reporter animals represent an excellent means to track pericytic cells within the IFP. As with many reporter animal, however, cell types within our tissue compartments also demonstrate reporter activity, and care must be taken to appropriately interpret histologic findings.

Figure 6



4) Other achievements
No additional.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

Regarding Aim 1 studies, additional studies are in progress, including (1) the analysis of inflammatory cell quantity, composition and distribution within Pdgfrb reporter sections, as well as (2) the FACS isolation of mGFP+ pericytes followed by immunomodulatory cytokines expression by qPCR. Regarding Aim 2 studies, additional studies are underway, including the delivery of Pdgfrb+ pericytes to the stifle joint among DMM or sham operated mice, followed by an assessment of joint damage severity, inflammatory cells, and pericyte persistence and distribution.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

Our findings that dynamic vascular and perivascular changes occur in joint-associated tissue during the progression of osteoarthritis. Interestingly, these changes are somewhat transient and occur at early stages that precede the more obvious changes in cartilage degradation. These findings call into question the potential contributory / paracrine roles of Pdgfrb+ pericytes and their descendants in cartilage damage.

What was the impact on other disciplines?

Our findings strongly suggest that tissue injury induces a pericyte-to-myofibroblast transdifferentiation, and that transgenic Pdgfrb reporter animals represent an excellent tool to examine this phenomenon. This has significant potential impact in other disease of fibrosis, including wound healing or fibrosis of internal organs such as the liver, lung or kidney.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Over the last year, we have noted that our transgenic Pdgfrb reporter animals do not have large litter sizes and have a lower frequency than otherwise expected of Cre^+ animals. For this reason, major task 1 subtask 3 has been modestly delayed and we anticipate completion by month 18. This is countered by more rapid completion of major task 2 subtask 3, which is ahead of our estimated completion date.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Aaron W. James*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-2002-622X
Nearest person month worked:	*1*
Contribution to Project:	*Dr. James is responsible for the overall conduct of the project.*
Funding Support:	*NIH, DoD, American Cancer Society, MTF Biologics, Maryland Stem Cell Research Fund.*
Name:	*Carolyn Meyers*
Project Role:	*Research Technologist*
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-0734-029X
Nearest person month worked:	*12*
Contribution to Project:	*Carolyn is responsible for all technical aspects of the project, including performing histology, cell culture, and animal studies.*
Funding Support:	*None.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

Endogenous and Exogenous Pericytes in the Pathobiology and Treatment of Osteoarthritis

PR170080

W81XWH-18-0121

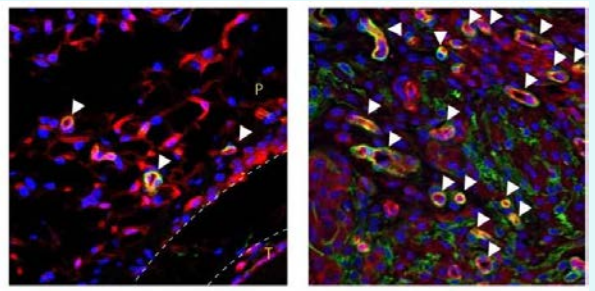
PI: Aaron W. James, MD, PhD **Org:** Johns Hopkins University **Award Amount:** $322,680

Study/Product Aim(s)

- Develop PTOA model in pericyte reporter animals (Aim 1)
- Determine the therapeutic potential of intra-articular pericyte delivery in mouse PTOA (Aim 2)

Approach

The present award seeks to explore the entirely novel hypotheses endogenous synovial pericytes may exert protective / immuno-modulatory effects in osteoarthritis, and that intra-articular delivery of purified pericytes will improve OA disease progression. The current work will systematically evaluate the location, function, and therapeutic potential of endogenous and exogenous pericytes using a Pdgfrb transgenic reporter animal.



The proposed work validates a Pdgfrb reporter mouse to study pericytes within osteoarthritis. Moreover, we examine the therapeutic potential of pericytes for osteoarthritis.

Accomplishment: In our first year, we have validated a pericyte reporter in osteoarthritis, and identified dynamic temporal changes in pericyte cellular descendants before (left) and after (right) destabilization of the medial meniscus (DMM) in mice (right).

Timeline and Cost

Activities CY	18	19
Develop PTOA model in pericyte reporter animals		
Determine the therapeutic potential of intra-articular pericyte delivery in mouse PTOA		
Estimated Budget ($K)	**$252**	**$71**

Updated: 07/30/2019

Goals/Milestones

CY18 Goal – Develop PTOA model in pericyte reporter animal

☑ Perform pilot PTOA studies in pericyte reporter animals

☑ Perform histologic analysis

☐ Perform flow cytometry and in vitro analysis

CY19 Goals – Evaluate the therapeutic potential of intra-articular pericyte delivery in mouse post-traumatic osteoarthritis

☑ Isolate adipose mouse pericytes

☑ Perform pilot PTOA studies with or without pericyte intra-articular injection

☐ Perform histologic analysis

Comments/Challenges/Issues/Concerns

- None.

Budget Expenditure to Date

Projected Expenditure: $292,978.53

Actual Expenditure: $252,772.53

PR170080: Endogenous and Exogenous Pericytes in the Pathobiology and Treatment of Osteoarthritis

PI: Aaron W. James, Johns Hopkins University, MD **Budget:** $322,680

Topic Area: Arthritis **Mechanism:** W81XWH-18-0121

Research Area(s): 0400 **Award Status:** 01 July 2018 – 30 June 2019

Study Goals:

The present Discovery award seeks to explore the entirely novel hypotheses that: *(1)* endogenous synovial pericytes may exert protective / immunomodulatory effects in osteoarthritis (OA), and *(2)* intra-articular administration of purified pericytes will improve OA disease progression. The current proposal will systematically evaluate the location and immunomodulatory function of pericytes within the OA afflicted synovium. Next, we will perform a pilot study examining the therapeutic potential of purified pericytes in OA.

Specific Aims:

Aim 1: Develop and evaluate a post-traumatic osteoarthritis model within pericyte reporter mice.

Aim 2: Evaluate the therapeutic potential of intra-articular pericyte delivery in mouse post-traumatic osteoarthritis.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date