COLLEGE DOCTORAL PAYS DE LA LOIRE ED BIOLOGIE SANTE

Year 2024 /2025

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Study of stromal cells - immune cells interactions during tendinopathy**		3 keywords: Inflammation Tendon Healing
Unit / team: **UMR1229-RMeS / team Rejoint**		
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Socio-economic and scientific context (approximately 10 lines):
Tendinopathies are common diseases, favored by excess load and repetitive movements. Their individual and societal impact is significant, linked to the chronicity of pain and the absence of curative therapy. Tenocytes, the main cells of the tendon, regulate the production and turnover of components of the extracellular matrix in response to different mechanical or molecular stimuli. A dysregulation of immune cells has been observed within pathological tendons. The existence of tissue resident macrophages (TRMs) within tendons has been demonstrated, but their role and origin are little known. Interactions of these tendon resident cells could result in pathological trajectories of tendon progenitor stem cell differentiation, leading to lower tissue quality. In turn, these abnormal tenocytes and niche alterations could lead to a pathological MRT phenotype.

Working hypothesis and aims (approximately 8 lines):
The general objective of this study is to better characterize the interactions between macrophages and stromal cells within the tendon, which result in the deviation of normal healing towards degeneration of the tendon tissue. The modification of the MRT phenotype within tendon tissue could involve several factors: the ontogeny of these cells, modifications of the macrophage niche including the tenocyte-macrophage axis, and a pro-inflammatory "memory" of these cells. Our working hypothesis is that repeated microtrauma of the tendon would lead to an impairment of tissue healing linked to these MRTs. Aberrant activation in particular of the IL-6 pathway would divert the differentiation of progenitors towards osteochondrogenic or fibrotic pathways rather than tenogenic.

Main milestones of the thesis (approximately 12 lines):
We will use samples of human ruptured supraspinatus (established tendinopathy) and subscapularis (early-stage tendinopathy) tendons from the same shoulders, as well as healthy rotator cuff tendons. Each biopsy will be analyzed by immunohistochemistry (IHC), single cell RNA sequencing (scRNAseq), single cell ATAC-seq, and spatial multi-omics.
The factors identified as key will be studied in a macrophage-tenocyte co-culture model. The use of monocytes extracted from the blood of healthy volunteers associated with tenocytes extracted after digestion of human rotator cuff tendons will make it possible to study their interactions under different culture conditions, the transcriptome of each cell type using transwell culture inserts and to quantify the efferocytosis capacities of macrophages on apoptotic tenocytes.
A mouse model of partial rupture of the patellar tendon will make it possible to study the different stages of the normal healing process. The latter will be studied by histology, IHC and scRNAseq in the lesion area, and functional measurements will be carried out (gait analysis - cat walk). The targets selected in vitro will be evaluated in our mouse model (anti-IL6R antibodies, siRNA, IL6 KO mice, JAK inhibitors, etc.).

Scientific and technical skills required by the candidate (2 lines):
Skeletal pathophysiology
Molecular and cellular biology (histology, PCR, cell culture, etc.), bioinformatics

3 publications from the team related to the topic (last 5 years):
1. Darrieutort-Laffite C, Beach ZM, Weiss SN, *et al.* Knockdown of biglycan reveals an important role in maintenance of structural and mechanical properties during tendon aging. *Journal of Orthopaedic Research*. 2023;41:2287–94.
2. Herman J, Le Goff B, De Lima J, Brion R, Chevalier C, Blanchard F, Darrieutort-Laffite C. Pro-inflammatory effects of human apatite crystals extracted from patients suffering from calcific tendinopathy. *Arthritis Res Ther.* 23:131, 2021.
3. Darrieutort-Laffite C, Varin S, Coiffier G, *et al.* Are corticosteroid injections needed after needling and lavage of calcific tendinitis? Randomised, double-blind, non-inferiority trial. *Ann Rheum Dis*. 2019;78:837–43.

National and international collaborations:

Pr Anne des Rieux, UCLouvain, Belgium
Pr Manuela Gomes, University of Porto, Portugal