Defining the Pro-fibrotic function of S100a4 during scar-mediated tendon healing

Wednesday, February 7, 12:00 p.m. East Hall Room 1232

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Abstract  
Effective surgical repair of tendon injuries is limited due to a propensity for scar tissue mediated healing rather than regeneration of native tendon structure. This fibrotic scar tissue results in impaired tendon function due to extracellular matrix (ECM) disorganization and inferior mechanical properties, relative to healthy tendon. Type II Diabetes Mellitus (T2DM) dramatically exacerbates this healing paradigm resulting in a more profound loss of tendon function, and increased incidence of re-rupture. Our understanding of the mechanisms that govern increased fibrotic healing in diabetic tendon remains limited, and this gap in knowledge has resulted in a paucity of therapeutic targets to improve clinical outcomes. We have identified S100a4 (S100 calcium binding protein 4A) as a key driver of fibrotic tendon healing in non-diabetic animals. S100a4-haploinsufficiency decreases scarring and accelerates improvements in mechanical properties, relative to WT. Consistently, S100a4-cell depletion also decreases scar tissue formation, however mechanical properties are decreased, suggesting that S100a4-producing cells are required for mechanically sufficient tendon healing. Moreover, we have found that S100a4 promotes scar-mediated healing as an extracellular signaling molecule, via binding to RAGE (Receptor for Advanced Glycation Endproducts). Given that S100a4 and RAGE expression are dramatically increased in diabetic tendon repairs we propose that fibrotic healing occurs to a greater degree in diabetic tendons than non-diabetic due to elevated S100a4-RAGE signaling. To facilitate a more efficient understanding of how S100a4-RAGE modulates scar formation we have developed an ultrasound (US)-based approach to longitudinally and non-invasively assess tendon healing, and observe strong correlations with US-based metrics and terminal measures of tendon function.

Biography  
Dr. Loiselle received her Bachelors Degree in Biology from Niagara University and completed her PhD in Pathology at the University of Rochester Medical Center under the direction of Dr. Regis O’Keefe. Her PhD research established the first murine model of flexor tendon healing and demonstrated that bone marrow derived cells promoted scar-mediated healing via expression of Mmp9. From there she joined the lab of Dr. Hank Donahue at Penn State College of Medicine and focused on the role of the gap junction protein Connexin 43 in bone regeneration and utilized a nanotopographic resurfacing technique of donor bone to enhance
allograft healing. In 2013 she returned the University of Rochester and developed her laboratory with a focus on identifying therapies to promote regenerative tendon healing. In 2014 she was awarded the Goldner Pioneer Award from the American Society for Surgery of the Hand in 2014. Her laboratory is currently funded by NIH/NIAMS.