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Supplemental information

Defining the spatial-molecular map

of fibrotic tendon healing and the drivers

of Scleraxis-lineage cell fate and function

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Supplemental Figure 1. Matrix elaboration by Scx^{Ai9} cells, Related to Figure 1.

Immunofluorescence of Scx^{Ai9} (pink) at days 8, 10, and 12 post-repair. Nuclei stained with DAPI. Coverslips were removed and samples were then stained with Masson's Trichrome to analyze localization of organized collagen deposition at the repair site. White arrows used to indicate Scx^{Ai9} cells and yellow arrows used to indicate non- Scx^{Ai9} cells between fluorescent and Masson's trichrome images. Scale bars represent 200µm for low power images and 50µm for higher power images. Co-immunofluorescence for Scx^{Ai9} (red) and Hsp47 (white) between D8-12 post-repair. Blue arrows indicate examples of co-localization. N=3-5 per time-point. Scale bars represent 100µm.



Supplemental Figure 2. Selection of tendon/scar ROI for downstream integrative analysis, Related to Figure 2. Each timepoint is labeled with the harvest day post-injury, along with the technical replicate identifier. For each sample the original H&E-stained image (left), the spots encompassing the tendon/scar using coordinates exported from selection in Loupe (middle), and UMAP of the unsupervised clustering captured from the ROI in (right) is shown. Scale bars represent 1mm.



Supplemental Figure 3. Integrated cluster annotation confirmation, Related to Figure

2. The top 3 distinguishing marker genes for each cluster in the integrated dataset were mapped with violin plots, and gene ontology lists generated for each to confirm each annotation: (A,B) C0^{synthetic}, (C,D) C1^{native_tendon}, (D,E) C2^{reactive}, (G,H) C3^{fibrotic}, (I,J) C4^{inflammatory}, and (K,L) C5^{muscle_assoc}.



Supplemental Figure 4. Scx^{Ai9} cells co-express CD45 throughout tendon healing, Related to Figure 3. Co-immunofluorescence of Scx^{Ai9} (red) and CD45 (green), between 8-28 days post-repair. Nuclei are stained with DAPI. Tendon is outlined by white dotted lines and scar tissue by yellow dotted lines. Blue and yellow boxes represent higher magnification images taken from the tendon stub and bridging scar tissue, respectively. Scale bars of low magnification images are 200µm and 50µm for

higher magnification images.



Supplemental Figure 5. Differential expression of fibroblast activation markers in tdTomato.neg vs tdTomato.pos populations, Related to Figures 1 & 3-5. (A) Integrated UMAPs for tdTomato.neg (tdTomato <1) and tdTomato.pos (tdTomato > 1) subsets. Violin plots split by tdTomato.neg (blue) and tdTomato.pos (red) depicting expression of (B) *Pcna*, (C) *Fap*, (D) *Vcam1*, and (E) *Acta2*. Bottom row depicts corresponding feature plot for each activation marker.



Supplemental Figure 6. Identification of the interactome between molecular clusters, Related to Figure 6. (A) Circle plot of integrated clusters shows relative number of interactions between each cluster (line color corresponds to originating source of signal), while (B) quantifies overall interaction strength of each cluster. (C) Outgoing, incoming, and overall signaling pattern strength are quantified and shown for each cluster. Green boxes highlight Periostin and Complement signaling. (D) Dot plot of ligand-receptor interactions within and between C2^{reactive} and C4^{inflammatory}. Dot size and color indicate the significance of the interaction (given as a range of p values), and the probably of communication, respectively.

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Supplemental Figure 7. Interactome of top ten pathways present during tendon healing,

Related to Figures 2 & 6. Dot plot of ligand-receptor interactions within and between each cluster of the integrated dataset. Dot size and color indicate the significance of the interaction (given as a range of p values), and the probably of communication, respectively.