

A unique Schwann cell subtype contributing to keloid formation

Rigorosum to obtain the academic degree

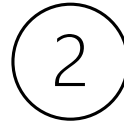
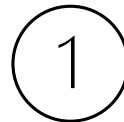
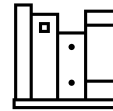
„Doctor of Philosophy“

by

Dr. med. univ. Martin Direder

Presentation structure

- Personal Background
- General Introduction
- First study
- Second study
- Conclusion

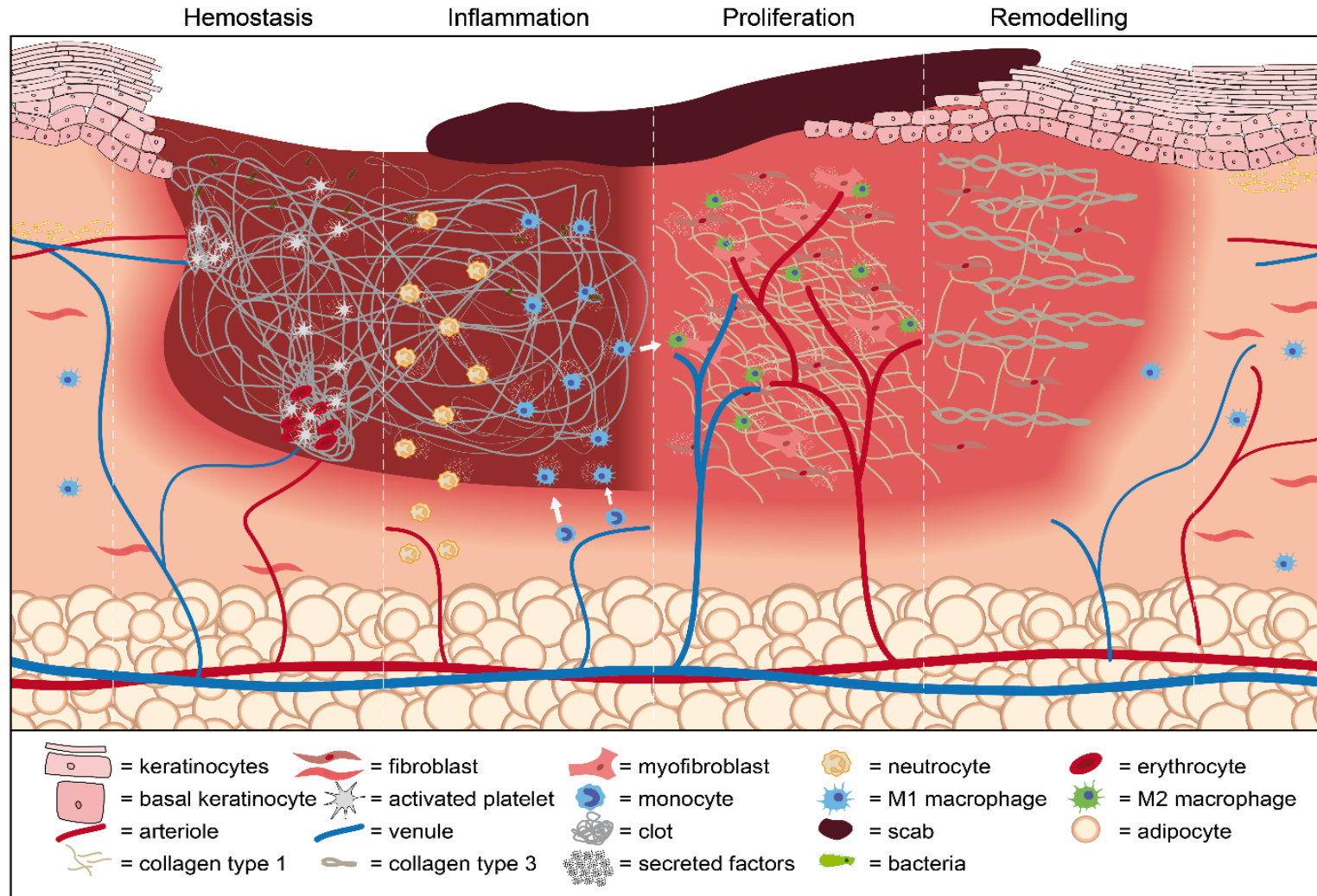
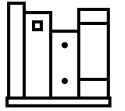


Personal Background

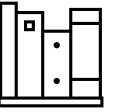


- Born 1993 Tulln, Lower Austria, Austria
- 2008 – 2013 Priv. HTL for Foodtechnology and Foodsafety Hollabrunn
- 2013 – 2014 Civilian Service, Red Cross Austria
- 2014 – 2020 Medical Studies, Medical University of Vienna
- 2019 – 2020 MDPHD Studies „Vascular Biology“, Medical University of Vienna
- Since 2020 PhD Studies, Medical University of Vienna
- Since 08/2022 Resident, Department of Orthopedic and Trauma-Surgery,
Medical University of Vienna

Stages of wound healing

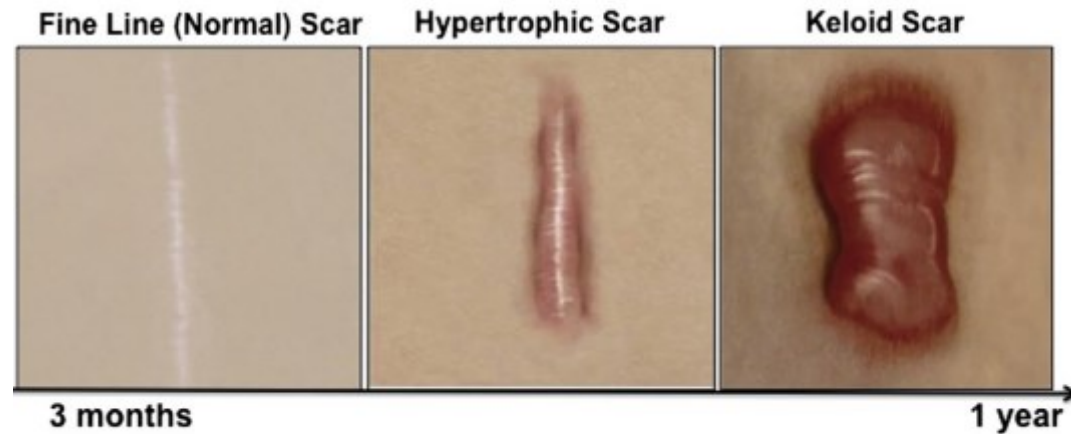


Wound healing & Scarring



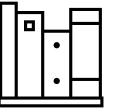
Processes affecting the extent of scar formation:

- Contraction
- Mechanical stretching
- Inflammation



Ud-Din S, Bayat A. New insights on keloids, hypertrophic scars, and striae. *Dermatol Clin.* 2014 Apr;32(2):193-209. doi: 10.1016/j.det.2013.11.002. PMID: 24680006.

Keloids



- Scar-like pathology
- Excessive and invasive growth beyond the wound borders
- Symptoms:
 - Pruritus
 - Pain
 - Dysesthesia
 - movement restriction
 - psychosocial impairment
- Limited treatment possibilities
- Genetic factors & chronic inflammation discussed
- **Pathogenesis still unclear**



https://images-prod.healthline.com/hlcmsresource/images/topic_centers/2019-6/Large-keloid-1296x728-gallery_slide4.jpg
https://s3-us-west-2.amazonaws.com/utsw-patientcare-web-production/original_images/keloid_ear_320.jpg
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http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-59322014000800565

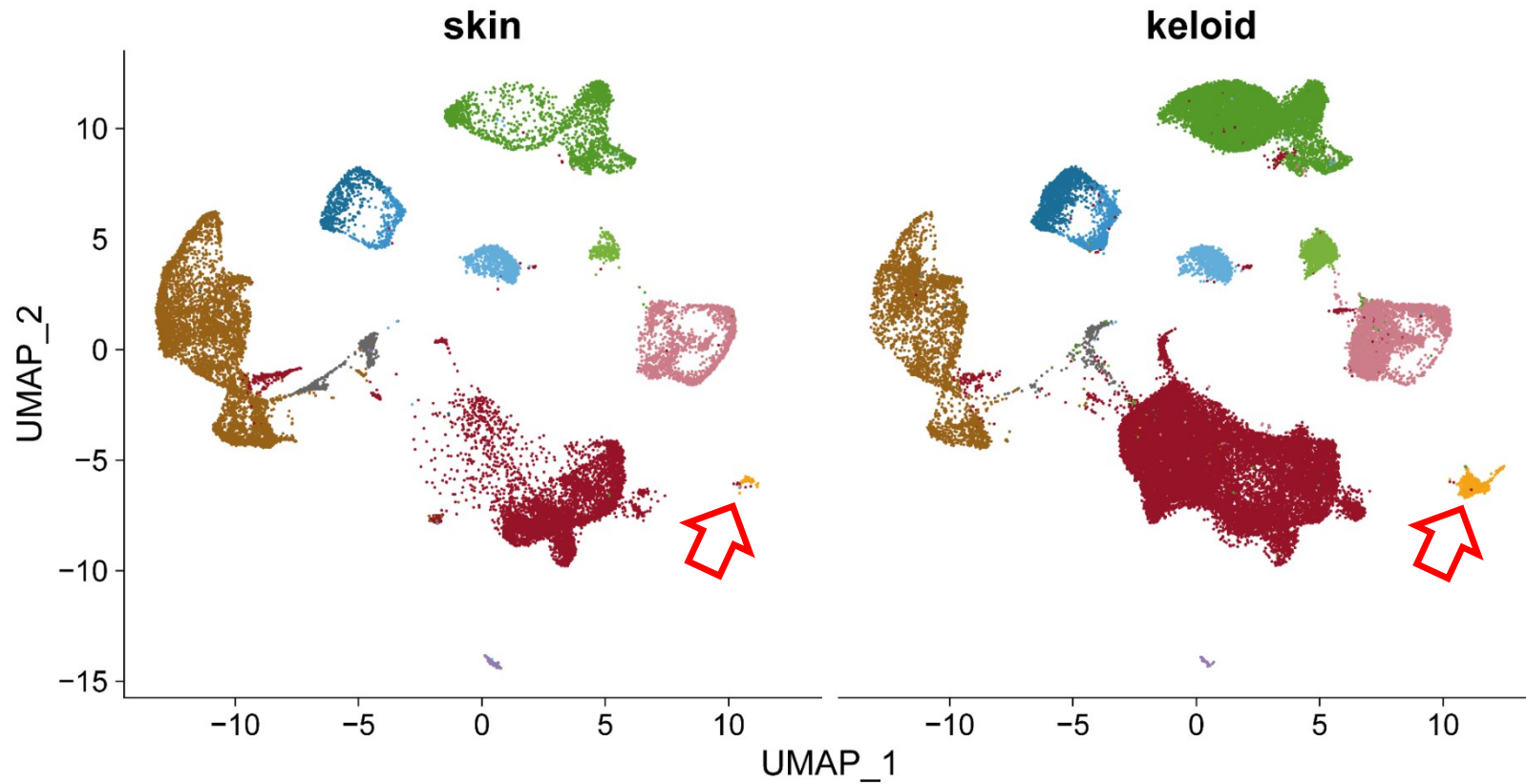
Aim of the first study

1

„Application of scRNAseq
to uncover so far unrecognized cellular contributions
and pathologic mechanisms in keloids “

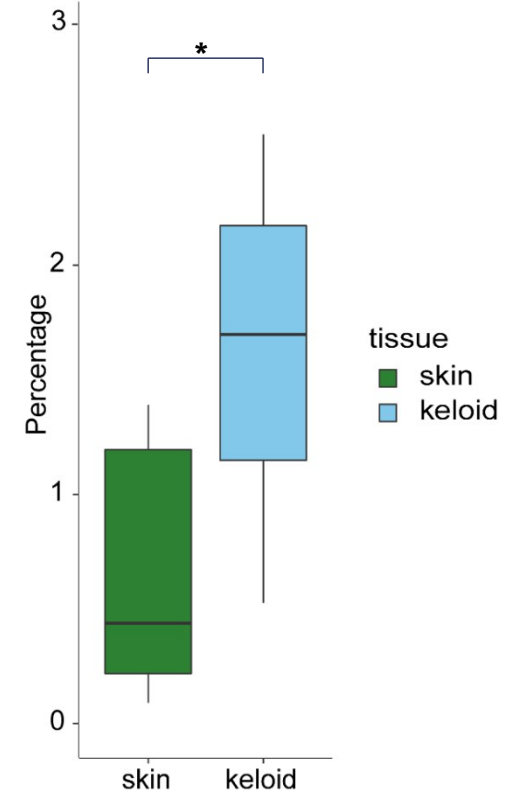
Single Cell RNA sequencing – Skin vs. Keloid

Basic-UMAP



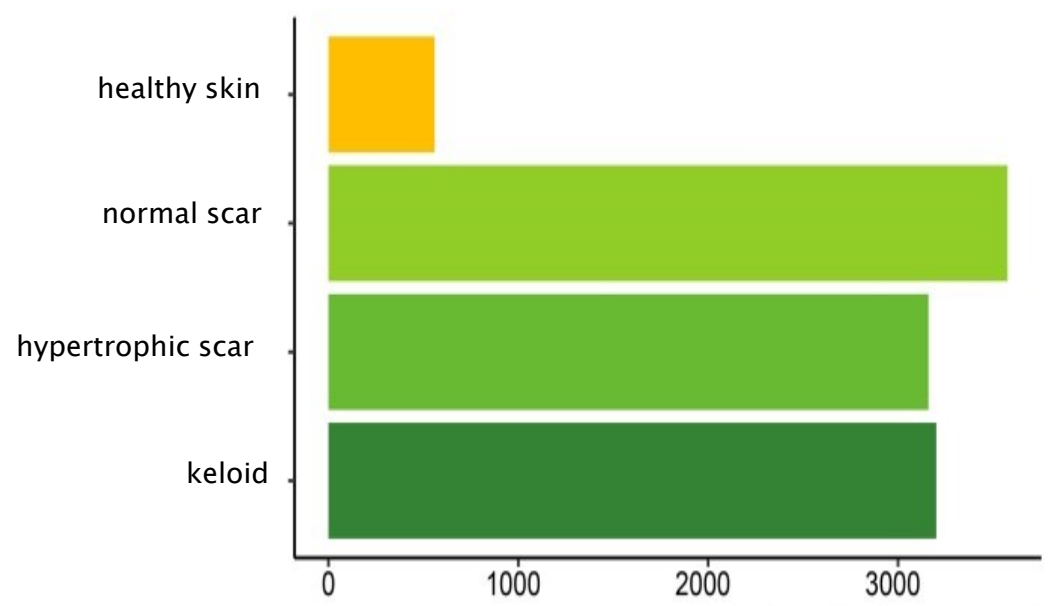
- FB
- SMC/PC
- KC
- EC
- LEC
- TC
- MAC
- DC
- SC
- MEL
- ERY

SC-Percentage comparison

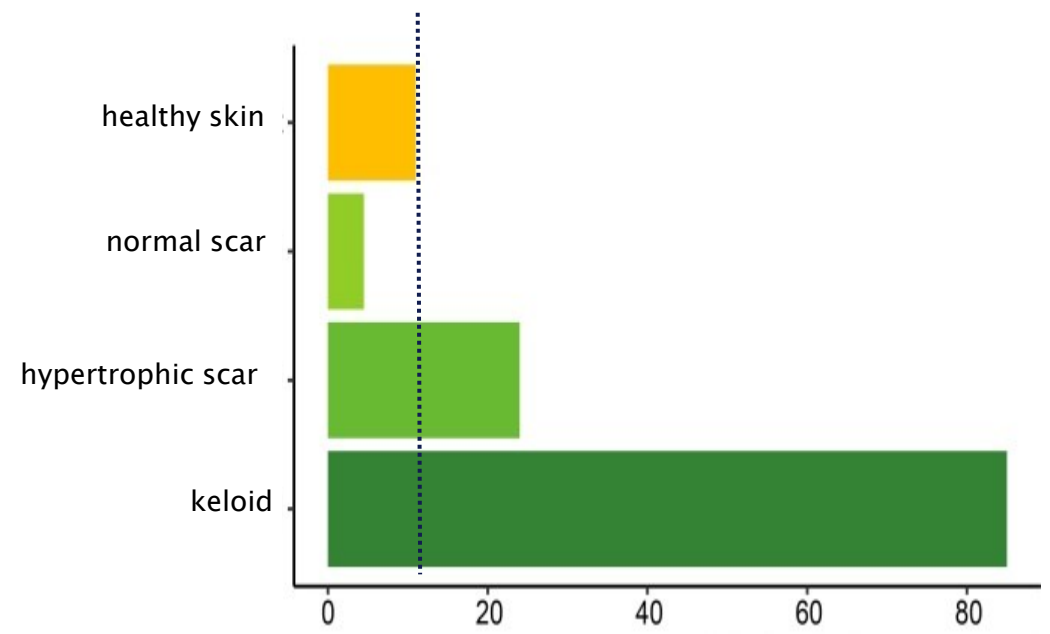


Comparison of fibroblasts and Schwann cells in different scar types

absolute numbers of Fibroblasts

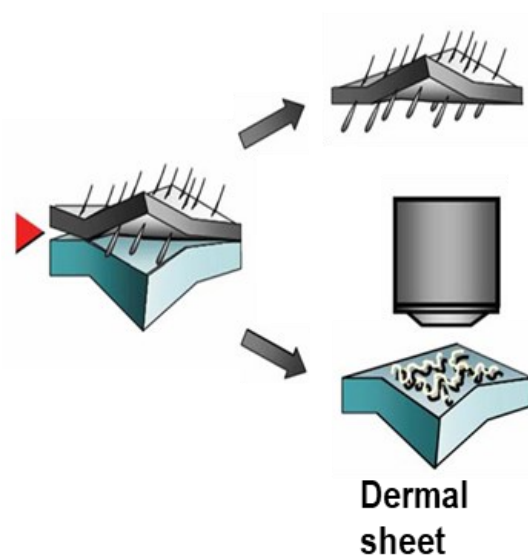
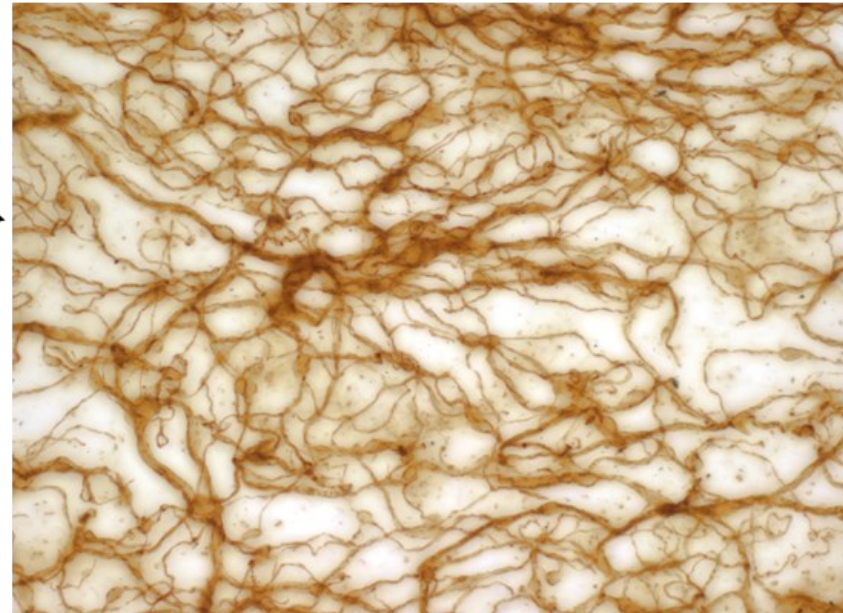
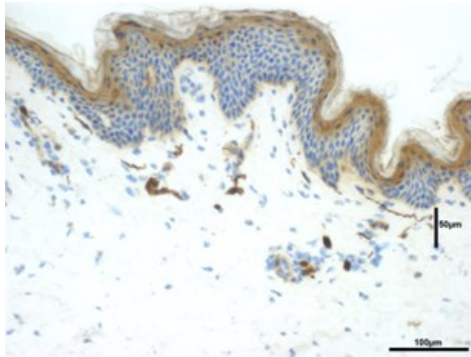


absolute numbers of Schwann cells



The subepidermal nerve plexus in a bird's eye view

1

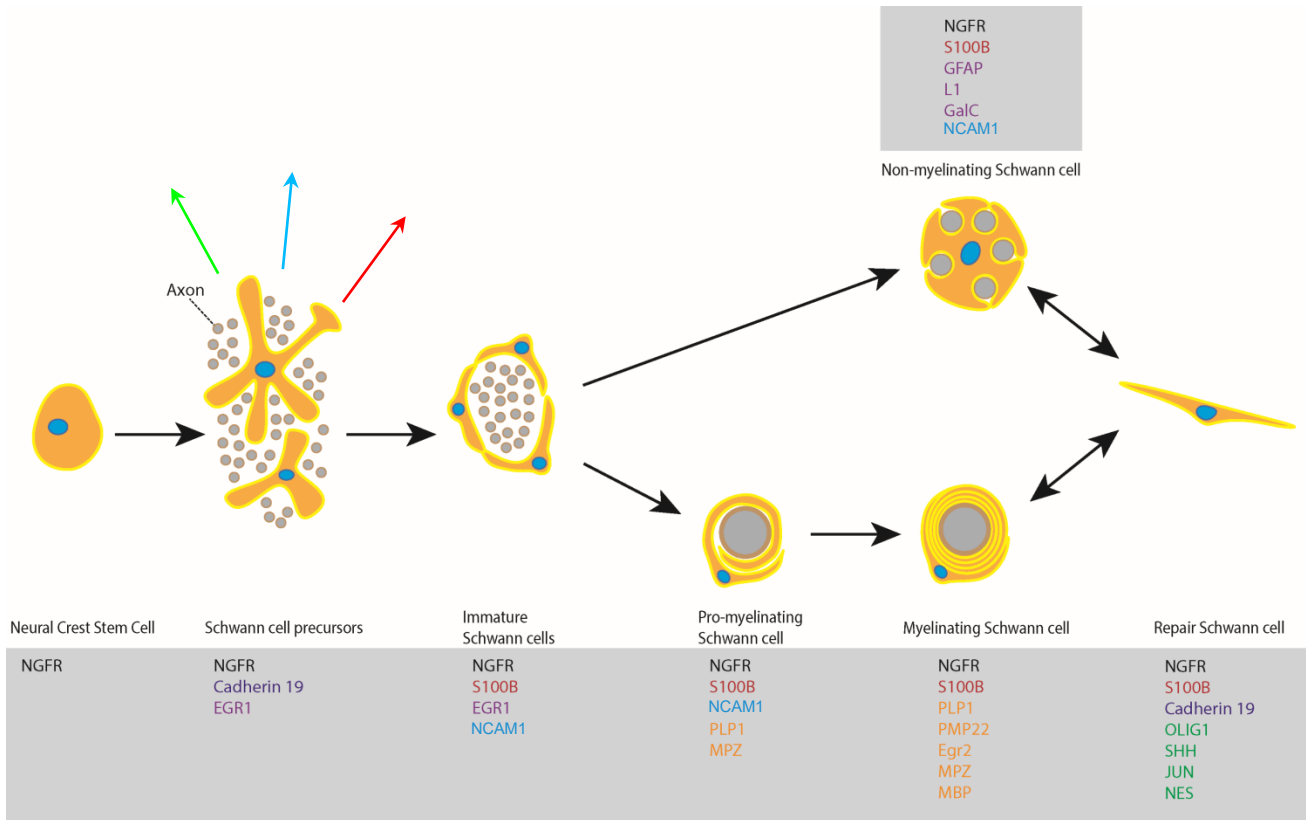


Reinisch CM, Tschachler E.
The dimensions and characteristics of the subepidermal nerve plexus in human skin--terminal Schwann cells constitute a substantial cell population within the superficial dermis.
J Dermatol Sci. 2012 Mar;65(3):162-9. doi: 10.1016/j.jdermsci.2011.10.009. Epub 2011 Nov 11. PMID: 22305014.

Reinisch CM, Tschachler E.
The touch dome in human skin is supplied by different types of nerve fibers.
Ann Neurol. 2005 Jul;58(1):88-95. doi: 10.1002/ana.20527. PMID: 15984029.

Tschachler E, Reinisch CM, Mayer C, Paiha K, Lassmann H, Weninger W.
Sheet preparations expose the dermal nerve plexus of human skin and render the dermal nerve end organ accessible to extensive analysis.
J Invest Dermatol. 2004 Jan;122(1):177-82. doi: 10.1046/j.0022-202X.2003.22102.x. PMID: 14962106.

Schwann cell development



ARTICLE

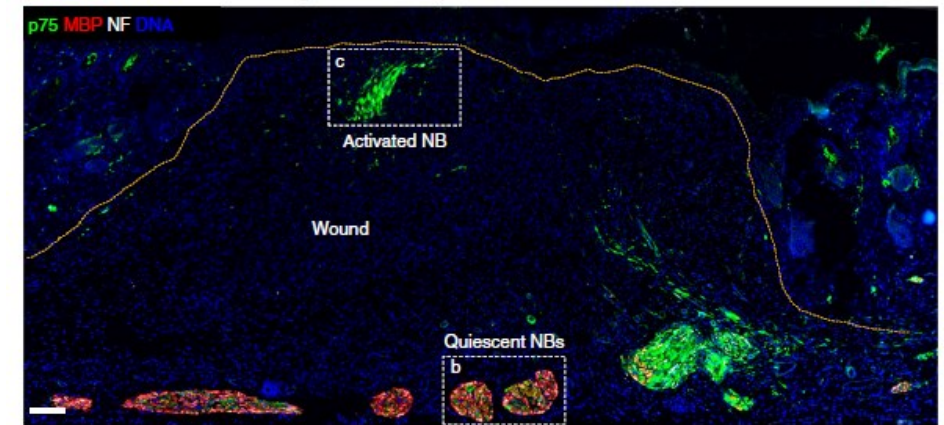
DOI: 10.1038/s41467-017-01488-2

OPEN

Injury-activated glial cells promote wound healing of the adult skin in mice

Vadims Parfejevs^{1,2}, Julien Debbache¹, Olga Shakhova³, Simon M. Schaefer¹, Mareen Glausch¹, Michael Wegner⁴, Ueli Suter⁵, Una Riekstina², Sabine Werner⁵ & Lukas Sommer¹

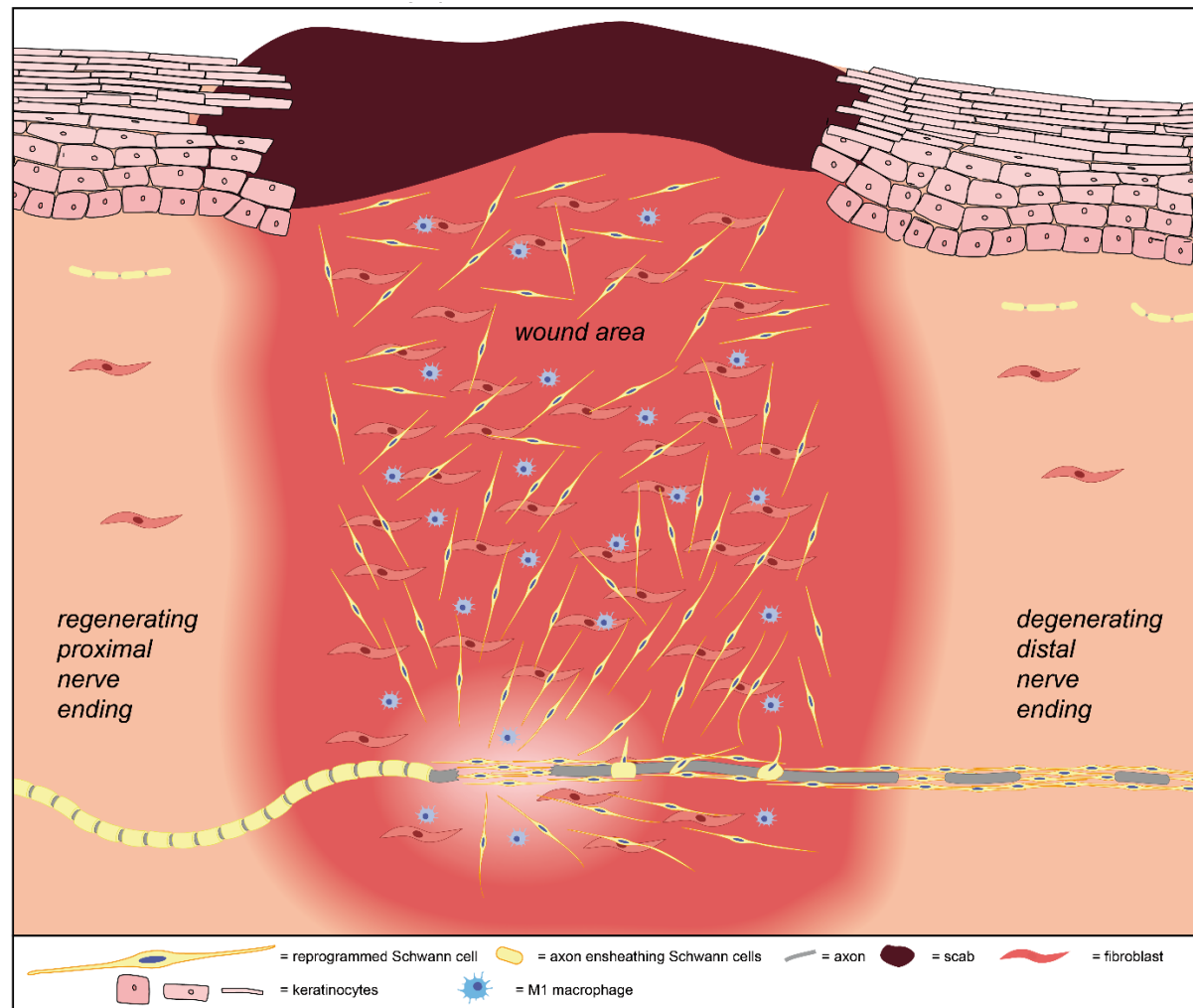
Histological marker expression in NBs of D7 Wounds



Parfejevs V, Debbache J, Shakhova O, Schaefer SM, Glausch M, Wegner M, Suter U, Riekstina U, Werner S, Sommer L. Injury-activated glial cells promote wound healing of the adult skin in mice. Nat Commun. 2018 Jan 16;9(1):236. doi: 10.1038/s41467-017-01488-2. PMID: 29339718; PMCID: PMC5770460. Format:

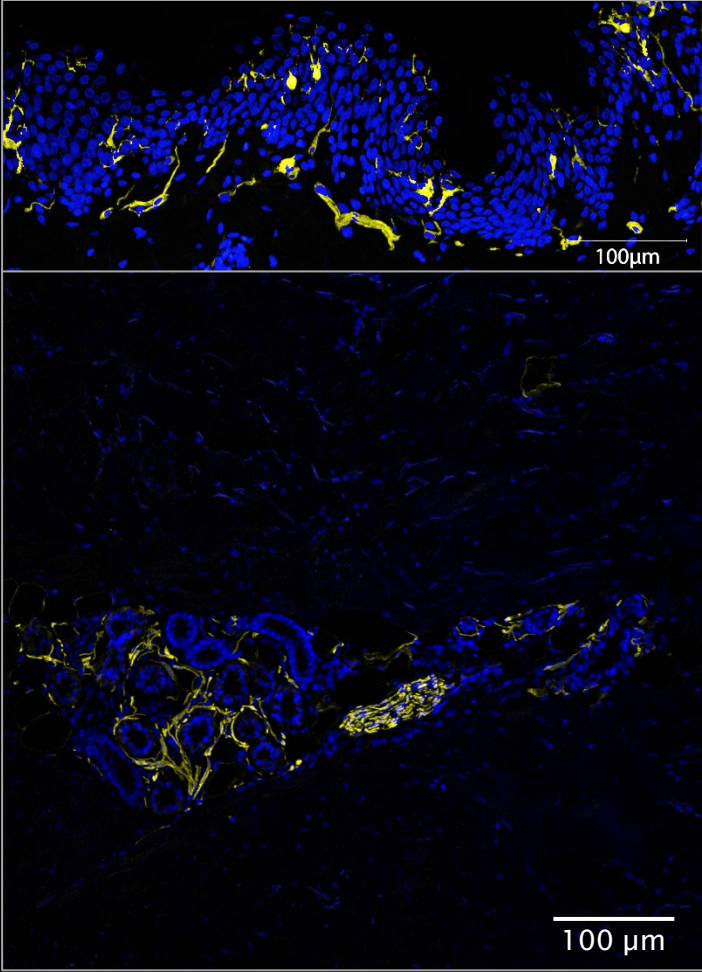
Schwann cell transformation upon injury

1

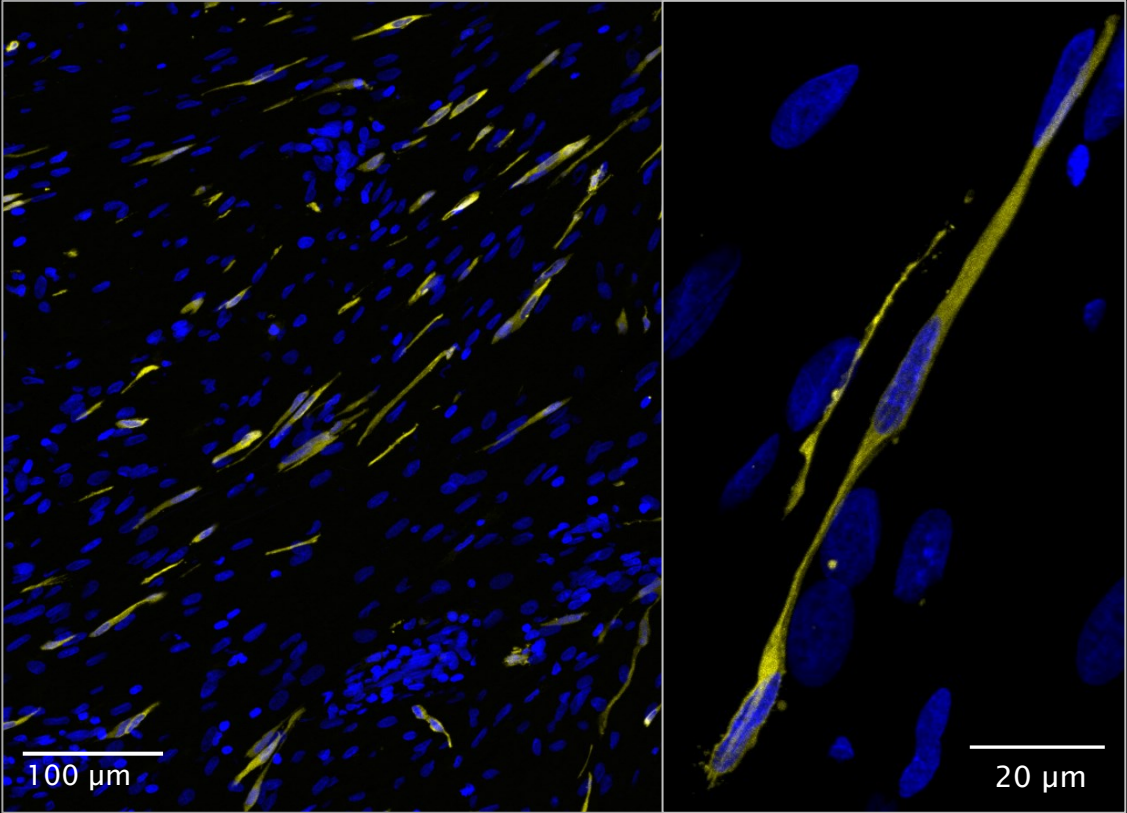


Schwann cells in Keloids vs. Healthy Skin

S100B DAPI



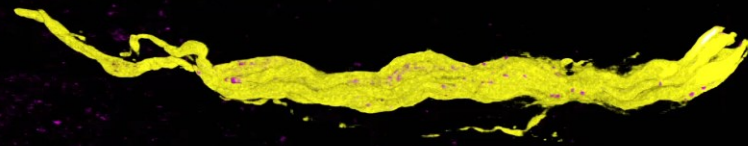
SKIN, 20x



KELOID, 20x

Autonomous Schwann cells in Keloids

Skin



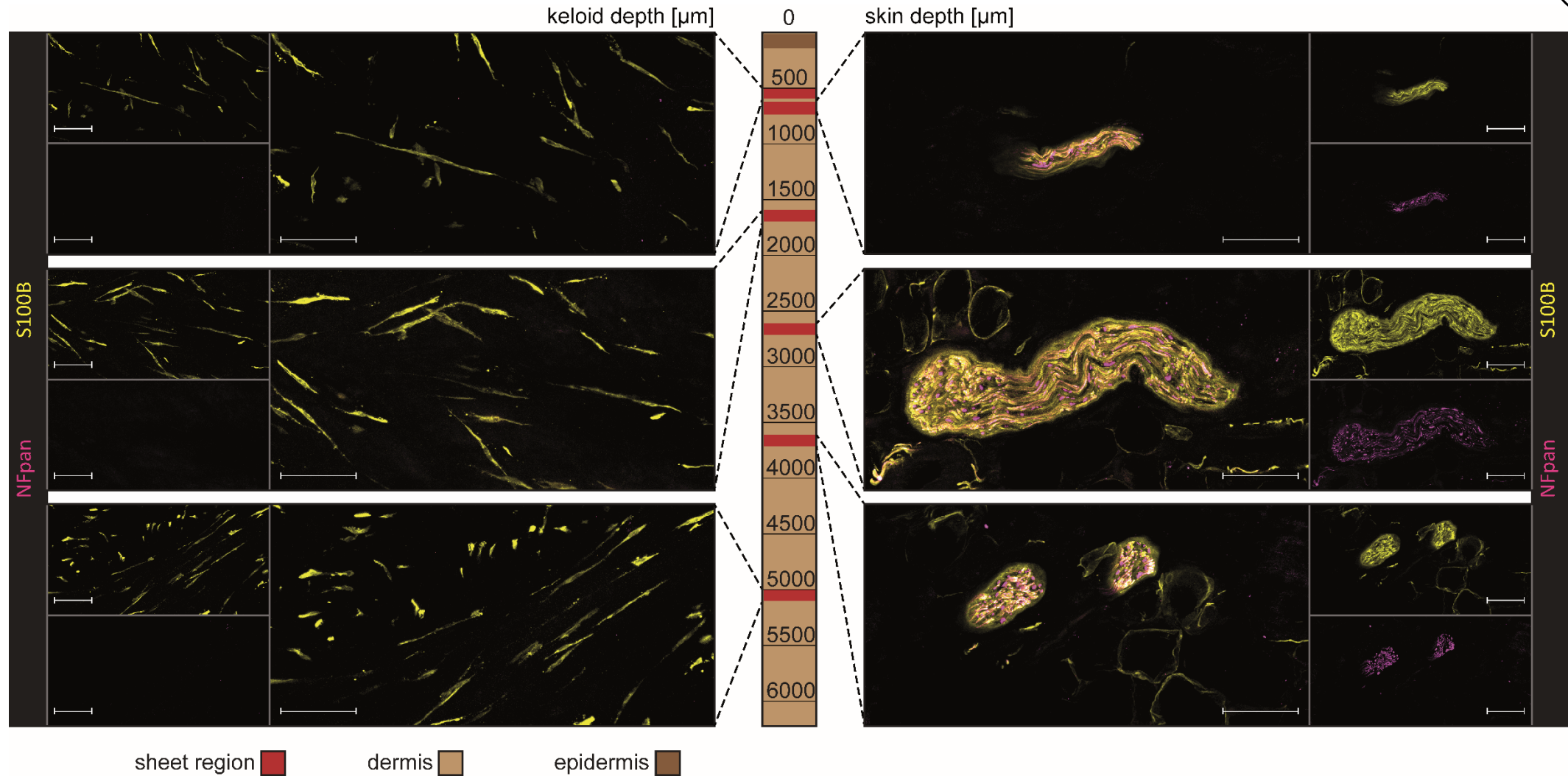
Keloid



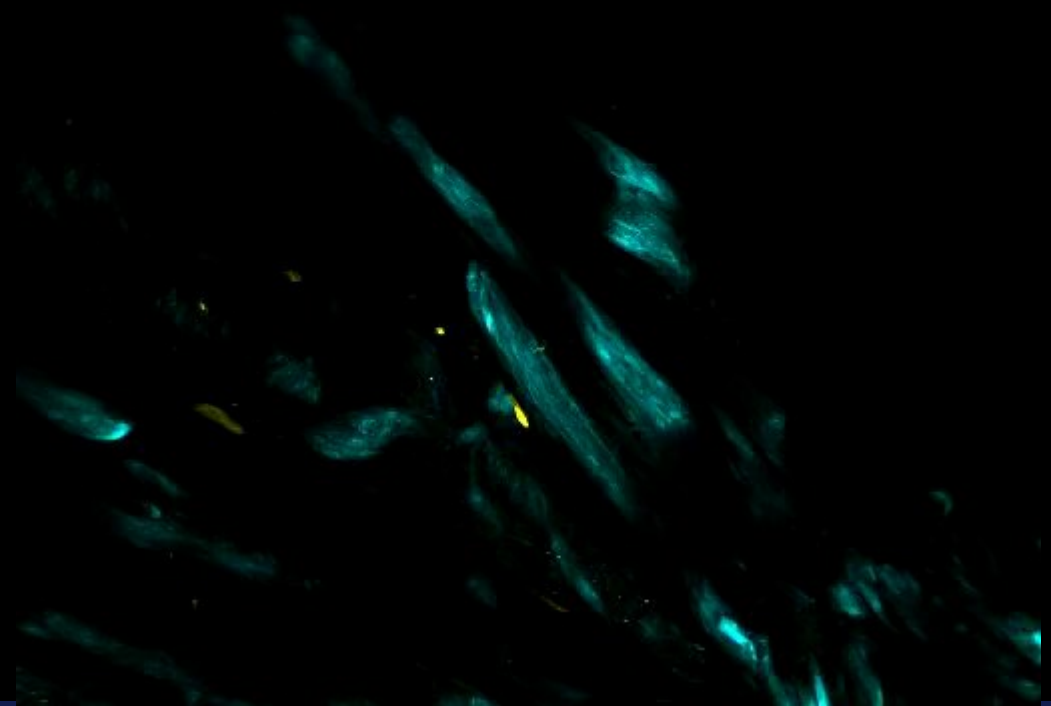
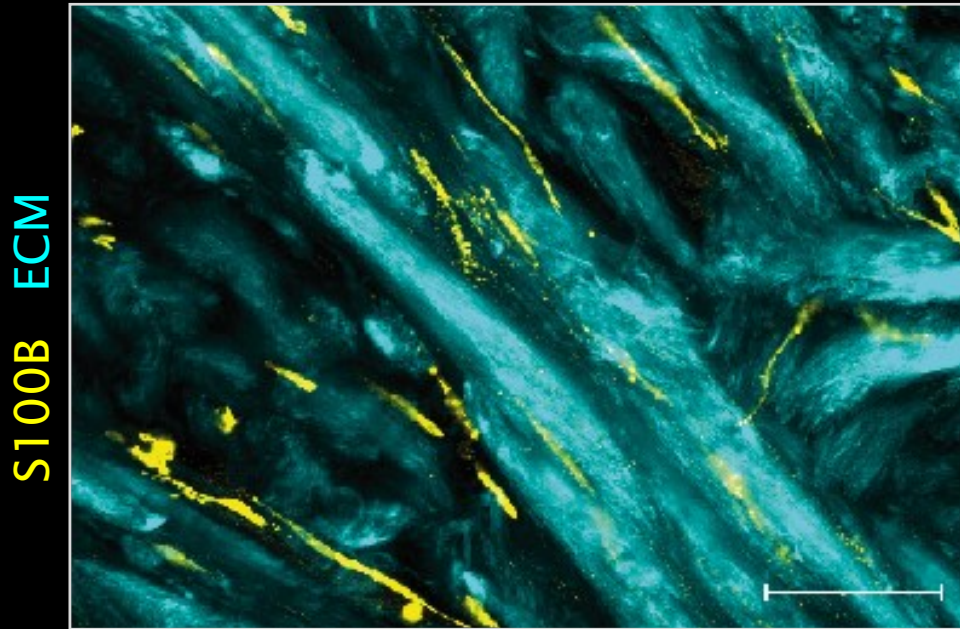
S100B- Schwann cells
PGP9.5 - Axon marker

Schwann cells in Keloids vs. Healthy Skin

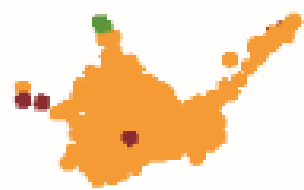
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Schwann cells align closely with collagen bundles



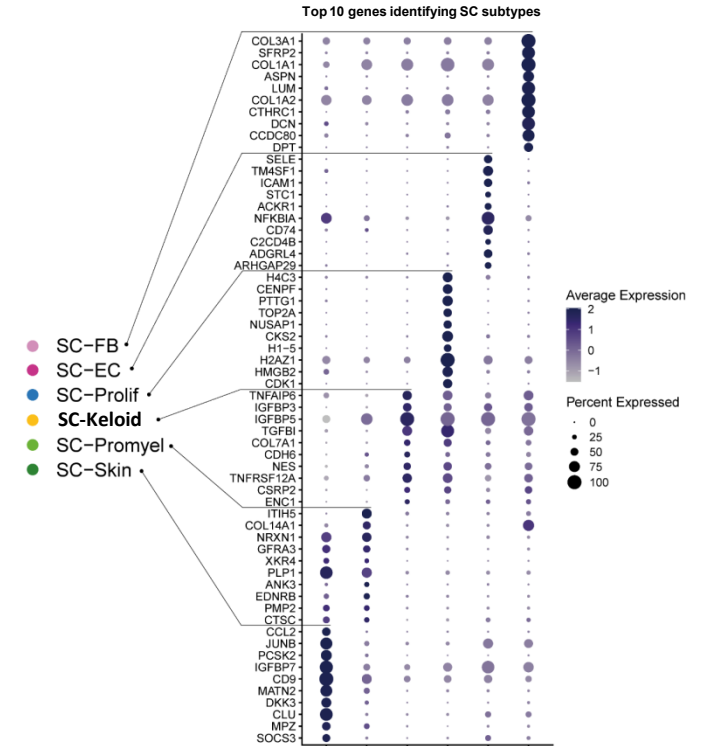
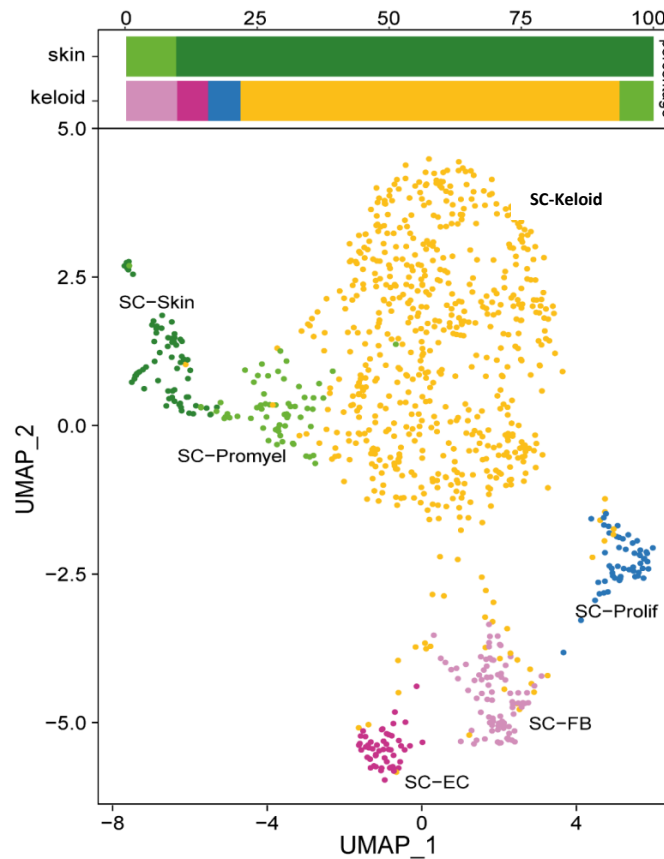
Subtype characterisation of Schwann cells



● SC



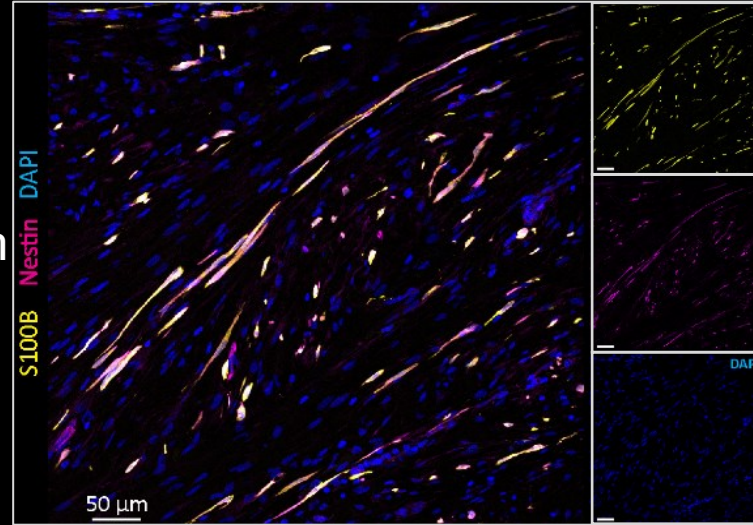
Schwann cell subset – Subtype characterisation



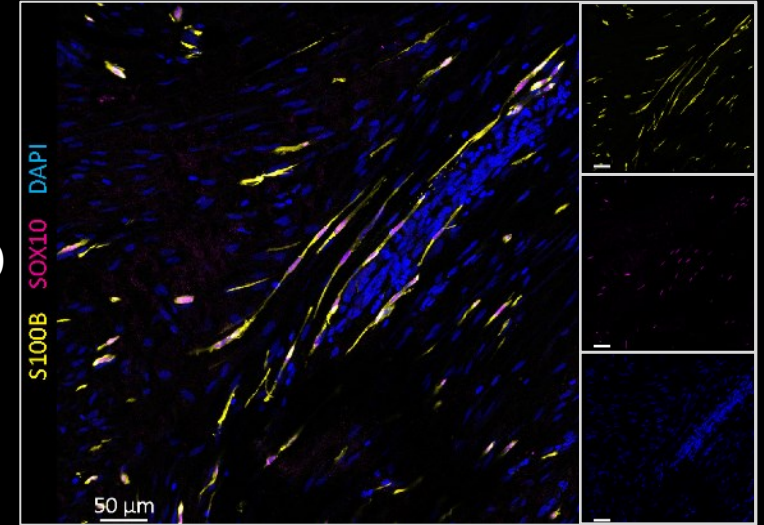
Most Schwann Cells express markers characteristic for repair Schwann cells in Keloids



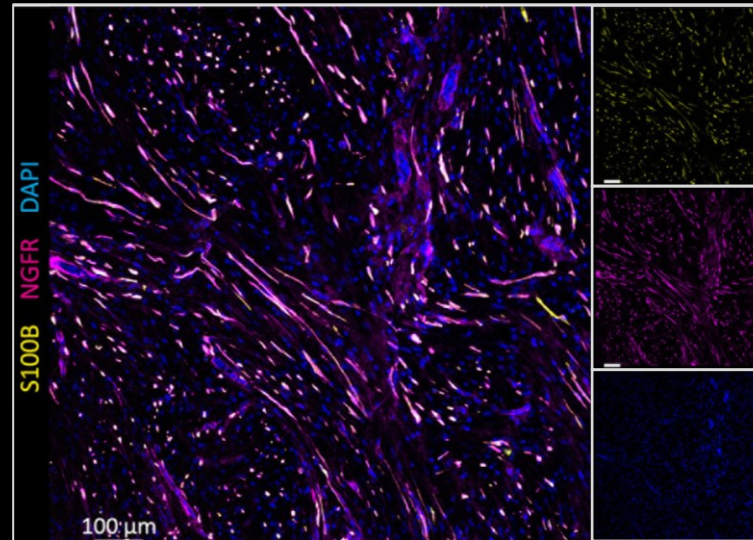
Nestin



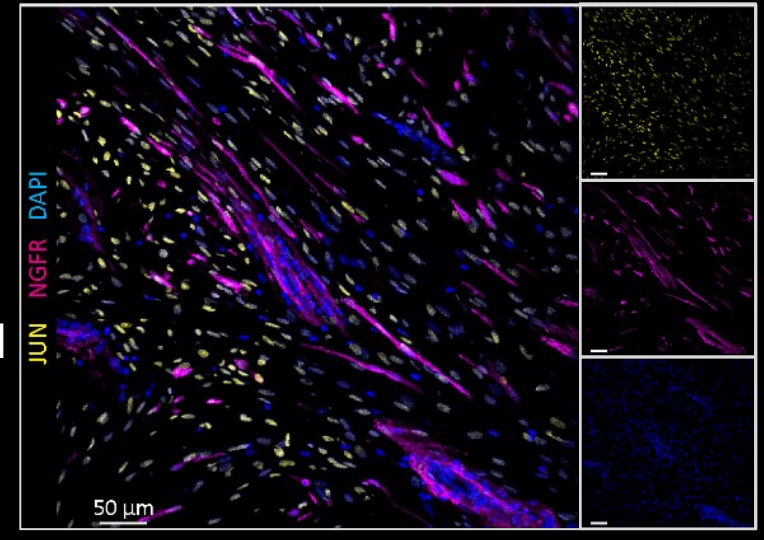
SOX10



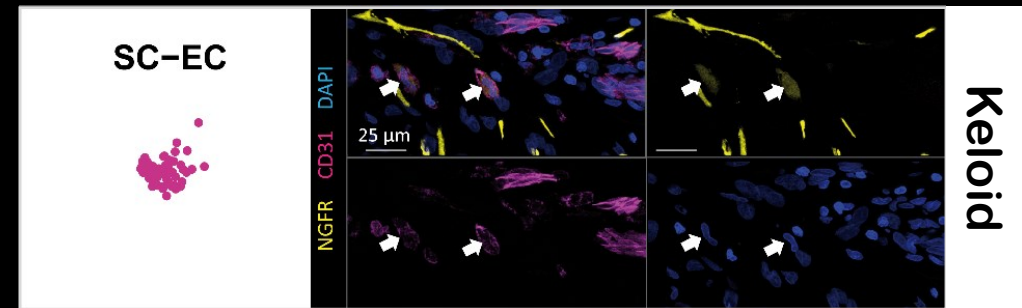
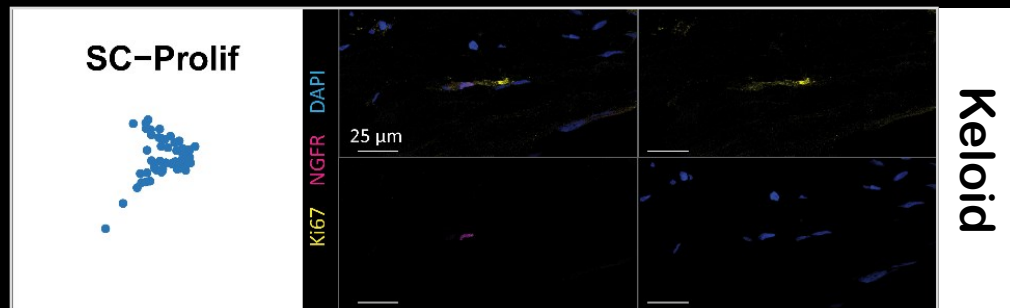
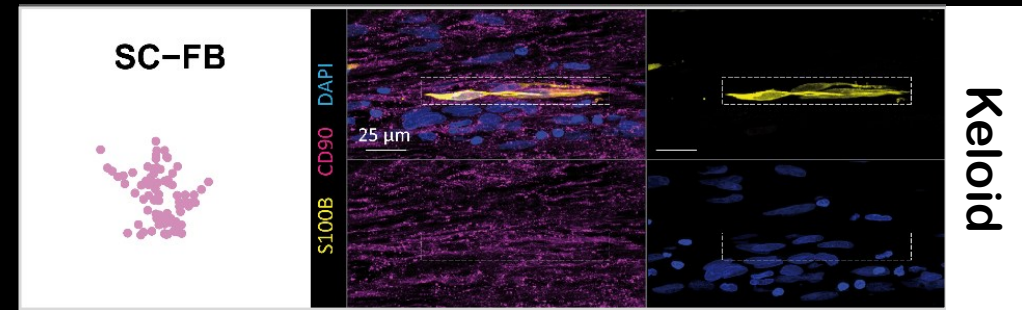
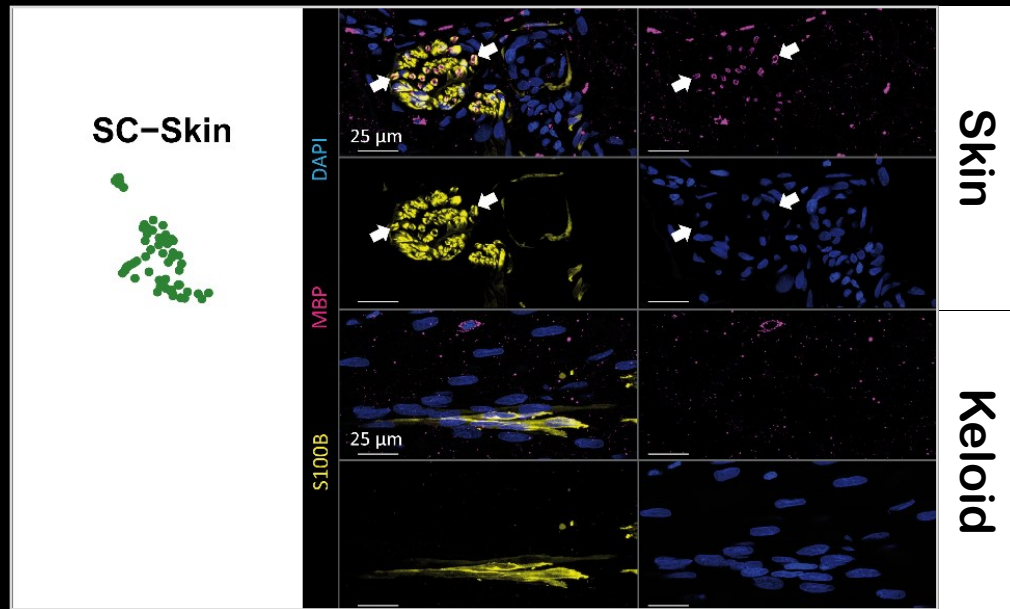
NGFR



JUN



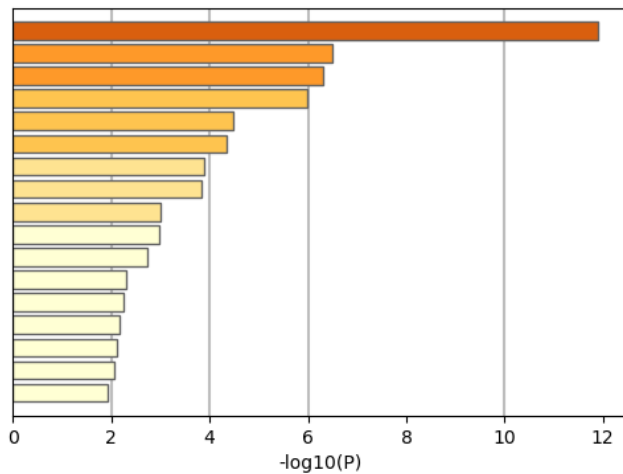
Verification of Schwann cell subtypes by IF-staining



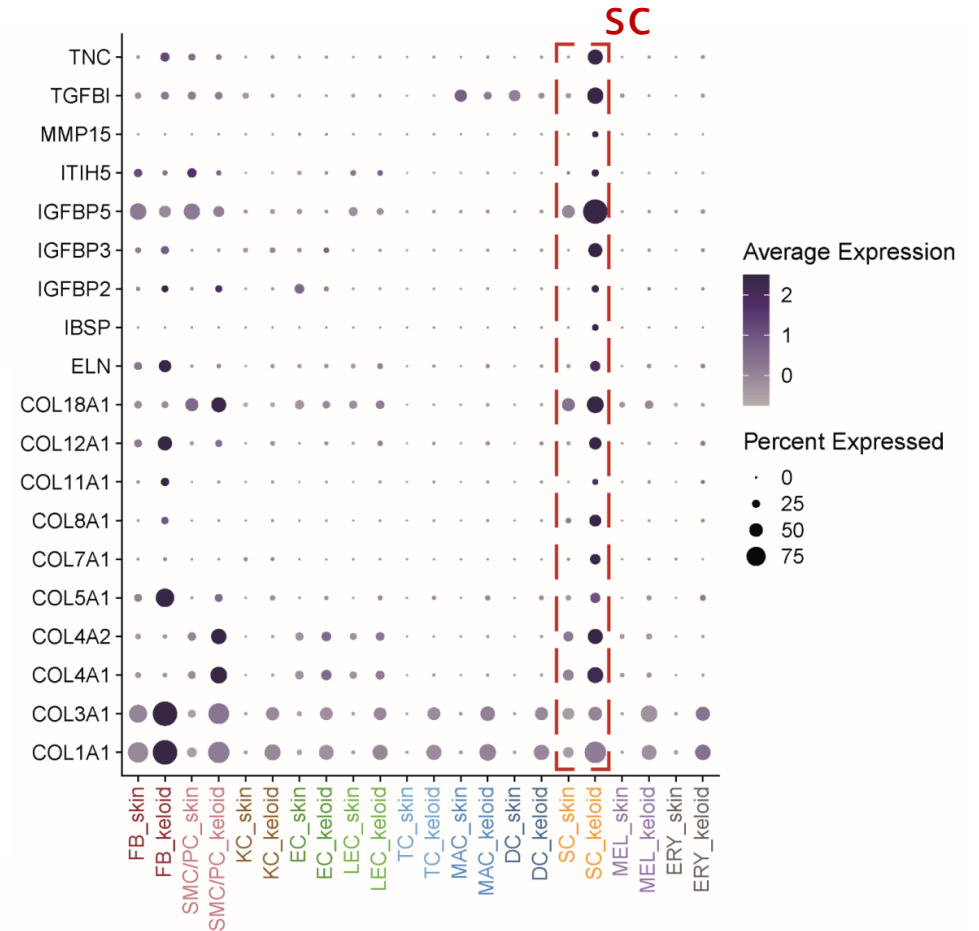
Involvement of keloidal repair-SCs in Matrix formation

1

SC-Keloid



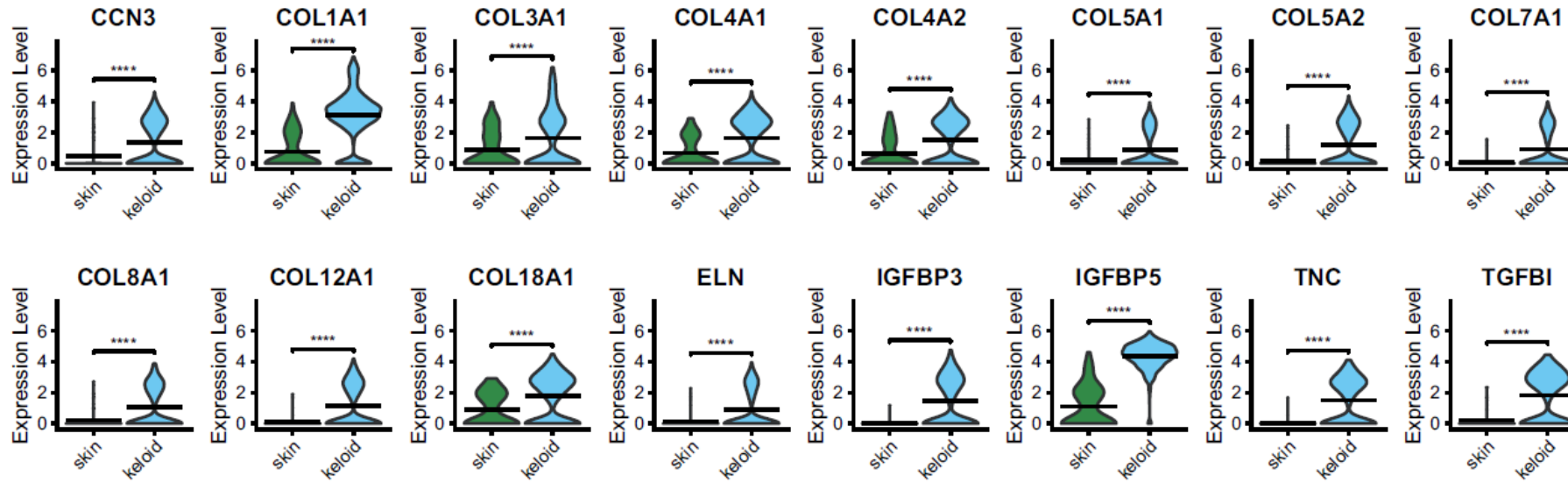
- GO:0030198: extracellular matrix organization
- GO:0014909: smooth muscle cell migration
- GO:0030029: actin filament-based process
- GO:0007528: neuromuscular junction development
- GO:0022612: gland morphogenesis
- GO:0010811: positive regulation of cell-substrate adhesion
- GO:0051017: actin filament bundle assembly
- GO:1903034: regulation of response to wounding
- GO:0043666: regulation of phosphoprotein phosphatase activity
- GO:0098742: cell-cell adhesion via plasma-membrane adhesion molecules
- GO:0001655: urogenital system development
- GO:0006006: glucose metabolic process
- GO:0051495: positive regulation of cytoskeleton organization
- GO:0070848: response to growth factor
- GO:0061448: connective tissue development
- GO:0045055: regulated exocytosis
- GO:0010035: response to inorganic substance



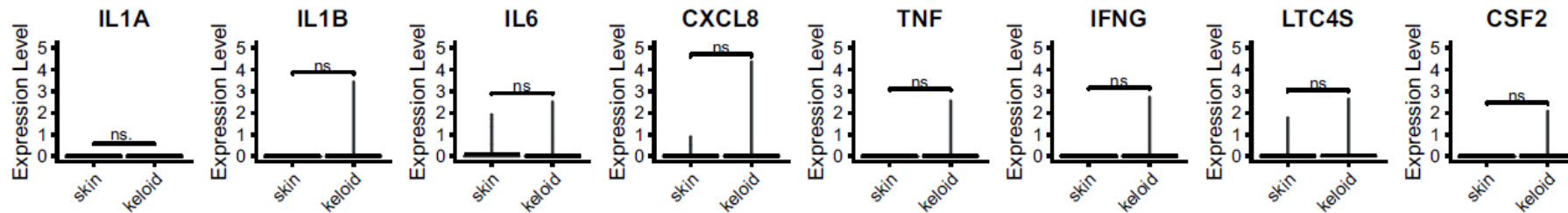
Involvement of keloidal SCs in Matrix formation

1

Matrix-associated gene expression in SCs

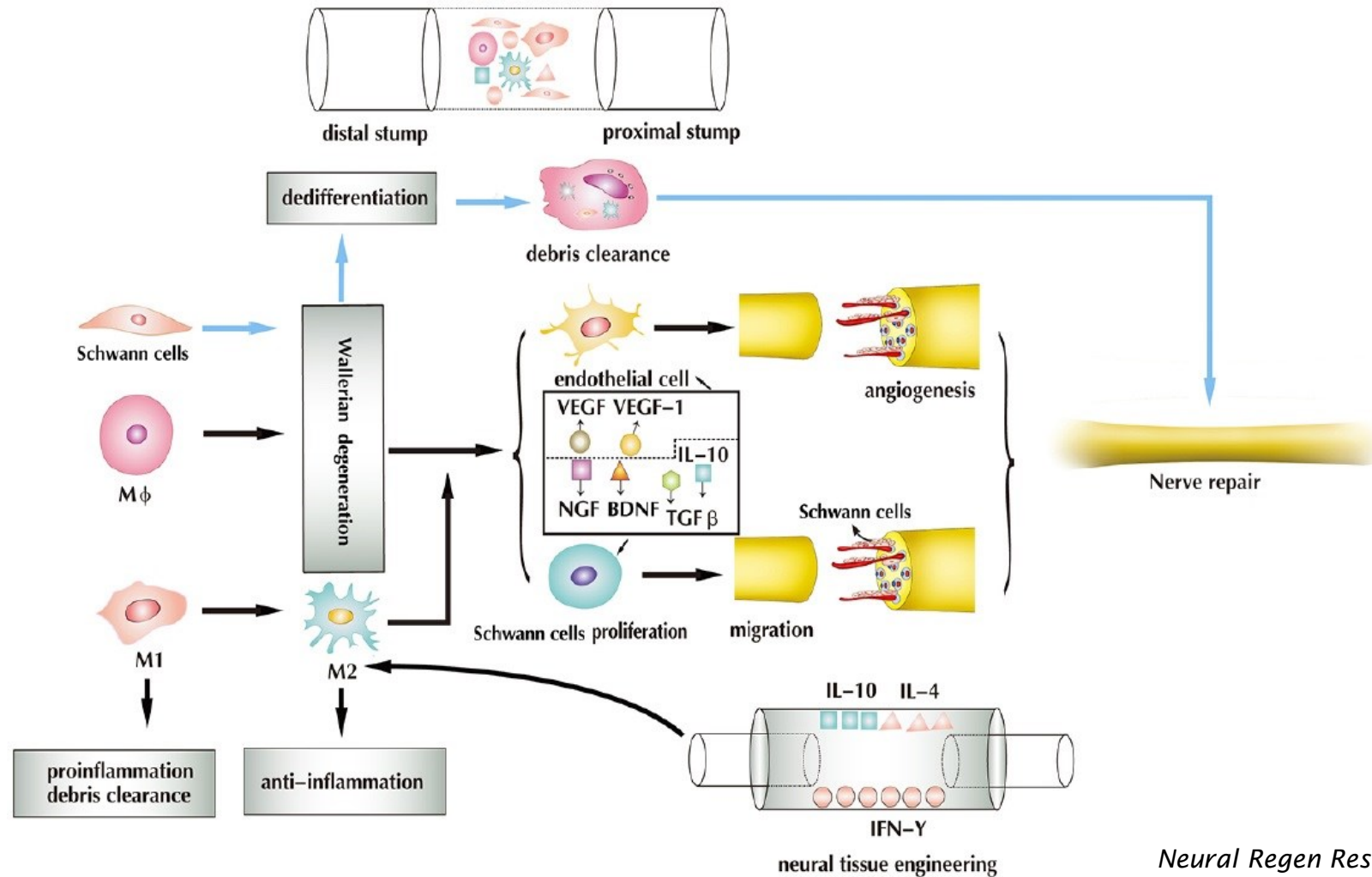


Inflammation-associated gene expression in SCs



Role of macrophages in peripheral nerve injury and repair

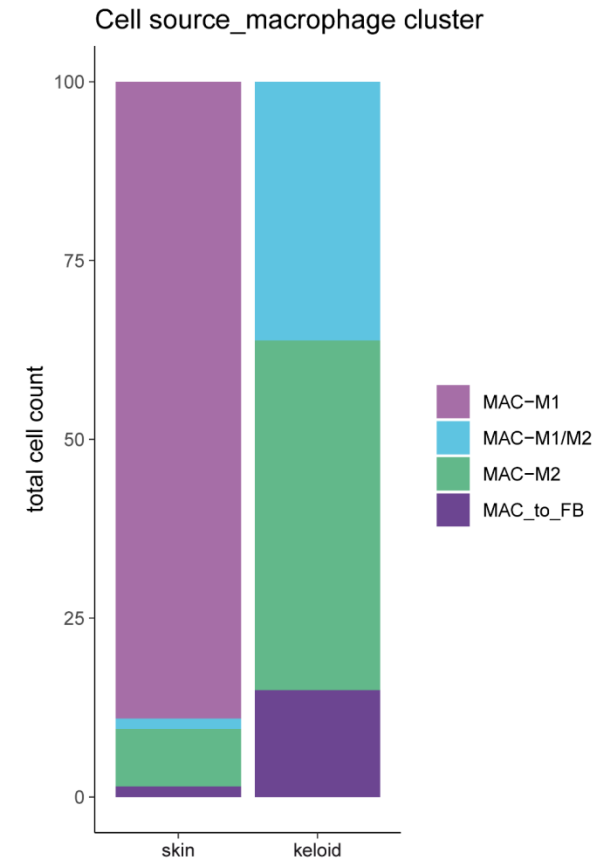
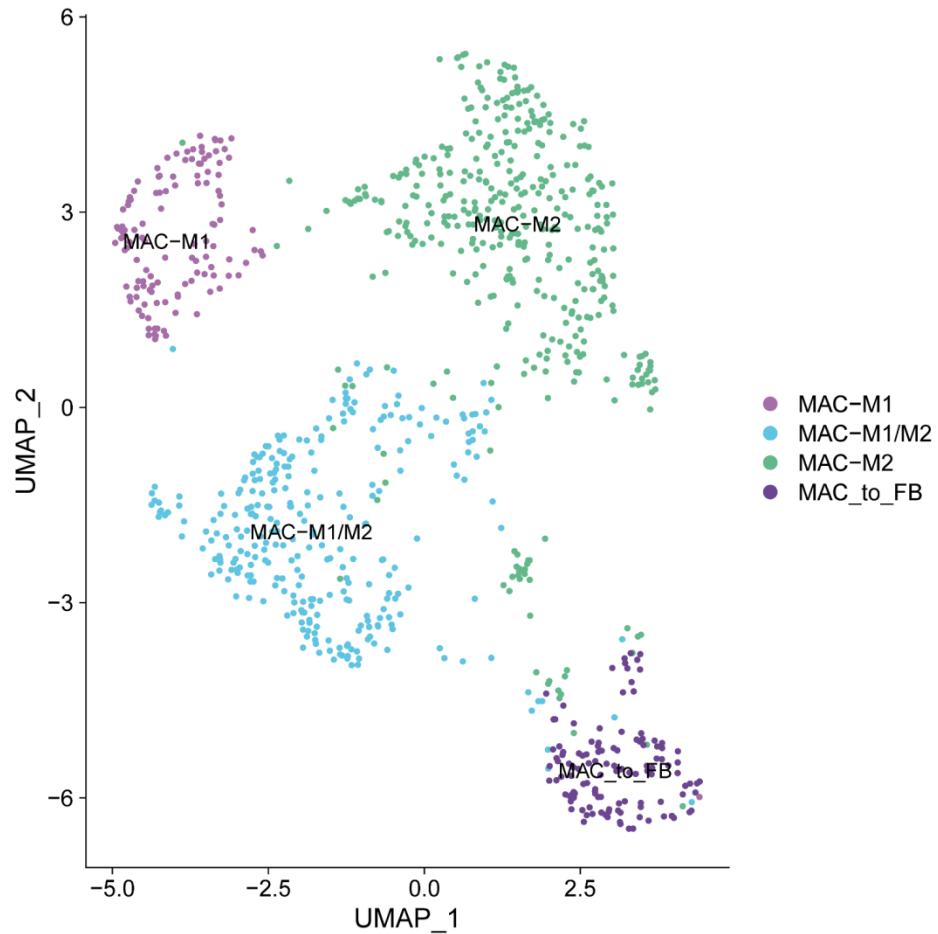
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Neural Regen Res. 2019 Aug;14(8):1335-1342

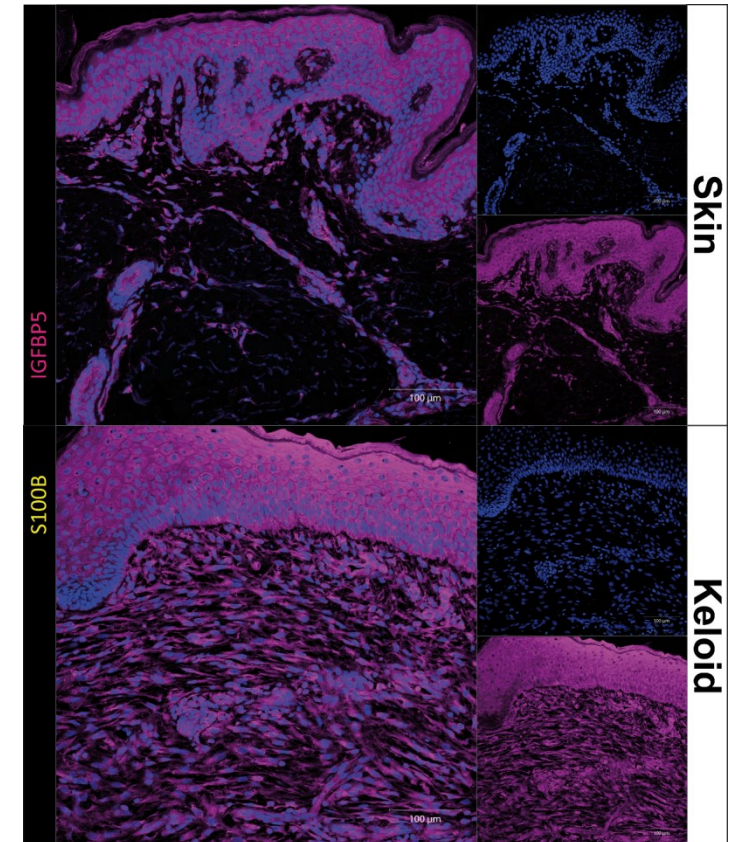
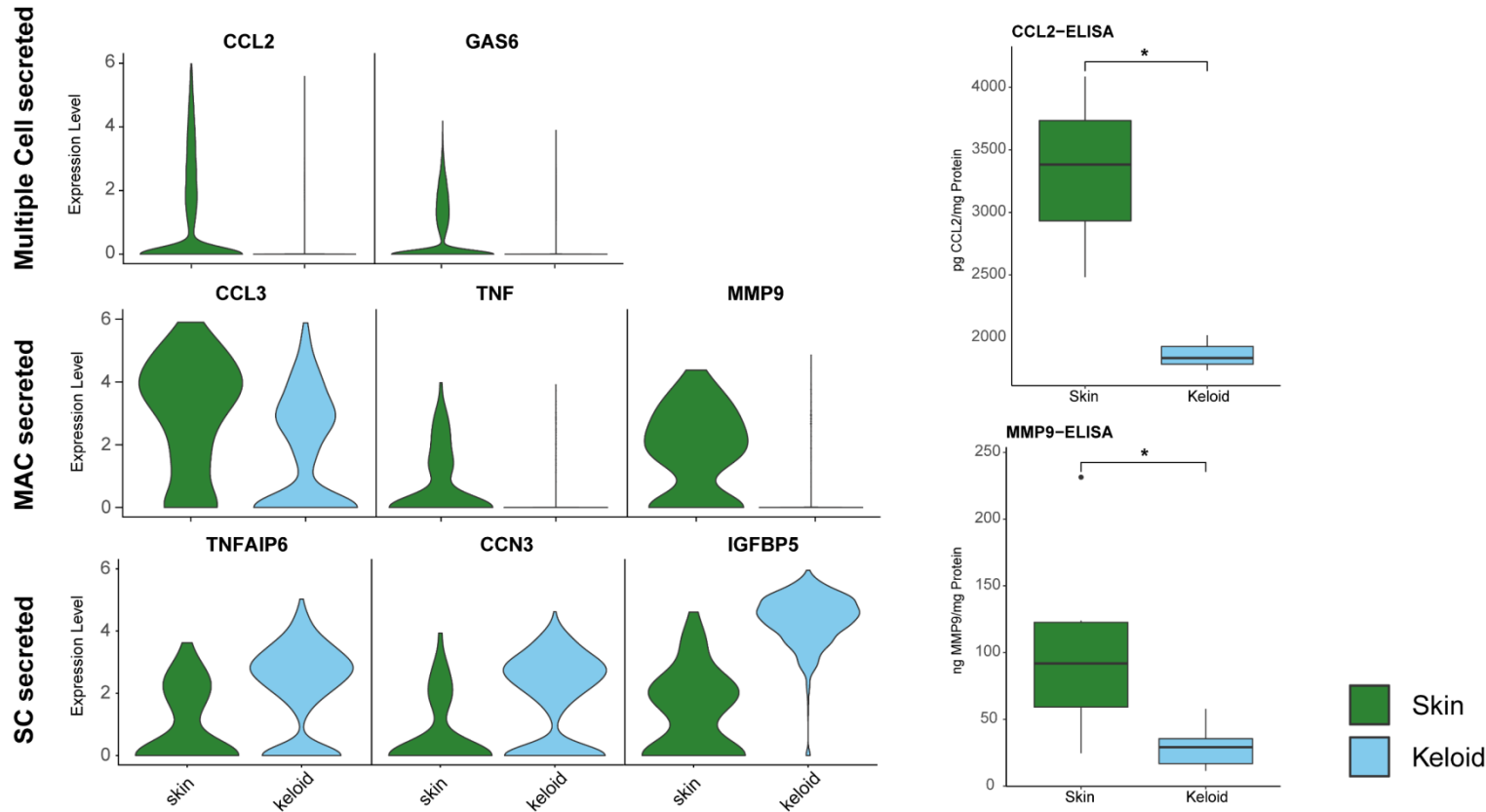
M2-Macrophage are enriched in Keloids

1



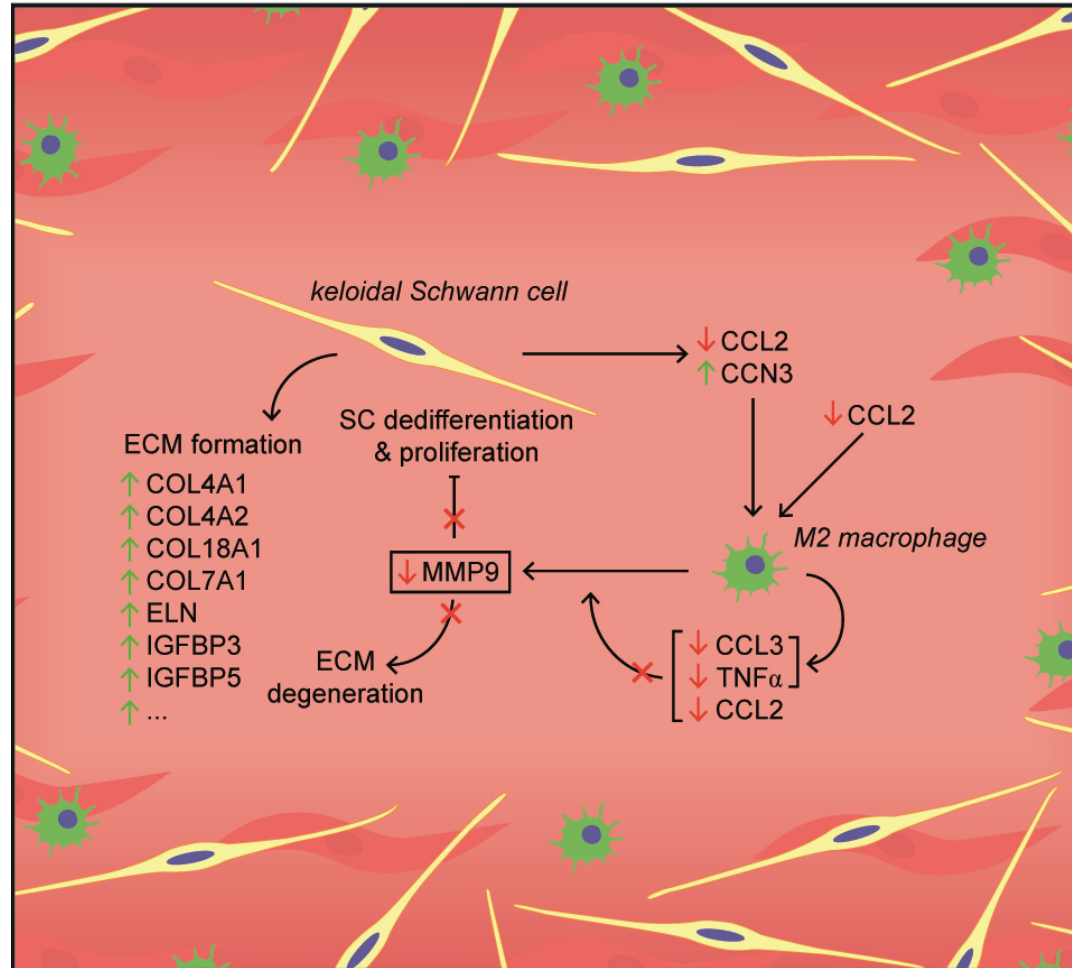
The Keloid microenvironment affects Macrophage function further promoting keloid growth

1



SC-MAC interaction

Schwann cell - Macrophage interaction in keloids



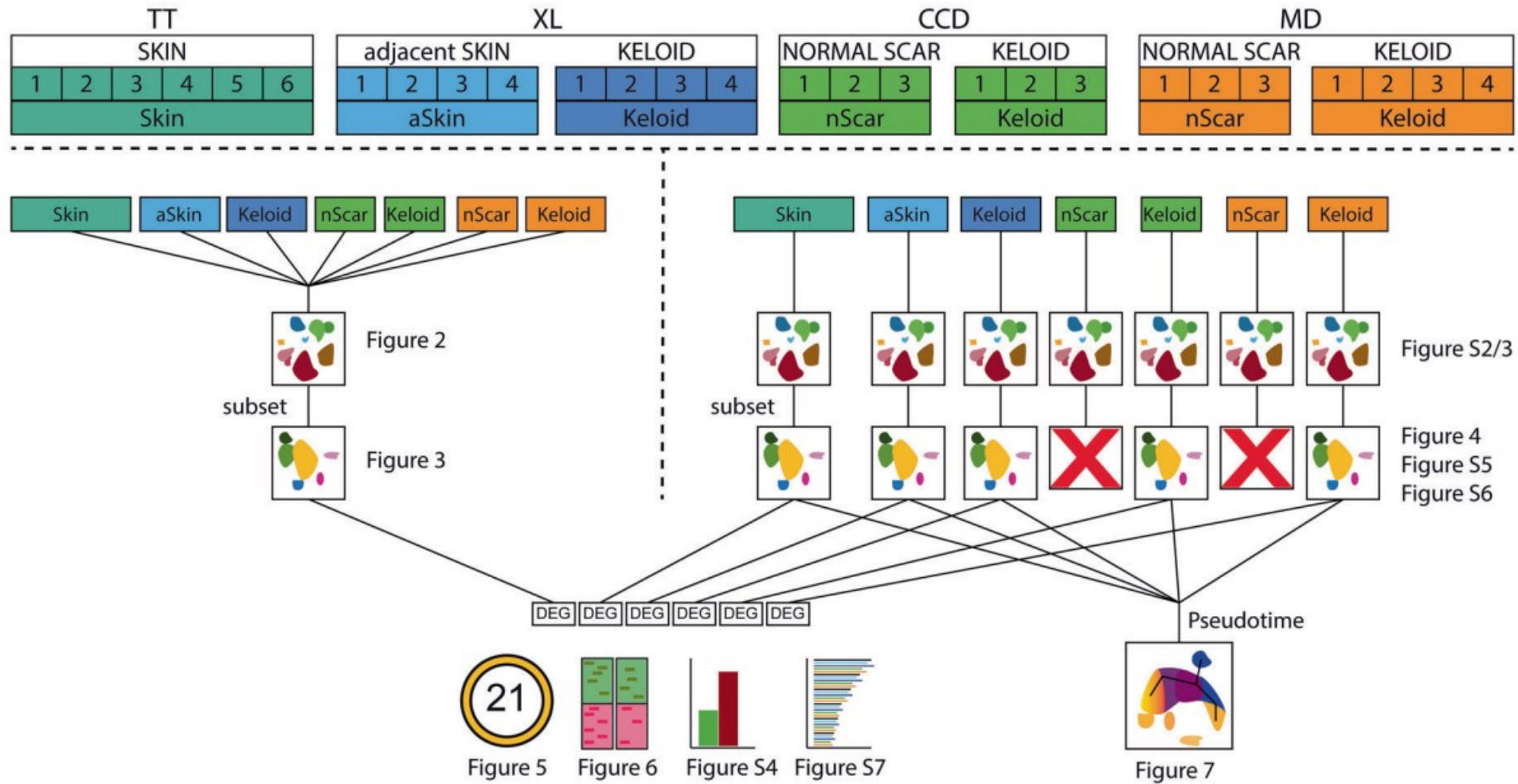
Aim of the second study

2

„Verification of keloidal Schwann cells by the investigation of independent datasets from skin, scars, and keloids “

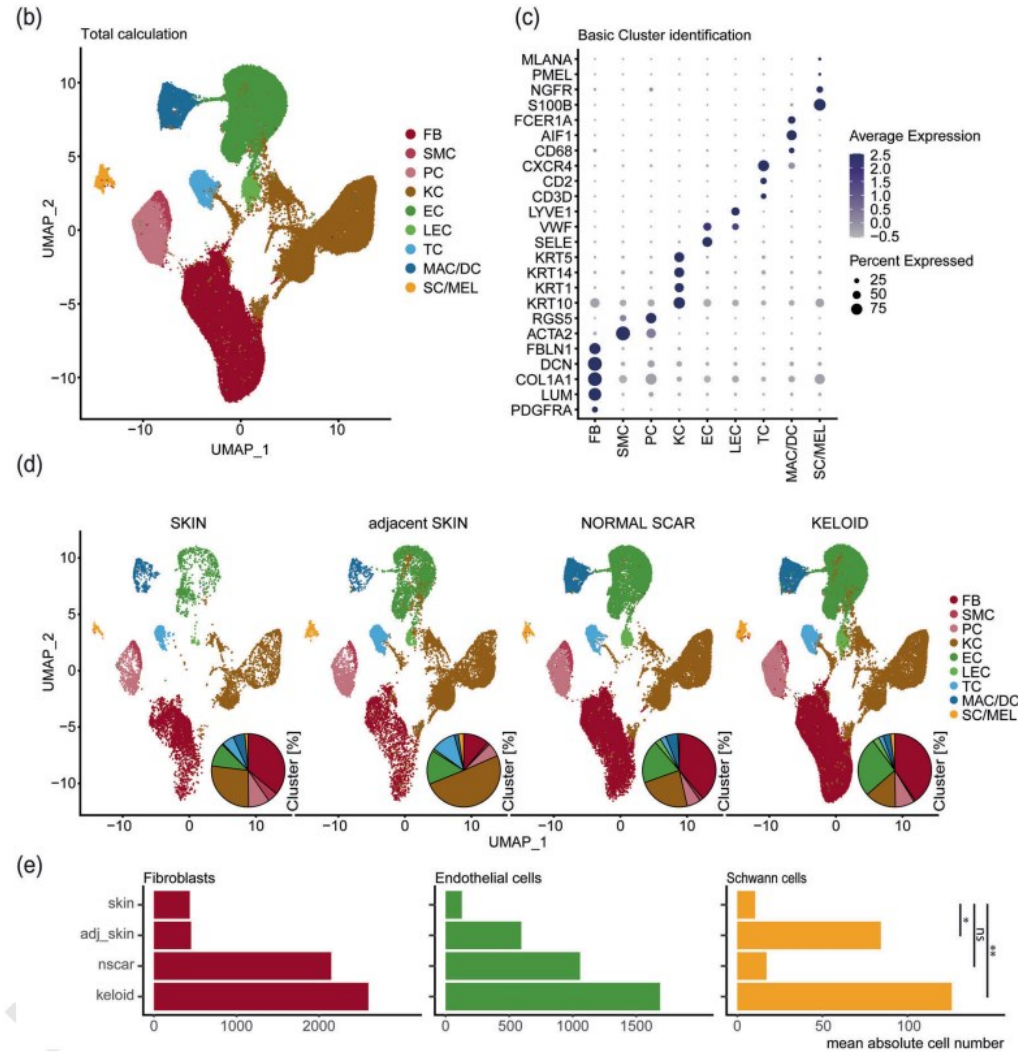
Extensive Data Analysis: total

2



Significant increase of SC-Keloid in Keloids confirmed

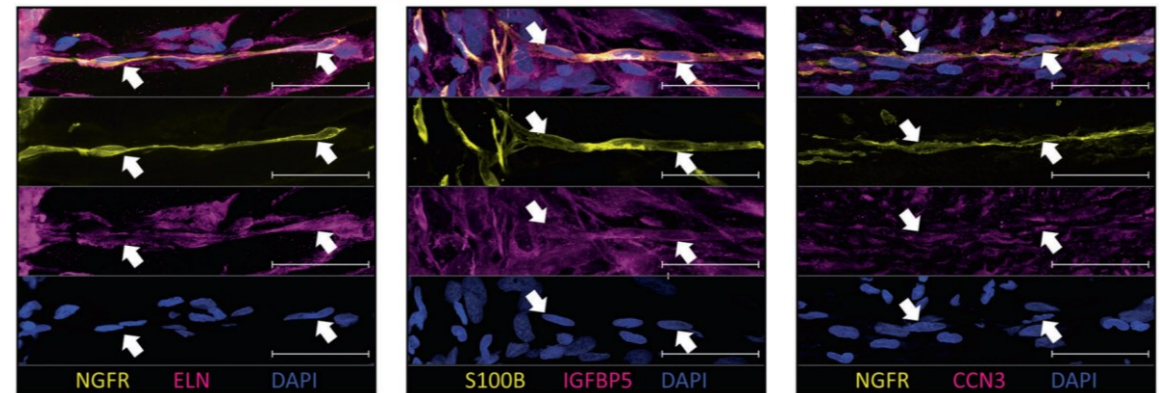
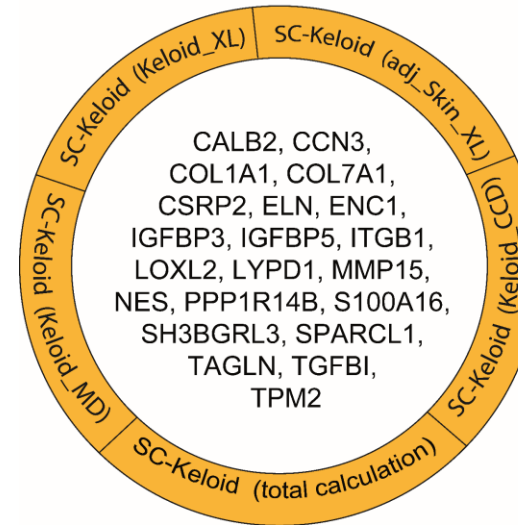
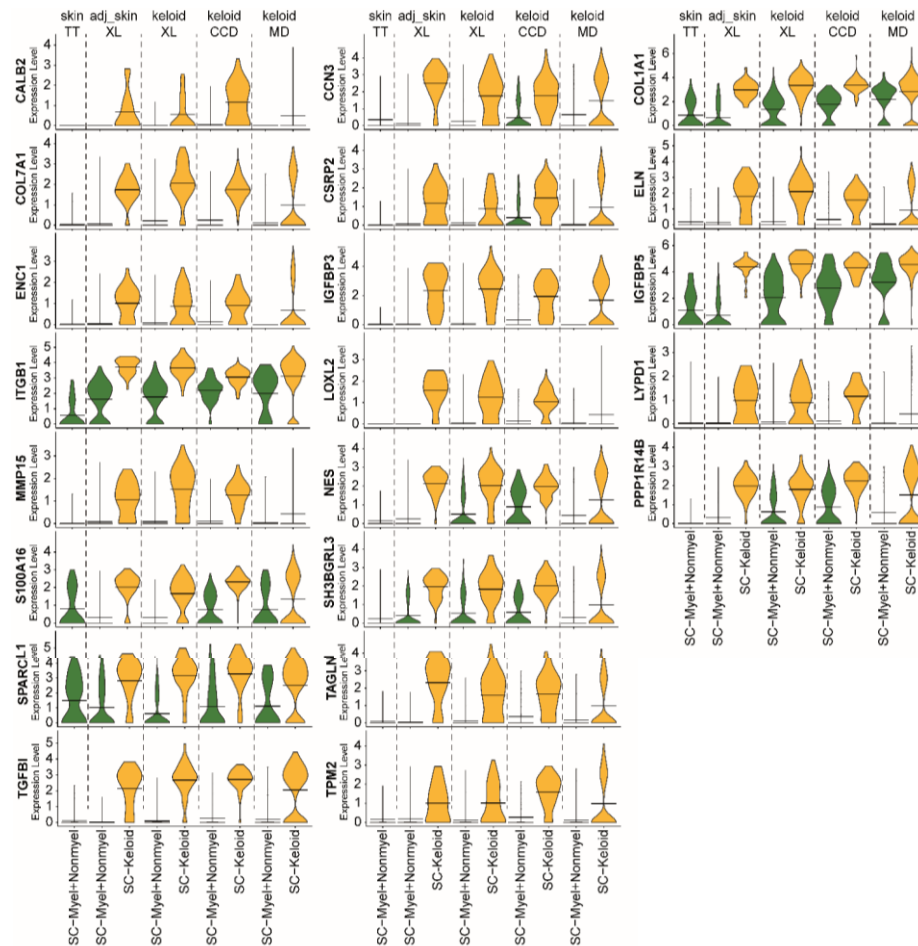
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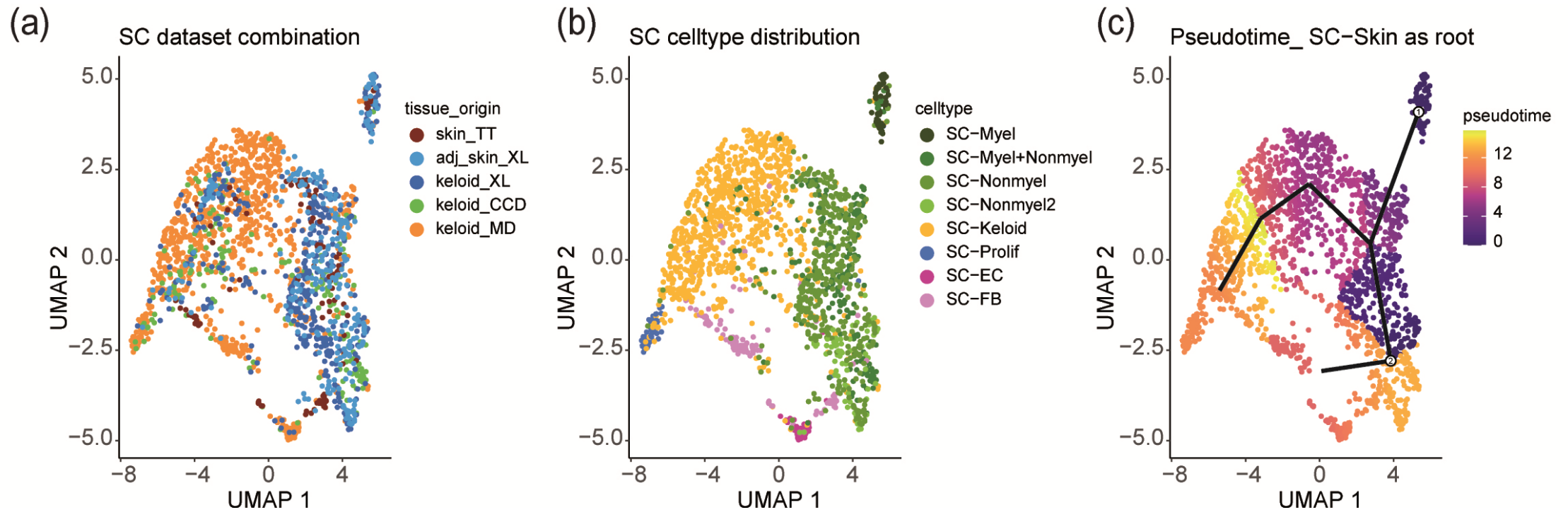
Transcriptional profile of SC-Keloid is conserved across multiple scRNAseq studies

2

SC-Keloid gene expression pattern

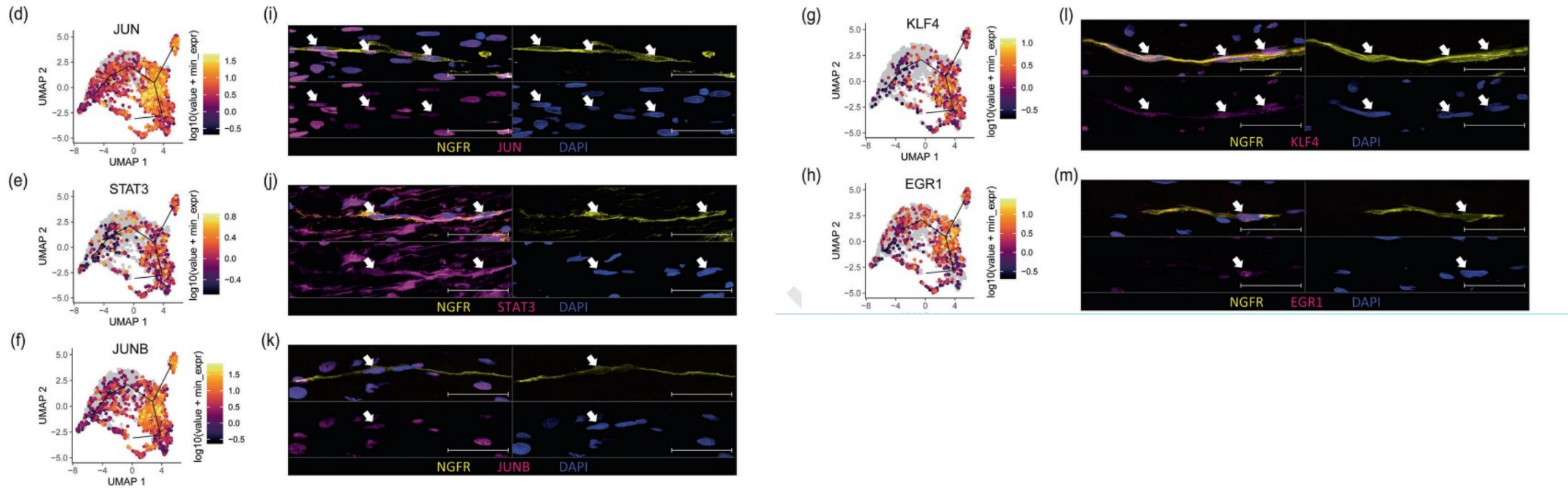


Pseudotime analysis uncovers pivotal genes in the dedifferentiation track of Schwann cells



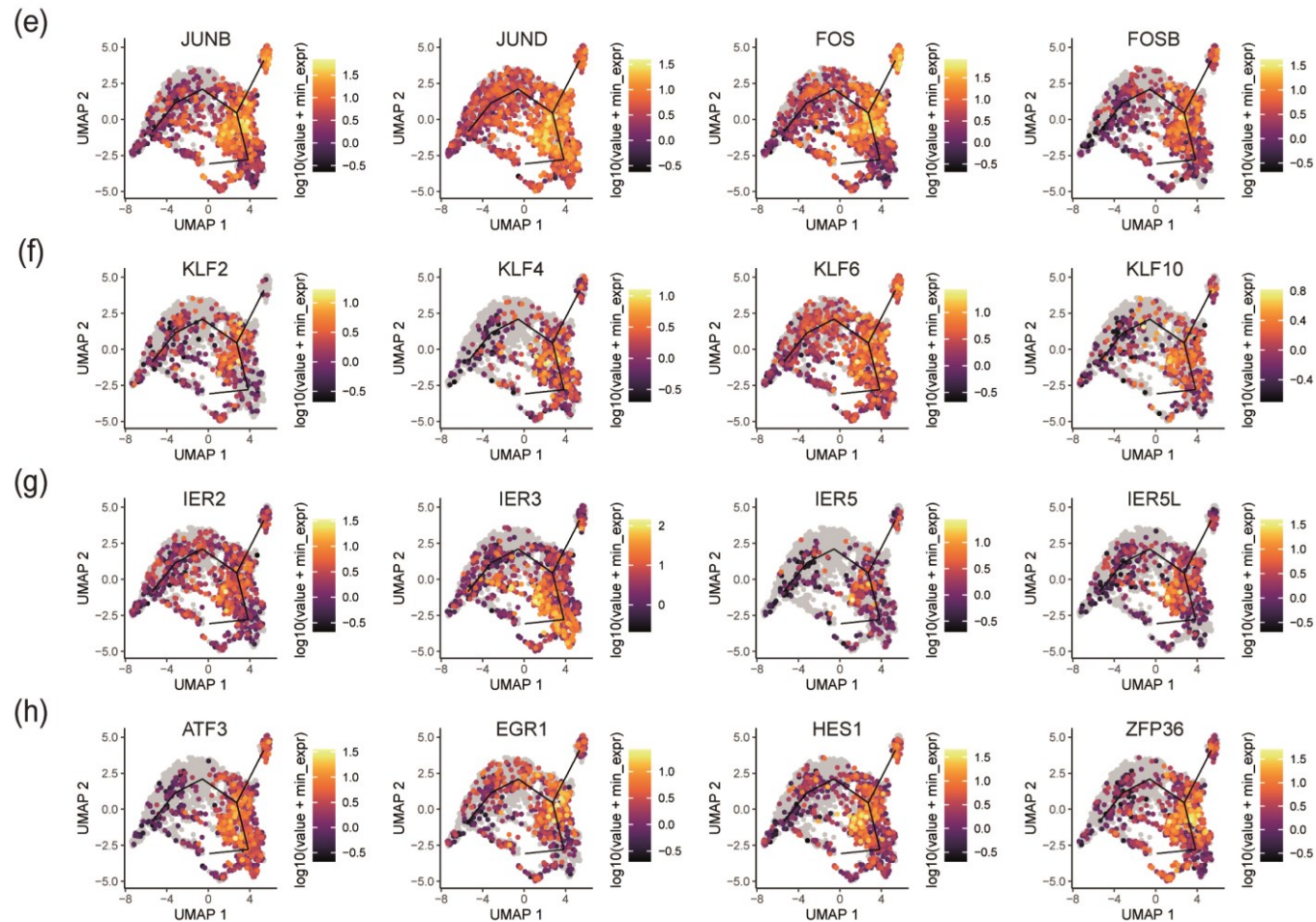
Pseudotime analysis uncovers pivotal genes in the dedifferentiation track of Schwann cells

2



Bioinformatics analysis provided evidence for a role of transcription factors of the AP1, STAT, and KLF families

2



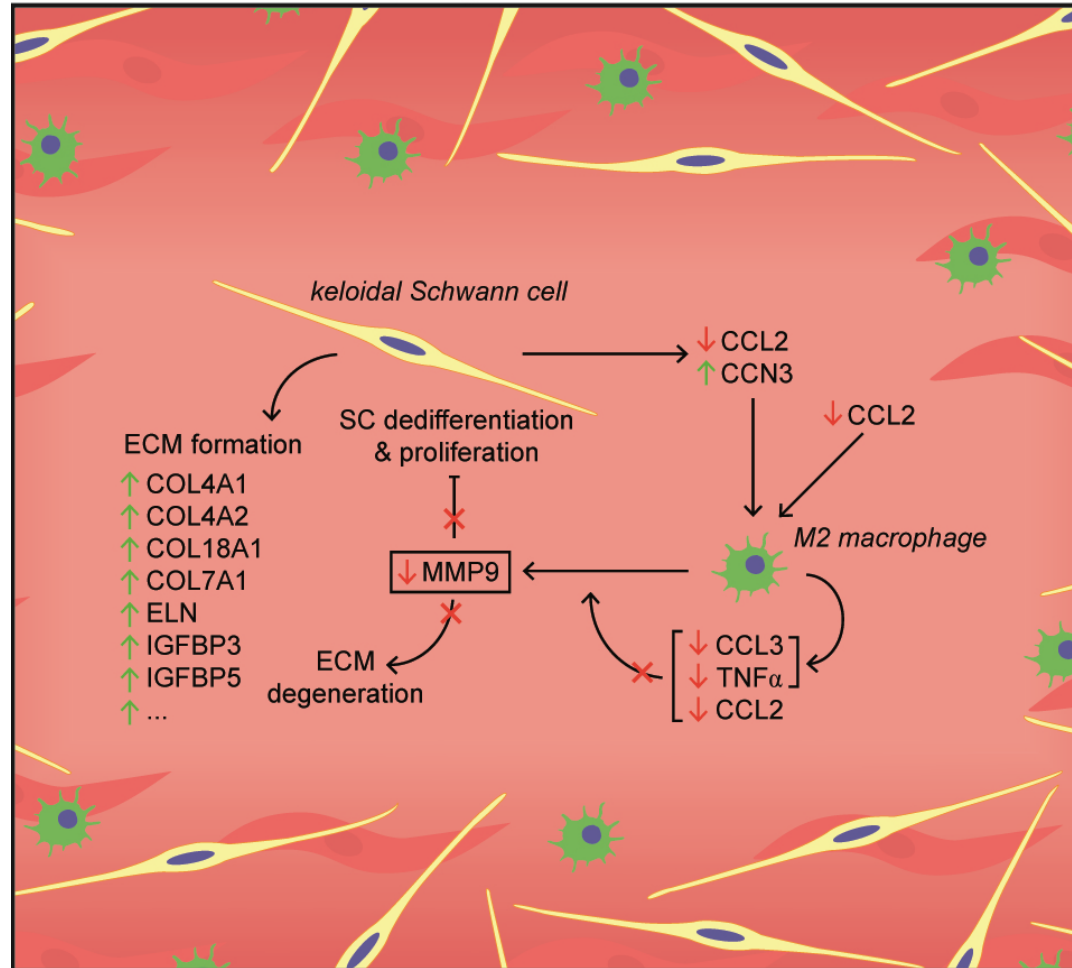


- 1) Schwann cells dedifferentiate, proliferate and in the keloid stroma
- 2) Schwann cells support extracellular matrix formation in keloids
- 3) Keloidal Schwann cells express a characteristic transcriptional pattern

SC-MAC interaction



Schwann cell - Macrophage interaction in keloids





Jan Ankersmit
Michael Mildner
Tamara Weiss
Maria Laggner
Dragan Copic
Katharina Klas
Daniel Bormann
Matthias Wielscher
Karin Pfisterer

Thank you!

„The time is out of joint!“

[William Shakespear, Hamlet]

Thank you!

