during aging, increased microbiota-derived circulating PAMPs signal into multiple hematopoietic populations, leading to increased BM levels of IL-1, which imposes a myeloid-differentiation bias in HSCs without affecting their self-renewal capacity (Kovtonyuk et al., 2022). Thus, while it is clear that the microbiome has an important effect on HSC biology and hematopoiesis, the mechanisms by which it does so are diverse. It will be exciting and medically relevant to achieve a comprehensive integration of all these components into a more complete picture.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Cut out that YAPping: Mechanisms to reduce scar formation

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https://doi.org/10.1016/j.stem.2022.01.005

Tissue repair in adult mammals lacks the regenerative ability of many tissues in other adult organisms like axolotl and newts. In this issue of *Cell Stem Cell*, Mascharak et al. use multi-omics approaches to identify an essential role for the transcription factor Trps1 in Yap-inhibited fibroblasts' tissue regenerative responses in murine skin.

Tissue repair requires a coordination of cellular and molecular mechanisms to return an injured tissue back to a functional state. While these mechanisms vary from tissue to tissue, mammalian skin repair primarily prioritizes wound closure and scar formation to provide rapid re-establishment of the essential, external barrier against pathogen invasion and water loss (Shook et al., 2018). While large wounds in *Mus musculus* can form a regenerative healing process that includes appendage reformation, including hair follicles and their associated dermal adipocytes, small wounds in mice and most wounds in adult human skin do not regenerate but rather repair into a less functional scar lacking skin appendages (Ito et al., 2007; Plikus et al., 2017). Yet, the mechanisms that control the balance between regenerative repair and scar formation are not well understood.

Yes-associated protein (YAP) is a transcription factor downstream of the Hippo signaling pathway that impacts cellular growth and response to mechanical stimuli (references within Mascharak et al., 2021). Recent work by the Longaker laboratory showed that inhibition of YAP signaling in fibroblasts after skin injury results in skin regeneration, including hair follicle regeneration, and extracellular matrix (ECM) deposition like non-wounded skin (Mascharak et al., 2021), rather than skin repair and scar formation. In this issue of *Cell Stem Cell*, Mascharak et al. identify the molecular mechanisms that underlie the ability of fibroblasts to execute a regenerative program of tissue repair (Mascharak et al., 2022) (Figure 1).

Using multiple unbiased "-omics" approaches, the authors compared fibroblasts from a regenerative program (YAP-inhibited) and reparative programs across multiple time-points of wound healing (Mascharak et al., 2022). The authors found that fibroblasts upregulated stem cell and developmental pathways when in a regenerative program. Specifically, after injury, YAP-inhibited fibroblasts upregulated Transcriptional Repressor GATA Binding 1 (Trps1) and activated Wnt signaling, implicating these

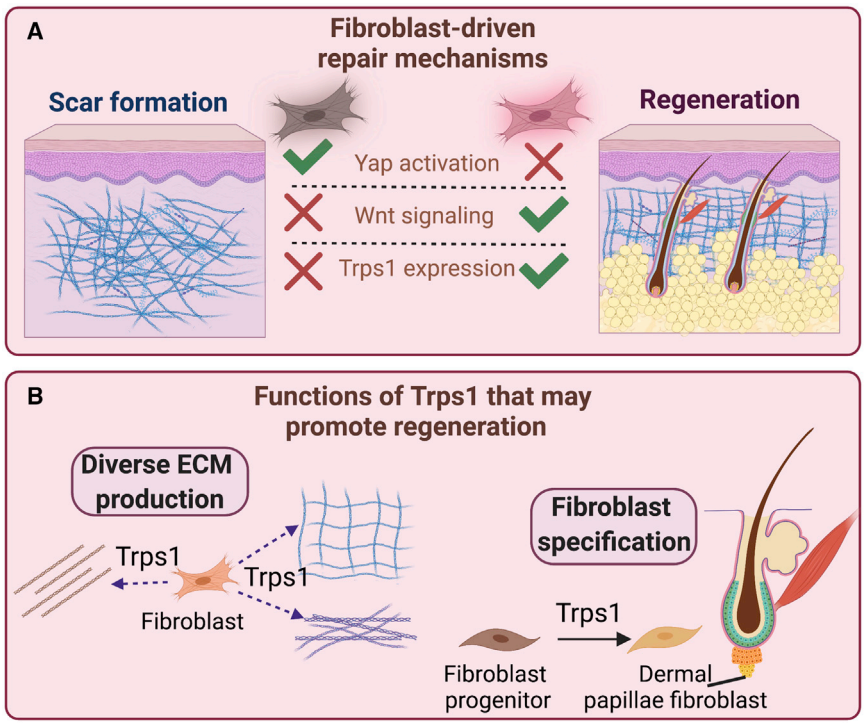

Figure 1. Yap and Trps1 promote skin regeneration instead of scar formation

(A) During reparative wound healing, healed skin forms a scar with disorganized extracellular matrix (ECM), and fibroblasts activate YAP signaling. When YAP signaling is inhibited in fibroblasts during repair, Wnt signaling is activated, Trps1 is expressed, and regenerative healing occurs, including hair follicle formation and organized ECM.

(B) Trps1 is known to regulate diverse ECM gene expression and fibroblast specification. These roles may allow Trps1 to contribute to skin regenerative phenotypes in fibroblasts.

transcriptional and signaling mechanisms in promoting tissue regeneration and reducing scar formation.

To investigate whether Trps1 functions to regulate tissue repair, Mascharak et al. performed gain- and loss-of-function studies after skin injury (Mascharak et al., 2022). Lentiviral-induced overexpression of *Trps1* broadly in *Col1a1*+ fibroblasts resulted in regeneration of a few hair follicles and a shift toward ECM organization found in naive skin. In contrast, hair follicle regeneration and unwounded ECM deposition was abrogated in YAP-signaling-inhibited wounds in which *Trps1* was lentivirally knocked down in *Col1a1*+ skin fibroblasts. Thus, Trps1 is necessary for Yap-inhibition-induced skin regeneration and partially sufficient to promote fibroblast phenotypes that promote regeneration rather than scar formation.

Growing evidence is emerging that implicates a role for Trps1 in regulating the specification of unique fibroblasts in several tissues (Figure 1). Trps1 expression in pre-odontoblasts in the developing tooth prevents premature maturation of these specialized dental fibroblasts into mature odontoblasts, which secrete components of the dental ECM for mature tooth formation (Goss et al., 2019). Trps1 is also expressed in fibroblasts during hair follicle morphogenesis (Fantauzzo et al., 2008a), where it activates mRNA expression of Wnt inhibitors and ECM proteins (Fantauzzo and Christiano, 2012). In the skin, Trps1 is upregulated in developing dermal papillae during the mid-stage specification of dermal papillae, the specialized fibroblasts that drive and control hair follicle formation (Mok et al., 2019), and mouse skin expressing a transcriptionally inactive Trps1 develop fewer hair follicles (Fantauzzo and Christiano, 2012). These functions of Trps1 likely partially contribute to the clinical phenotypes associated with trichorhinophalangeal syndrome, which results from Trps1 mutations, including sparse scalp hair and craniofacial/skeletal abnormalities (Fantauzzo et al., 2008b).

Given that mechanisms that drive hair follicle formation in large skin wounds also promote regenerative phenotypes (Ito et al., 2007; Plikus et al., 2017), exploration of additional roles of Yap signaling and Trps1 in tissue repair may lead to clinical improvements in regeneration and abrogation of scar formation. Future work exploring Trps1's role in dermal papillae specification and hair follicle reformation in skin wounds may reveal additional mechanisms that influence skin repair. Alternatively, Trps1's role in regulation of ECM gene expression in heterogenous fibroblast populations, which has been reported after skin injury (Shook et al., 2018), may reveal how distinct ECM molecules and the timing of their production influences tissue regeneration. Finally, future studies that identify additional targets of Hippo signaling that prevent tissue regeneration, and whether Yap's role in mechanical and/or cellular growth behavior can be modulated to promote tissue regeneration, will be of use to the field.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Quickly moving too slowly: Interneuron migration in Timothy Syndrome

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https://doi.org/10.1016/j.stem.2022.01.004

Aberrant migration of GABAergic interneurons during cortical neurodevelopment is implicated in Timothy Syndrome, yet the underlying mechanisms remain elusive. In this issue of *Cell Stem Cell*, Birey et al. model developing brain circuitry using "assembloids" from patients, characterizing a bimodal mechanism of mechano-chemically driven interneuron migration inefficiencies.

Timothy Syndrome (TS) is a rare multisystem disorder ranging from arrythmia to autism and is primarily driven by mutations in *CACNA1C*, encoding the pore-forming subunit of the L-type calcium channel (LTCC) $Ca_V1.2$. Voltage-gated calcium channels couple neuronal depolarization to calcium entry, triggering physiological responses that include neurotransmission and gene expression. Rare mutations and common polymorphisms in voltage-gated calcium channel genes are associated with a variety of neurological and psychiatric diseases, including autism, schizophrenia, and epilepsy.

The Paşca Lab previously applied human induced pluripotent stem cell (hiPSC) organoid models to demonstrate that TS-patient-derived glutamatergic (Birey et al., 2017; Paşca et al., 2011) and GABAergic (Birey et al., 2017) neurons show deficits in calcium signaling. Perhaps less expected, they further uncovered a cell-autonomous migration defect in TS GABAergic interneurons that can be rescued by pharmacologically manipulating LTCCs (Birey et al., 2017). This inefficiency in interneuron migration reflected a reduction in saltation length despite a surprising concomitant increase in saltation frequency (Birey et al., 2017). It was unclear at the time how these apparently contradictory outcomes were mediated. Here, Birey et al. resolve how interneuron saltation length and frequency are regulated by distinct molecular mechanisms (Birey et al., 2022), elucidating an LTCC-mediated regulation of interneuron migration and its disruption under the context of TS.

The authors first combined fast, high-resolution long-term live cell imaging and applied markerless pose estimation based on transfer learning and deep neural networks to precisely track simultaneously moving cellular compartments of migrating cortical interneurons in forebrain assembloids. Whereas in control interneurons the rear and front of the soma moved in synchrony, TS interneurons revealed an uncoupling of soma rear-front coordination. Given that cellular contractility is a calcium-dependent process (Bers, 2002), pharmacological modulation of $Ca_V1.2$ revealed an impact on saltation length but not frequency of interneuron migration in TS. Reducing extracellular concentrations of calcium reduced interneuron saltation frequency in control and TS spheroids but revealed genotype-dependent effects on saltation length, partially restoring saltation length in TS interneurons and reducing length in control interneurons.

These seemingly distinct observations were mechanistically connected; the team demonstrated that changes in cell-rear actomyosin signaling mediate the saltation length difference, whereby calcium-bound calmodulin activates Myosin Light Chain Kinase (MLCK), which in turn phosphorylates Myosin Light Chain (MLC) and induces MLC interaction with F-actin and contraction at the soma rear.