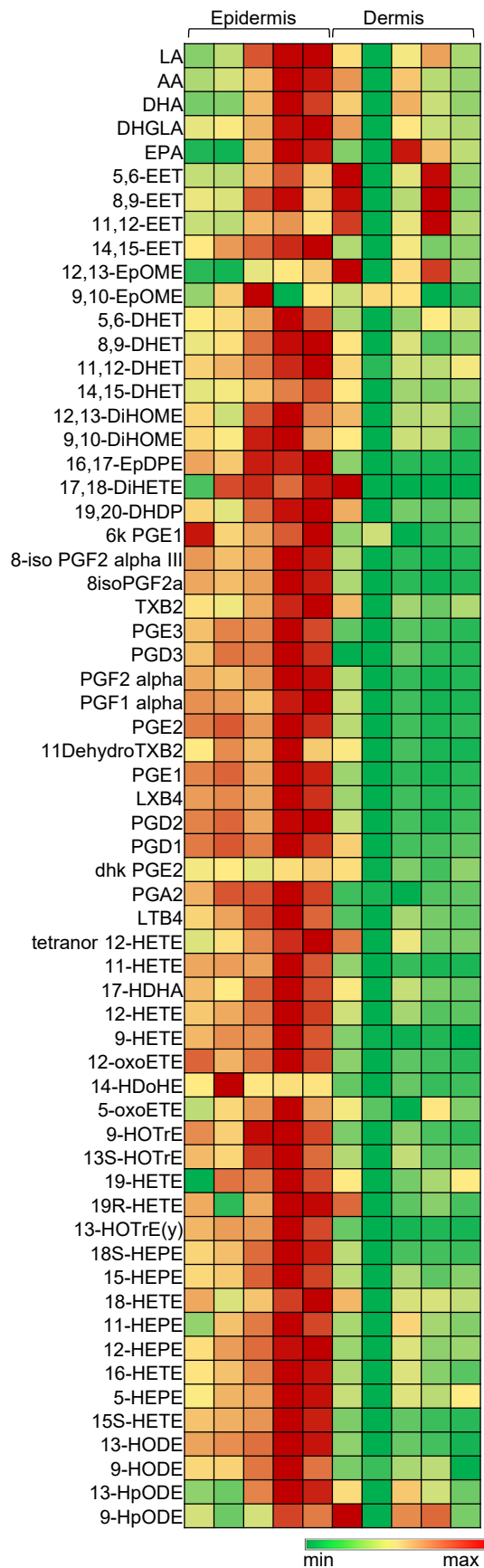
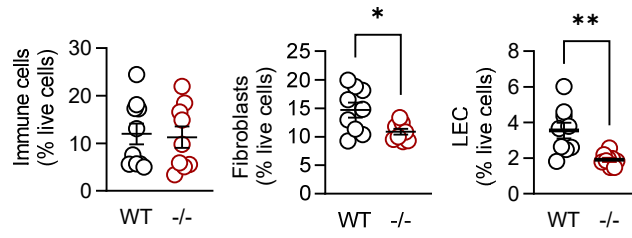


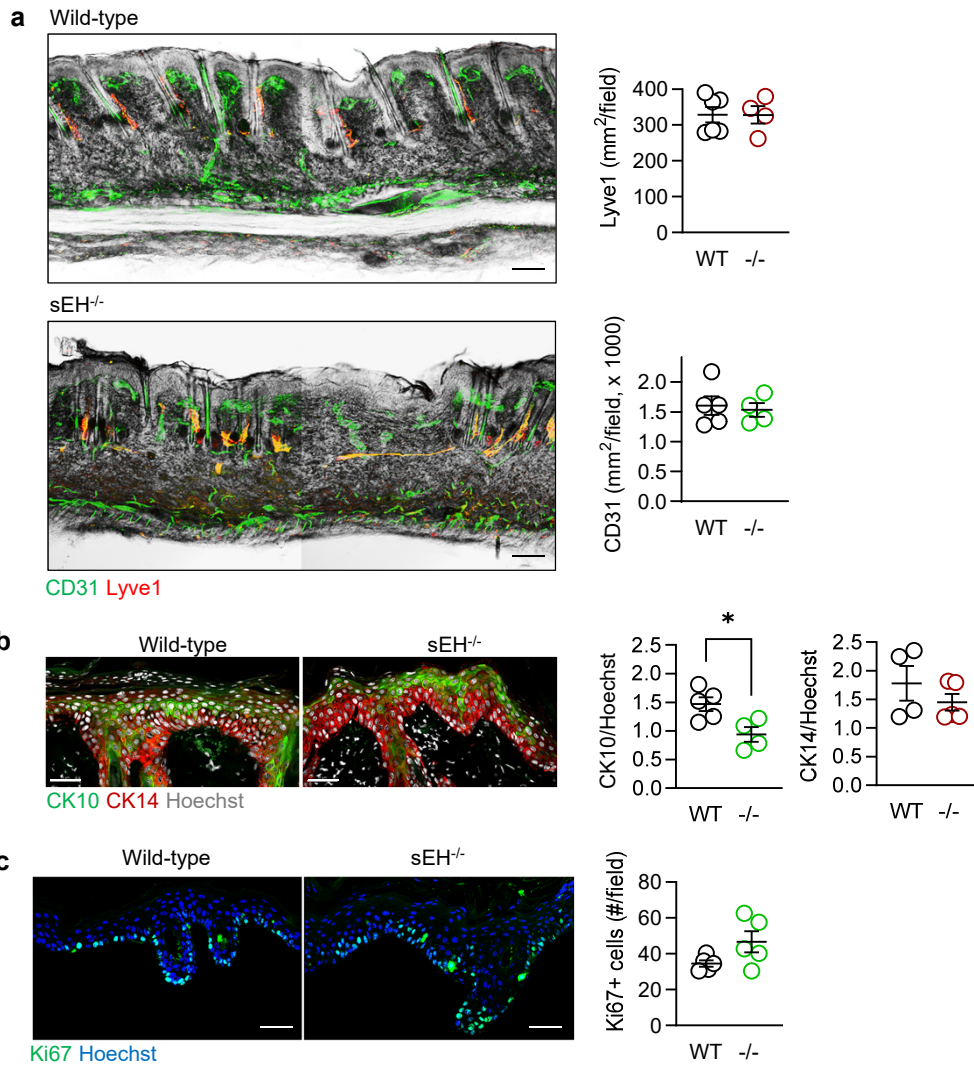
**Supplementary Fig. 1. Confocal images showing the localization of the sEH in dorsal skin from Ephx2-td-mCherry mice.** (a) Immunofluorescent signal of mCherry (red), sEH (green) and DAPI (blue) in Ephx2-td reporter mice dorsal skin. (b) Staining of wild-type skin with secondary antibody only were used as negative control. Comparable results were obtained in skin from 3 additional mice.



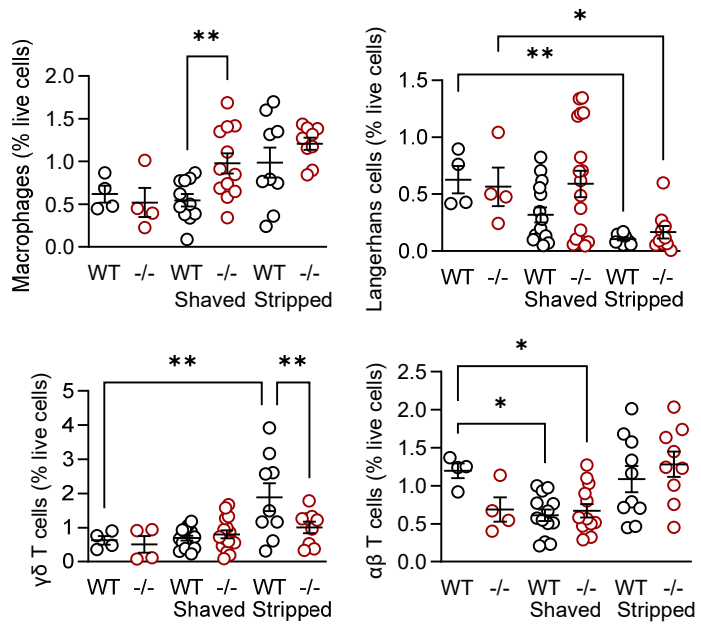
**Supplementary Fig. 2.** LC-MS/MS-based quantified of free fatty acids and PUFA mediators in the epidermis and dermis of murine skin: n=5 animals. AA, arachidonic acid; LA, Linoleic acid; DHA, Docosahexaenoic acid; DHGLA, dihomo-gamma-linoleic acid; EPA, Eicosapentaenoic acid; EET, epoxyeicosatrienoic acid; DHET, dihydroxyicosatrienoic acid; EpOME, epoxyoctadecenoic acid; DiHOME, dihydroxyoctadecenoic acid; DHDP, dihydroxyicosapentaenoic acid; PG, prostaglandins; TX, Thromboxane; LTB4, Leukotriene B4; HETE, hydroxyeicosatetraenoic acid; HDHA hydroxydocosahexaenoic acid; oxoETE, oxo-eicosatetraenoic acid; HOTrE, hydroxy-10E,12Z,15Z-octadecatrienoic acid; HEPE, hydroxy-5Z,8Z,10E,14Z,17Z-eicosapentaenoic acid; HpODE, hydroperoxy-9Z,11E-octadecadienoic acid; HODE, hydroxy-10E,12Z-octadecadienoic acid.



**Supplementary Fig. 3.** FACS analysis of fibroblasts, lymphatic endothelial cells (LEC), and immune cells in skin from wild-type (WT) and sEH<sup>-/-</sup> (-/-) mice; n=9 mice per group. (Student's t test). \*P<0.05, \*\*P<0.01



**Supplementary Fig. 4. Comparison of imiquimod-induced inflammation in wild-type and sEH<sup>-/-</sup> mice.** (a) CD31 and Lyve1 in dorsal skin from wild-type (WT) and sEH<sup>-/-</sup> (-/-) mice, 6 days after treatment with imiquimod, bar = 50  $\mu$ m; n = 4-5 mice per group. (b&c) CK10, CK14 (b) and Ki67+ cells (c) in dorsal skin from wild-type (WT) and sEH<sup>-/-</sup> (-/-) mice, 6 days after treatment with imiquimod, bar = 50 $\mu$ m for immunostained samples and 100 $\mu$ m for H&E staining; n = 4-5 mice per group (Student's t test). \*P<0.05.



**Supplementary Fig. 5. Consequences of sEH deletion on the immune response to mechanical skin injury.** Macrophages, langerhans cells,  $\alpha\beta$ T-cells and  $\gamma\delta$ T-cells in the dorsal skin of unshaven wild-type (WT) and sEH<sup>-/-</sup> (-/-) mice before and 24 hours after either shaving or shaving and stripping; n=4-9 mice per group (two way ANOVA and uncorrected Fisher's LSD test). \*P<0.05, \*\*P<0.01.