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Single-cell RNA sequencing analysis of a COVID-19-associated maculopapular rash in a pororid patient treated with ustekinumab

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The 2019 novel coronavirus (COVID-19) primarily affects the respiratory system, but extra pulmonary manifestations, including the skin, have been well documented. However, transcriptomic profiles of skin lesions have not been performed so far. Here, we present a single-cell RNA sequencing analysis in a patient with COVID-19 infection suffering from a maculopapular skin rash while on treatment with ustekinumab for his underlying psoriasis. Results were compared to 4 healthy control individuals. Lesional tissue showed a primarily type-1 interferon triggered pattern with highest levels of genomic deregulation in keratinocytes, but no evidence of type-2, type-17 or type-22 T-cell immune activation. Viral entry receptors ACE2 and TMPRSS2 were sparsely expressed in keratinocytes of the patient, while ACE2 expression was not detected in healthy control individuals. Among immune cells, cytotoxic lymphocytes showed upregulation of IFNG and killer molecules GZMA, GZMB, GZMH and GZM1, and high expression of killer molecules was not detected in several anti-inflammatory mediators in stromal cells including fibroblasts, including the dual specificity protein phosphatase 2 DUSP2. This first transcriptomic description of a COVID-19 associated rash might help to gain a better understanding of SARS-CoV-2 associated skin conditions.

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Dissecting key features of early-stage atopic dermatitis in pre-clinical models

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Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with barrier defects and dysbiosis. The development and progression of AD critically depends on the action of type 2 immune cells and mediators, whose identity and chronic appearance in the establishment of AD are still elusive. We aim to disclose the kinetics and cellular contributions of type 2 immune responses in AD, focusing on the dynamics of interleukin (IL)-4 induction during skin inflammation in pre-clinical models. To mimic barrier impairment, mice were subjected to repeated tape stripping (TS) of their shaved back skin. Medium containing Staphylococcus aureus was applied to induce dysbiosis. Both conditions were accompanied by increased mRNA expression levels of IL-13, IL-4 and CCL22. Analyses of the skin microenvironment in WT mice showed a shift toward predominance of Staphylococci one day after TS. Thus, skin barrier impairment likely serves as an entry point for inflammation. Among all type 2 relevant cytokines examined, IL-13 was the most prominent one. On day two, we detected the highest increase of IL-31 protein expression in the combined treatment, indicating an additive effect of TS and S. aureus. On day six, this effect was no longer visible, since S. aureus had a greater impact on IL-33 protein production. By contrast, TSLP protein expression was similarly high in all groups at that time point, indicating differentially regulated alarmins in all conditions. We show that the initial phase is a highly dynamic interplay between barrier damage and dysbiosis, contributing differently to AD-like inflammation. These findings will help to develop treatment strategies towards personalized therapy in AD.

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Mechanism of cytosolic nucleic acid-induced CXCL1 expression of human keratinocytes

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Cytosolic nucleic acids (cNAs) are highly abundant in psoriatic skin and contribute to the development and progression of AD, focusing on the dynamics of interleukin (IL)-4 induction during skin inflammation in pre-clinical models. To mimic barrier impairment, mice were subjected to repeated tape stripping (TS) of their shaved back skin. Medium containing Staphylococcus aureus was applied to induce dysbiosis. Both conditions were accompanied by increased mRNA expression levels of IL-13, IL-4 and CCL22. Analyses of the skin microenvironment in WT mice showed a shift toward predominance of Staphylococci one day after TS. Thus, skin barrier impairment likely serves as an entry point for inflammation. Among all type 2 relevant cytokines examined, IL-13 was the most prominent one. On day two, we detected the highest increase of IL-31 protein expression in the combined treatment, indicating an additive effect of TS and S. aureus. On day six, this effect was no longer visible, since S. aureus had a greater impact on IL-33 protein production. By contrast, TSLP protein expression was similarly high in all groups at that time point, indicating differentially regulated alarmins in all conditions. We show that the initial phase is a highly dynamic interplay between barrier damage and dysbiosis, contributing differently to AD-like inflammation. These findings will help to develop treatment strategies towards personalized therapy in AD.

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Abnormal type VII collagen expression in non-lesional psoriatic skin

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The healthy-looking non-lesional (NL) psoriatic skin already carries some alterations. These alterations include extracellular matrix defects such as the disruption of laminnan networks, which may lead to impaired keratocyte adhesion to the basal membrane. This process is associated with aberrant expression of the EDA-TN integrin complex and the extracellular-matrix-containing fibronectin (EDA-TN) around basal keratinocytes. In our previous work, in NL psoriatic skin the expression of EDA-TN was increased compared to healthy (H) skin. Fibronectin is a key type VII collagen. Therefore, we aimed to examine type VII collagen presence and function in NL and H skin. We found that NL skin displayed reduced expression of type VII collagen compared to H skin by immunostaining and transmission electron microscopy. Type VII collagen protein decreased in NL and H skin by western blot. We detected the TH domain by polyclonal antibody but not the monomeric form of type VII collagen. Cultured fibroblast from NL skin showed reduced type VII collagen expression compared to the H fibroblast while there was no change observed in keratinocytes by RT-qPCR and western blot. In NL skin pSTAT3 activation was increased compared to H skin. Blocking STAT3 resulted in increased type VII collagen in H fibroblasts but it didn’t change in NL derived fibroblasts, indicating the role of STAT3 in the regulation of type VII collagen expression.

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Eukaryotic translation initiation factor 4e (eIF4E) as a target of anti-psoriatic treatment

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Eukaryotic translation initiation factor 4e (eIF4E) has been known to play a crucial role in the regulation of gene expression in eukaryotes and to affect many essential cellular processes, including proliferation, apoptosis and differentiation. We and others found eIF4E and other eIFs upregulated in human psoriatic skin and thus hypothesized that they are involved in the pathophysiology of psoriasis and can serve as direct topical targets for anti-psoriatic treatment. We used specific eIF4E siRNA or birciclib an eIF4E inhibitor in HaCaT cells, a human 3D-psoriasis tissue model as well as the imiquimod and TGFβ mouse model to downregulate the protein and mRNA expression of eIF4E itself and its two complex partners eIF4A and G, as well as other eIFs (e.g. eIF1A, eIF2β, eIF3A, eIF1B, eIF5 and eIF6). This inhibition abolished psoriatic inflammation in both the imiquimod and TGFβ mouse model, as well as in a human 3D-psoriasis tissue model. Downregulation of eIF4E and the other eIFs by application of birciclib (particularly when given topically) was linked to the normalization of cellular proliferation, restoration of the inflammatory milieu and epidermal hyperplasia of psoriasis, and normalization of levels of pro-inflammatory cytokines (e.g. TNFα, IL-1β and IL-22), as well as keratocyte differentiation markers (e.g. KRT16 and FG). These results demonstrate translational imbalance and underline the crucial role played by eIF4E and other eIFs in the pathophysiology of psoriasis. This work opens up new avenues for the development of novel topical anti-psoriatic treatment strategies targeting eIF4E and/or other eIFs.