FA 1468/2-1

Gefördert durch DFG Deutsche Forschungsgemeinschaft

Keratinocyte-Specific Function of Hypoxia-Inducible Factor-1alpha (HIF1a) in UVB-Induced Immunosuppression

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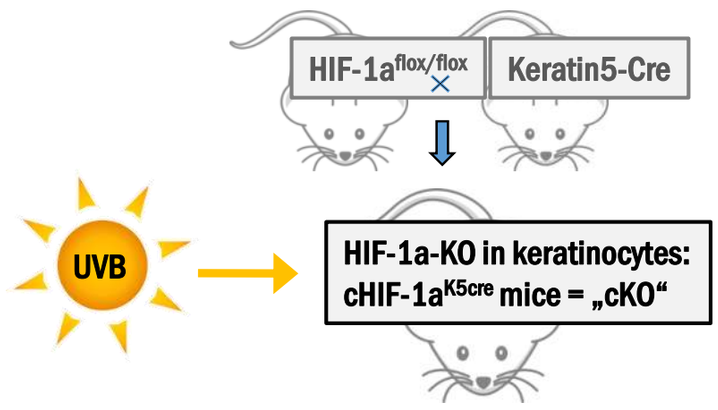
Background

- ○Trancription factor HIF1a: Per-Arnt-Sim Family → responsive to environmental change
- ○Cell-type specific functions
- ○Low steady state expression in epidermis, increases with age
- ○Involved in immune reactions
- ○Inducible by UVB irradiation in keratinocytes

→ How does HIF1alpha in keratinocytes contribute to extrinsic aging consequences including immunosuppression?

UVB-induced photodamage:

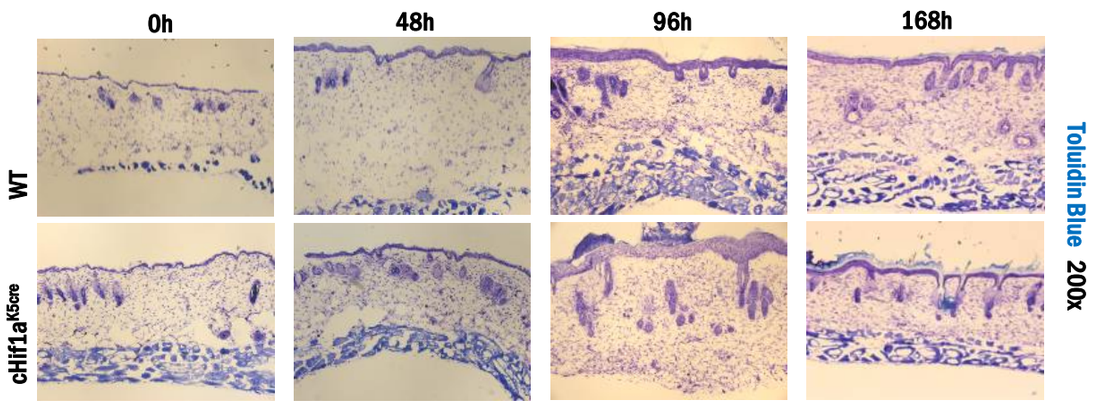
- Acute inflammation
- **Immunosuppression**
- Skin Aging
- Photocarcinogenesis

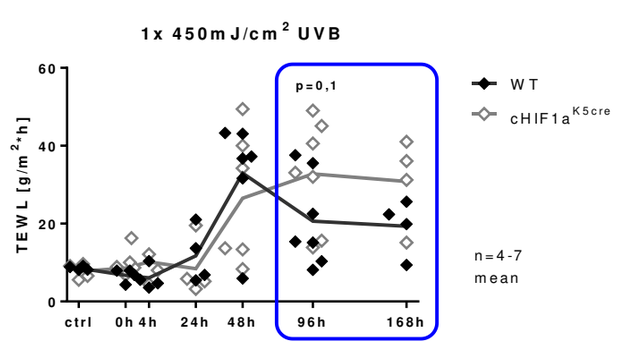


Mice with HIF1a-deficient keratinocytes and littermate controls

Methods & Results

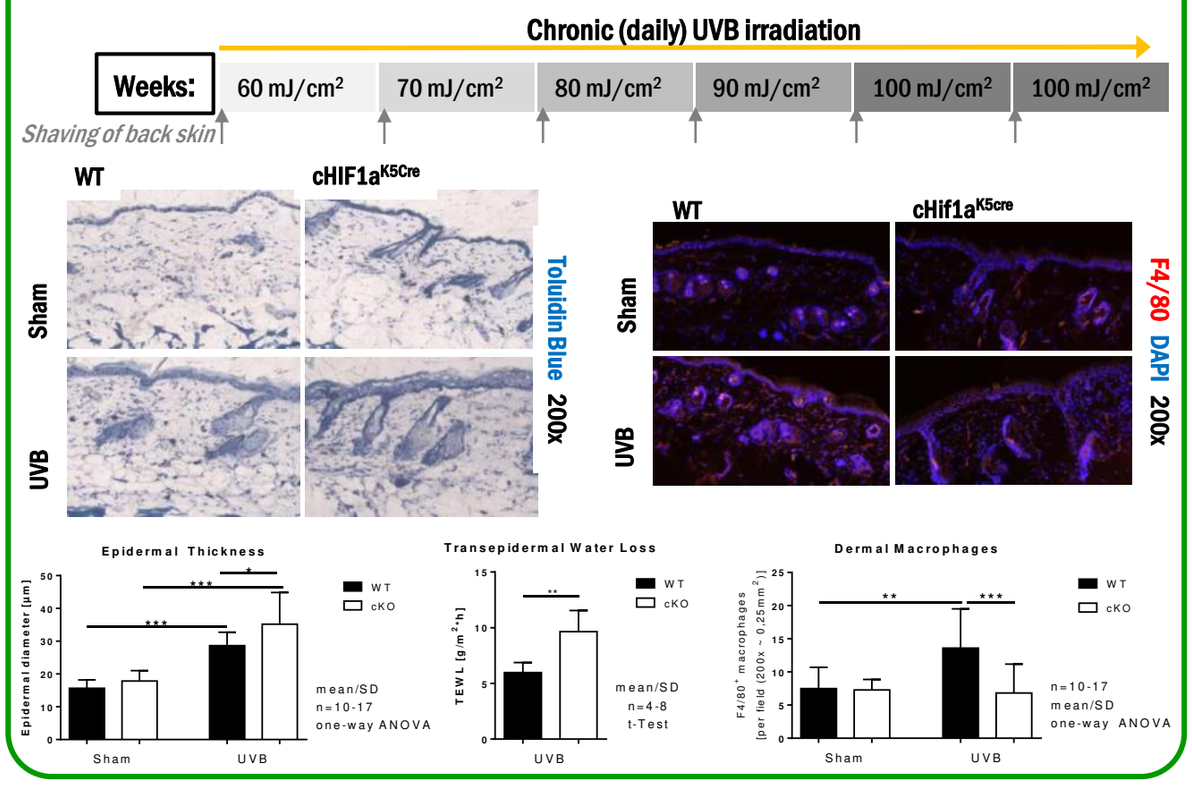
Acute High-Dose UVB Exposure



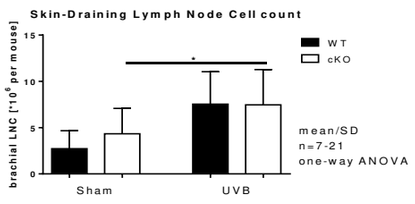


→Increased epidermal hyperplasia and delayed restoration of epidermal integrity in mice with HIF1a-deficient keratinocytes

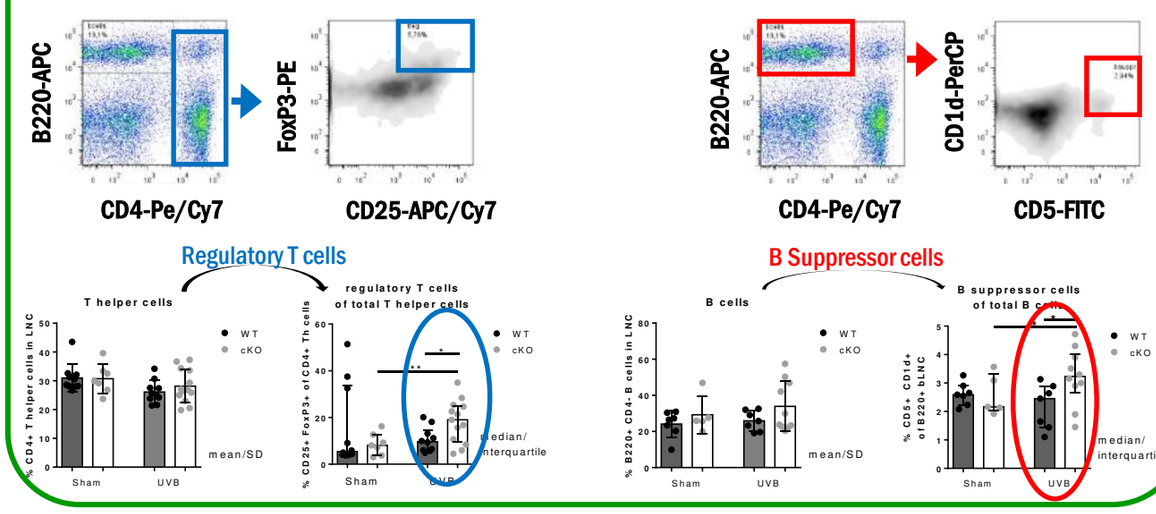
Skin Status after Chronic UVB Exposure



Skin-Draining Lymph Nodes After Chronic UVB



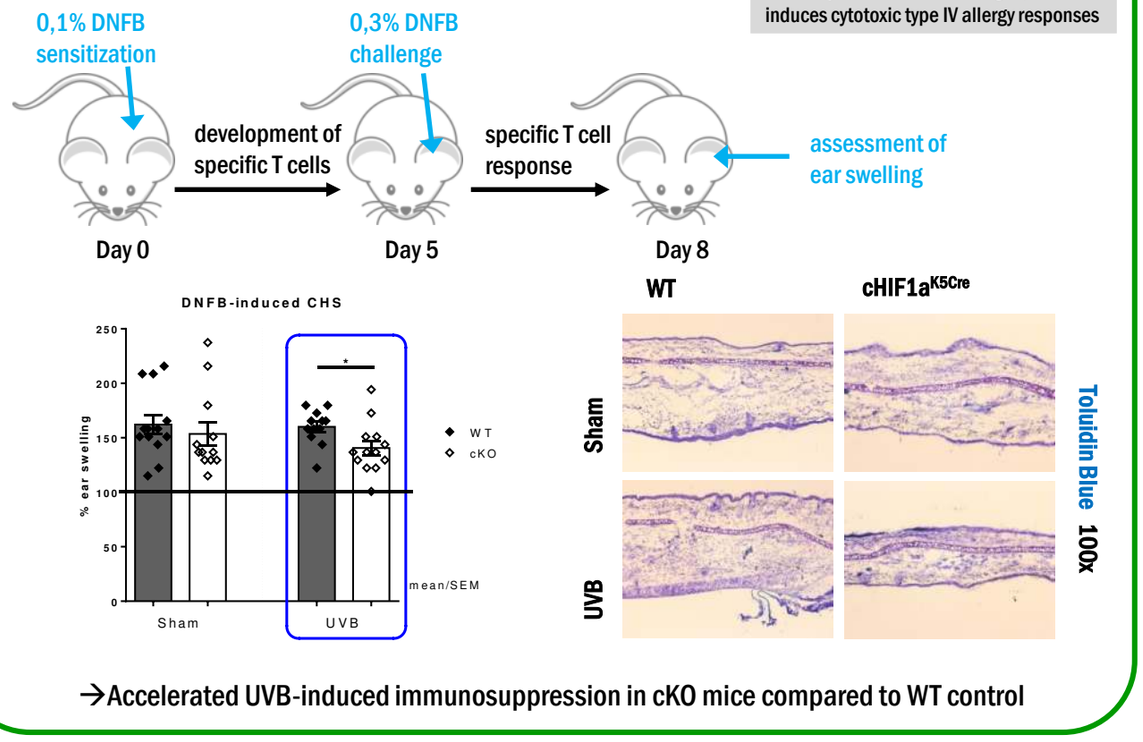
Gating strategy for lymphocytes:



Suppression of Contact Hypersensitivity After Chronic UVB

→ day 6 post chronic UVB exposure:

DNFB: synthetic contact allergen, induces cytotoxic type IV allergy responses



→Accelerated UVB-induced immunosuppression in cKO mice compared to WT control

Discussion

Conclusion / Outlook

- ○ HIF1a signaling in keratinocytes is necessary to protect epidermal integrity during both acute and chronic UVB exposure
- ○ Loss of HIF1a in keratinocytes inhibits UVB-induced intradermal accumulation of macrophages
- ○ Upon chronic UVB exposure, mice with HIF1a-deficient keratinocytes display increased frequencies of regulatory T and B cells in exposed skin-draining lymph nodes
- ○ In DNFB-induced CHS, HIF1a-deficient keratinocytes facilitate development of extrinsic skin-aging-induced immunosuppression by chronic UVB exposure

Further Analysis:

- ○Composition of immune cells in inflamed ear tissue
- ○Visulation of dermal vasculature in back skin and ears
- ○Cytokine release pattern of lymph node cells upon chronic UVB exposure
- ○Activity of HIF1a-related signaling pathways
- ○HIF1a-dependent interaction of keratinocytes with immune cells

→ Further: assessment of a different inflammatory skin disease model