IL-36 receptor antagonistic antibodies inhibit inflammatory response in IL-23 model of psoriasiform dermatitis

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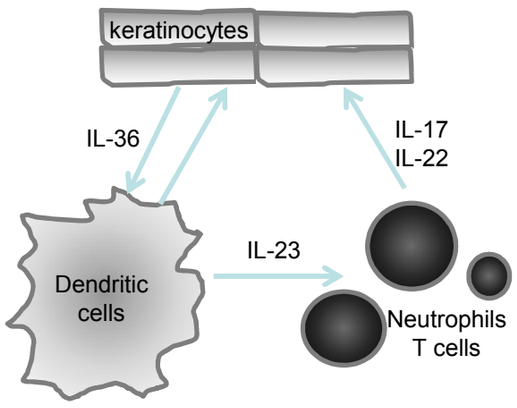
Introduction:

Psoriasis vulgaris (PV) results from activation of IL-23/Th17 immune pathway and is further amplified by skin responses. Among skin derived pro-inflammatory cytokines, IL-36 family members are highly upregulated in PV patients and play a critical role in general pustular psoriasis. However, there is limited data showing crosstalk between the IL-23 and IL-36 pathways in PV. Herein we interrogate, using antagonistic mouse IL-36R antibodies, if functional inhibition of IL-36 receptor (IL-36R) in the IL-23-induced mouse model of psoriasiform dermatitis attenuates skin inflammation.

Hypothesis

IL-36 drives PV through the IL-23 signaling pathway in humans and mouse models of psoriasiform dermatitis

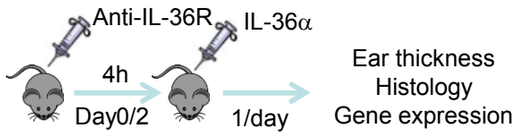


Adapted from Tortola L et al., JCI 2012

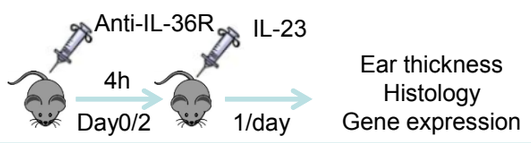
In Vivo Models

Acute IL-36R target engagement assay

IL-36α induced psoriasiform dermatitis assay



IL-23 induced psoriasiform dermatitis assay



Results:

- All recombinant rat/mouse chimeric IL-36 Abs bound to cell surface IL-36 receptors expressed in HEK293-IL-36R/IL-1AcP cells, dose-dependently increasing geometric mean fluorescence intensity (GMFI), with minimal binding to parental cell line (flow cytometry, Fig. 1A).
- These antibodies also blocked binding of IL-36α to IL-36R/IL-1AcP (HEK293 cells, Fig. 1B) as well as IL-36α induced CXCL1 release *in vitro* (not shown).

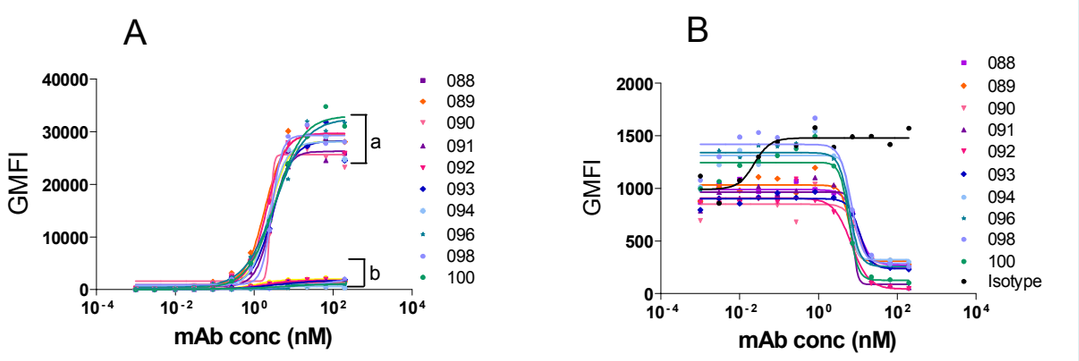


Figure 1: IL-36R antibodies bound to IL-36R and inhibit binding of IL-36α.

- IL-36α induced dose-dependent increase in plasma CXCL1 (Fig. 2A).
- IL-36R mAbs (0.3 mg/kg) prevented CXCL1 increase (60% to 92%, Fig. 2B).

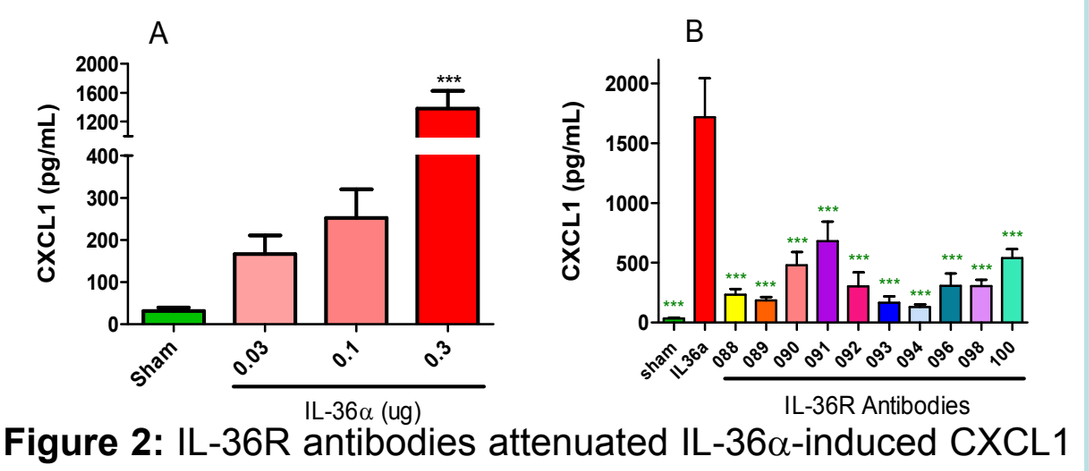
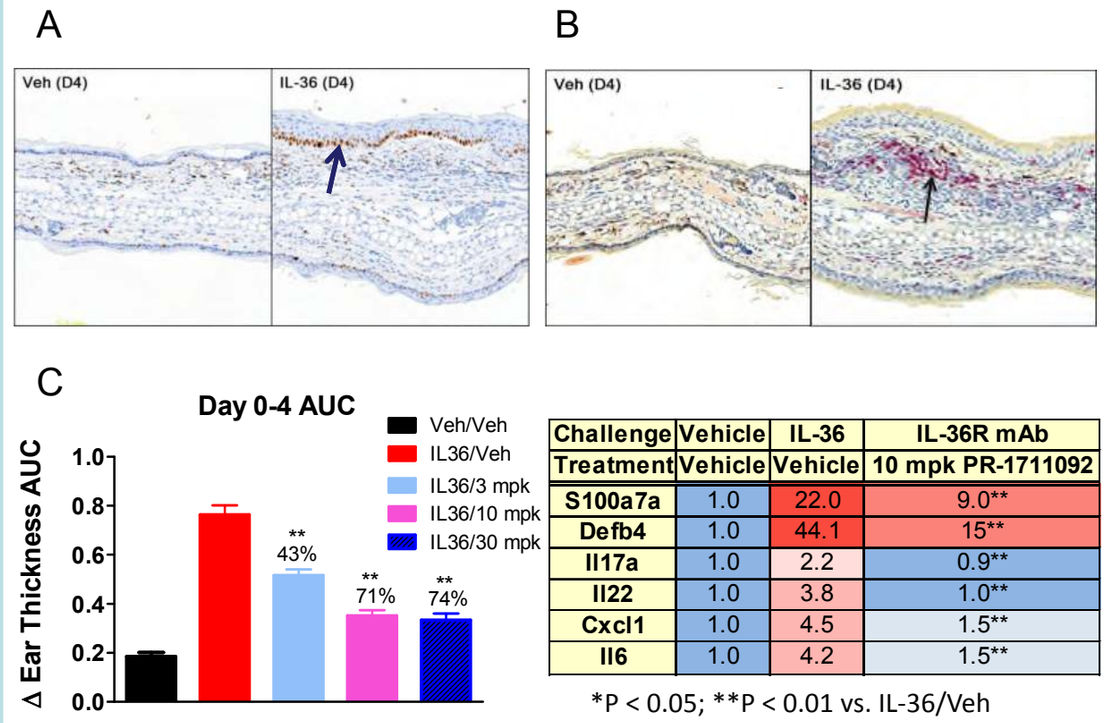


Figure 2: IL-36R antibodies attenuated IL-36α-induced CXCL1 release in mice.

- Injection of IL-36α into mouse ears caused psoriasis-like response including ear thickening, keratinocyte proliferation (Fig. 3A), and infiltration of CD3+ T cells (Fig. 3B).
- Pretreatment with the antagonistic IL-36 mAb dose dependently prevented this disease-like phenotype (Fig 3C) and suppressed elevated mRNA levels of S100a7a, Defb4, Il17a, Il22, Cxcl1, and Il6 in ear tissues (Table inset).

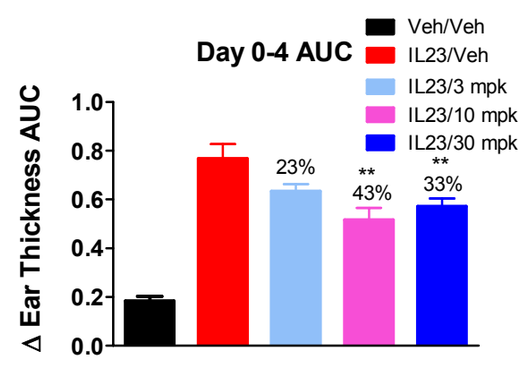


Challenge	Vehicle	IL-36	IL-36R mAb
Treatment	Vehicle	Vehicle	10 mpk PR-1711092
S100a7a	1.0	22.0	9.0**
Defb4	1.0	44.1	15**
Il17a	1.0	2.2	0.9**
Il22	1.0	3.8	1.0**
Cxcl1	1.0	4.5	1.5**
Il6	1.0	4.2	1.5**

*P < 0.05; **P < 0.01 vs. IL-36/Veh

Figure 3: IL-36R antibody attenuated psoriasiform dermatitis induced by IL-36α injection in mouse ears.

- Psoriasiform dermatitis was also induced by ear injection of IL-23 as previously described (Rizzo HL et al., J Immunol 2011).
- IL-23 induced ear thickness was modestly attenuated by an IL-36R Ab with significant effects at 10 and 30 mg/kg (Fig. 4).
- The IL-36R Ab also significantly decreased elevated mRNA levels of S100a7a, Defb4, Il22, and Il6 induced by IL-23 injection, but only had a marginal effect on Il17a and Cxcl1 gene expression (Table inset).



Challenge	Vehicle	IL-23	IL-23
Treatment	Vehicle	Vehicle	10 mpk PR-1711092
S100a7a	1.0	33.4	20.4**
Defb4	1.0	27.1	14.6**
Il17a	1.0	8.7	6.3
Il22	1.0	56.0	37.0*
Cxcl1	1.0	24.2	18.6
Il6	1.0	13.8	5.0**

*P < 0.05; **P < 0.01 vs. IL-36/Veh

Figure 4: IL-36R antibody attenuated IL-23 induced psoriasiform dermatitis in mouse ears.

Conclusions:

- Anti-mIL-36R antibodies were generated and validated *in vitro*.
- In *vivo* target engagement was demonstrated by inhibition of IL-36α induced CXCL1 in plasma.
- Anti-mIL-36R mAbs attenuated tissue inflammation and anti microbial protein gene expression after induction of psoriasiform dermatitis in a novel IL-36α ear injection model.
- Modest effects were also observed in the IL-23 induced psoariasiform dermatitis with attenuation of skin thickening and levels of psoriasis relevant gene expression.
- Collectively, these data suggest a role for IL-36 signaling in the IL-23/Th17 signaling axis driven skin inflammation.

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